AMERICAN SOCIETY FOR MICROBIOLOGY | Clinical Microbiology Reviews®

REVIEW

# Infectious Complications of Biological and Small Molecule Targeted Immunomodulatory Therapies

Joshua S. Davis,[a,b,c] David Ferreira,[d] Emma Paige,[e] Craig Gedye,[d,f] Michael Boyle[a,c]

[a]Department of Infectious Diseases and Immunology, John Hunter Hospital, Newcastle, NSW, Australia
[b]Global and Tropical Health Division, Menzies School of Health Research and Charles Darwin University, Darwin, NT, Australia
[c]School of Medicine and Public Health, University of Newcastle, Newcastle, NSW, Australia
[d]School of Medicine, University of New South Wales, Sydney, NSW, Australia
[e]Department of Infectious Diseases, Alfred Hospital, Melbourne, VIC, Australia
[f]Department of Oncology, Calvary Mater Hospital, Newcastle, NSW, Australia


(continued)

**Citation** Davis JS, Ferreira D, Paige E, Gedye C, Boyle M. 2020. Infectious complications of biological and small molecule targeted immunomodulatory therapies. Clin Microbiol Rev 33:e00035-19. https://doi.org/10.1128/CMR.00035-19.



Address correspondence to Joshua S. Davis, Joshua.Davis@menzies.edu.au.

**Published** 10 June 2020

(continued)

**SUMMARY** The past 2 decades have seen a revolution in our approach to therapeutic immunosuppression. We have moved from relying on broadly active traditional medications, such as prednisolone or methotrexate, toward more specific agents that often target a single receptor, cytokine, or cell type, using monoclonal antibodies, fusion proteins, or targeted small molecules. This change has transformed the treatment of many conditions, including rheumatoid arthritis, cancers, asthma, and inflammatory bowel disease, but along with the benefits have come risks. Contrary to the hope that these more specific agents would have minimal and predictable infectious sequelae, infectious complications have emerged as a major stumbling block for many of these agents. Furthermore, the growing number and complexity of available biologic agents makes it difficult for clinicians to maintain current knowledge, and most review articles focus on a particular target disease or class of agent. In this article, we review the current state of knowledge about infectious complications of biologic and small molecule immunomodulatory agents, aiming to create a single resource relevant to a broad range of clinicians and researchers. For each of 19 classes of agent, we discuss the mechanism of action, the risk and types of infectious complications, and recommendations for prevention of infection.

## INTRODUCTION

Infectious disease physicians, clinical microbiologists, and general internal medicine specialists are increasingly faced with a confusing panoply of new biological and targeted immunosuppressive agents, each with their own mechanism of action and complications. Oncologists and hematologists are generally familiar with new biological and targeted anticancer agents, rheumatologists with new agents to treat inflammatory arthritis, neurologists with anti-multiple sclerosis agents, transplant specialists with new antirejection drugs, and so on. In contrast, those practicing infectious disease and related specialties are the common denominator of all these specialties, often dealing with the consequences of these new agents. We must understand the nature, mechanism of action, and potential infectious complications of all these new agents, but such information is rarely gathered in a single resource. Seemingly every week we are faced with a patient presenting with an infection who has been treated with an agent we are unfamiliar with. This article seeks to collate the current knowledge on biological and small molecule immunosuppressive agents into one place, independent of body system or target disease, aiming to leave the reader with a comprehensive understanding of these agents, their infectious complications, and how to prevent such complications.

### Scope and Structure of This Article

"Biologic agents" broadly means those which are produced by living organisms or contain components of living organisms. However, using this definition, a vast array of commonly used drugs could be considered biologics, including many anti-infectious agents, blood products, many chemotherapy drugs, and vaccines, to name a few. Biologic agents are generally large, complex molecules produced in a living organism, as opposed to nonbiologic agents, which can be chemically synthesized. In this article, we use the term "biologic" to refer to monoclonal antibodies and fusion proteins. We have also included small molecule targeted therapies (such as Janus kinase [JAK] inhibitors), because they are also a recent innovation, are increasingly used yet poorly understood by most generalists, and are relatively specific in their actions. Biologic and small molecule immunosuppressive therapies are distinct from traditional immunosuppressive agents, which generally take a crude, blunderbuss approach. For example, corticosteroids affect the expression of hundreds of different genes important in the immune system, and cyclophosphamide and methotrexate are toxic to many types of rapidly dividing cells, of which leukocytes are only one.

For this article, we focused on agents which (i) are biological or targeted small molecule therapies, (ii) have a direct or indirect effect on one or more elements of the human immune system, and (iii) are approved for use in the United States (by the Food and Drug Administration [FDA]) or Europe (by the European Medicines Agency [EMA]). The indications listed in the article are those of the FDA and EMA combined. We have largely restricted discussion of the adverse effects of these agents to infections and have not gone into any detail about the risk of malignancy, infusion site reactions, or cytopenias.

It would be difficult or impossible to cover every biological agent or small molecule in one review article, and there are several groups of drugs we have omitted. These include those which target vascular structures and processes (e.g., vascular endothelial growth factor [VEGF] inhibitors, such as bevacizumab) and those with no known or expected action on the immune system (e.g., abciximab, a glycoprotein IIb/IIIa receptor antagonist which inhibits platelet function, or evolucumab, a monoclonal antibody [MAb] for lowering cholesterol).

Sections are arranged according to the drug class and mechanism of action, not the target disease. For each group of related agents, we present (i) a summary of the structure and function of the target cell, molecule or system, (ii) a review of the risk of infectious complications of the agent(s), based on published data, (iii) a brief discussion of recommended strategies to prevent infectious complications in those treated with

**TABLE 1** Strategies used to suppress the immune system and examples of traditional, biologic, and small molecule targeted agents used

| Strategy | Traditional immunosuppressive agent(s) | Biologic or small molecule targeted agent(s)[a] |
|---|---|---|
| Stop or inhibit the replication of immune cells | Cyclophosphamide, methotrexate, mycophenolate, azathioprine | |
| Selectively kill immune cells | | Alemtuzumab (anti-CD52 Ab, kills mature T and B cells, natural killer cells, and monocytes), rituximab (anti-CD20 Ab, kills B cells) |
| Inhibit direct cell-to-cell signaling | | Abatacept (CTLA-4 linked to a MAb) |
| Inhibit downstream second messenger signalling | Cyclosporin, tacrolimus, sirolimus | Tofacitinib, baricitinib (Janus kinase inhibitors) |
| Antagonize cytokines or their receptors | | Anakinra (targets IL-1), dupilumab (IL-4), mepolizumab (IL-5), tocilizumab (IL-6), ustekinumab (IL-12/IL-23), secukinumab (IL-17), infliximab (TNF) |
| Block cell trafficking | Fingolimod (sphingosine 1-phosphate receptor) | Natalizumab ($\alpha$4 integrin) |

[a]Ab, antibody; MAb, monoclonal antibody.

the agent(s) in question, and (iv) a brief summary of the current state of knowledge and any identified knowledge gaps.

### Immunosuppressive Therapies: Overview

In general, there are several strategies used to inhibit unwanted immune responses (such as in autoinflammatory conditions). These can involve either traditional immunosuppressive medications or newer biologic or small molecule targeted agents (Table 1). Cytokine-targeted agents discussed in this article, along with their sites of action, are shown in Fig. 1, cell-receptor targeted agents in Fig. 2, and small molecule targeted therapies in Fig. 3.

### Current and Projected Use of Biological Therapy

Since the FDA approved rituximab in 1997 and imatinib in 2001, the number of available biologics, as well as the number of patients treated with them annually, has exploded. From 2008 to 2013, the market for biologics increased from 39 to 75 billion dollars per annum (1). Currently, well over 70 monoclonal antibodies are used in clinical practice, with a yearly market value of 125 billion dollars (1, 2). Indications for biological therapy have also broadened, ranging from the treatment of autoimmune disease to cancer and chronic disease of various organ systems (3). Despite increasing popularity,

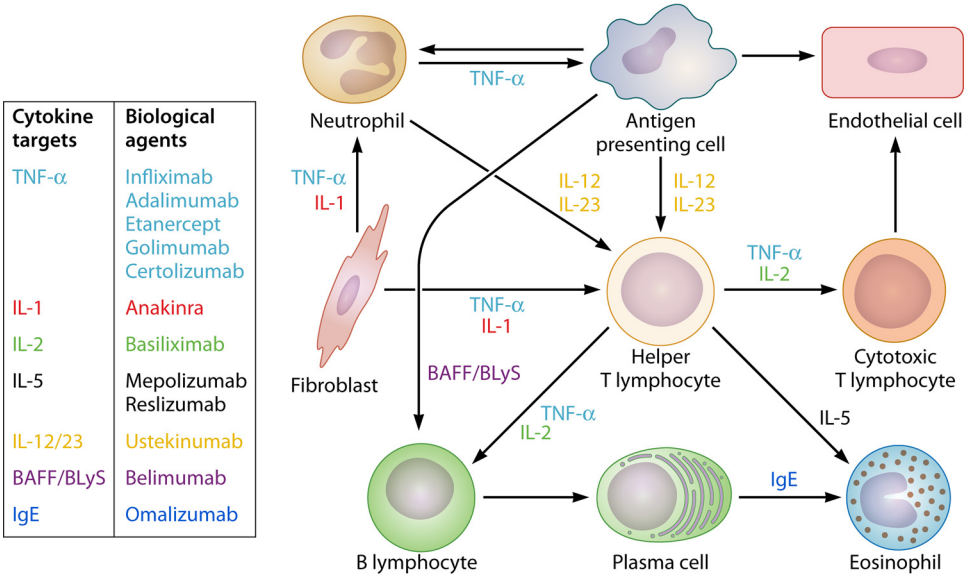


**FIG 1** Overview of cytokine-targeted agents included in this article.

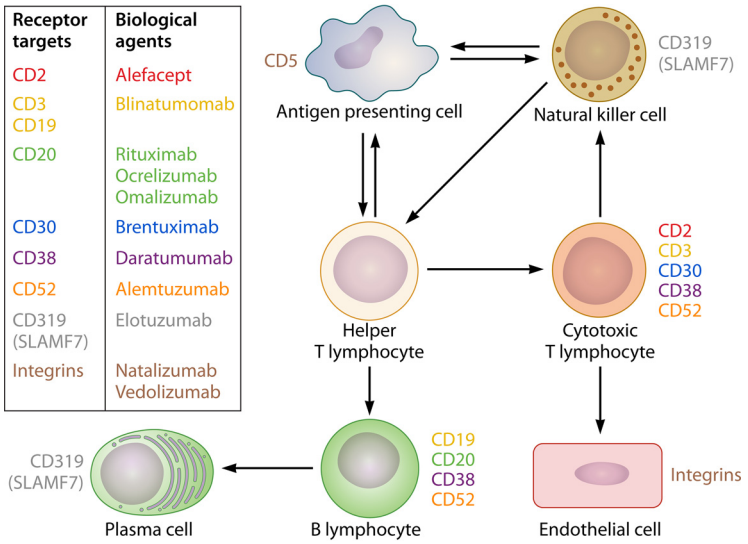


**FIG 2** Overview of cell receptor-targeted agents included in this article.

biologics are not without risk, and they have not turned out to be the "magic bullets" many predicted. Infections are increasingly recognized as a complication of these therapies (4, 5), knowledge of which is crucial for the practice of any up-to-date clinician (6).

## Basic Science of Biologic Therapy and Small Molecule Targeted Therapies

Monoclonal antibodies are similar in structure to human immunoglobulin. Variable regions (Fab) act as antigen binding sites, while constant regions (Fc [crystallizable fragment]) determine effector function (Fig. 4) (7). Variable regions are subdivided into complementarity-determining regions (CDRs) and framework regions (8). Monoclonal antibodies are classified based on their biological source: murine, chimeric, humanized,

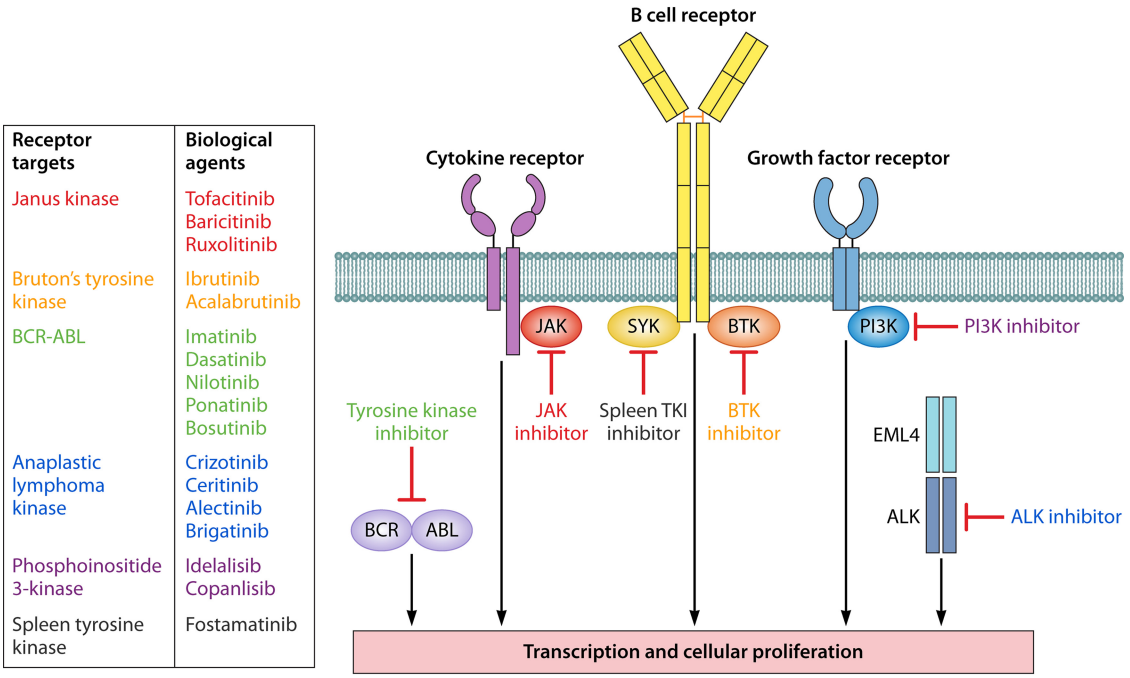


**FIG 3** Overview of small molecule targeted therapies included in this article.

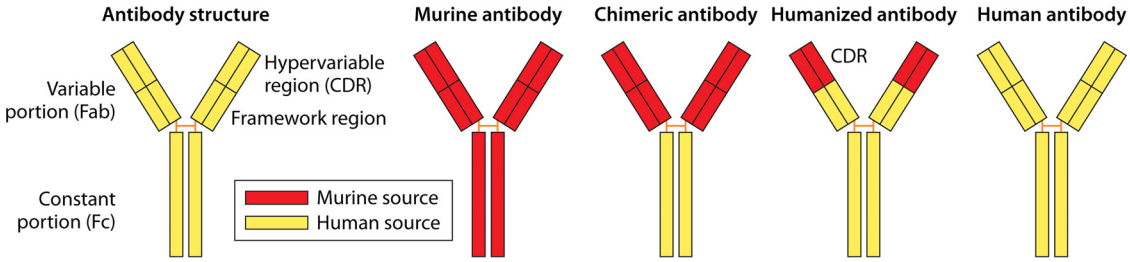


**FIG 4** Types of monoclonal antibodies.

or human antibodies (Table 2) (9). Murine antibodies (suffix "-omab") are formed from rodent sequences. Chimeric antibodies (suffix "-ximab") are produced from a combination of murine variable regions and human constant regions. Humanized antibodies (suffix "-zumab") only have CDRs of murine origin and are formed largely by human sequences (10). Human antibodies (suffix "-umab") are produced purely from human sequences and are less immunogenic (11). Fusion proteins are structurally different from monoclonal antibodies. These proteins are genetically engineered through the combination of an effector domain with an Fc crystallizable fragment (Fig. 5) (12). The human IgG1 Fc fragment is most commonly used due to its stability, extended half-life, and high affinity. The effector domain functions as the binding site, while the Fc portion causes activation or inactivation of the target.

Small molecule targeted therapies differ from monoclonal antibodies in many ways (Table 3). They are smaller and simpler molecules. They can enter cells and act on second messenger systems, rather than just cell surface elements like monoclonal antibodies (MAbs). They are generally orally bioavailable with short half-lives.

Small molecule targeted therapies are named with a suffix ending in "-ib" if they have an inhibitory action on the target ("ib" being short for "inhibitory"). The letters before this indicate which type of target they inhibit. Although this article only discusses tyrosine kinase inhibitors (TKIs) in any detail, examples of other types of these agents are given in Table 2 for completion. These agents are discussed below (see Tyrosine Kinase Inhibitor Overview).

The basic principles of biological therapy are simple. A healthy human immune system is characterized by a balance of pro- and anti-inflammatory responses (13). An exaggerated proinflammatory response with reduced self-tolerance results in autoimmune disease (14). A depressed inflammatory response and reduced immune surveillance results in infectious and neoplastic sequelae (15, 16). Most biologic therapies aim to restore the balance in the human immune system through altering pro- and anti-inflammatory responses. In attempting to restore balance, treatment may tip the balance in the opposing direction. Some biological therapies do not directly impact the immune system, targeting other molecular substrates instead.

**TABLE 2** Suffixes used for different types of biological and small molecule therapeutic agents

| Type of agent, source | Example (target) | Suffix |
|---|---|---|
| MAbs | | |
| Murine | Muromonab (CD3) | -omab |
| Chimeric | Infliximab (TNF) | -ximab |
| Humanized | Tocilizumab (IL-6) | -zumab |
| Human | Adalimumab (TNF) | -umab |
| Small molecule targeted therapies | | |
| Tyrosine kinase inhibitors | Tofacitinib | -tinib |
| Proteasome inhibitors | Bortezomib | -zomib |
| Angiogenesis inhibitors | Pazopanib | -anib |
| RAF kinase inhibitors[a] | Sorafenib | -rafenib |

[a]RAF, rapidly accelerated fibrosarcoma.

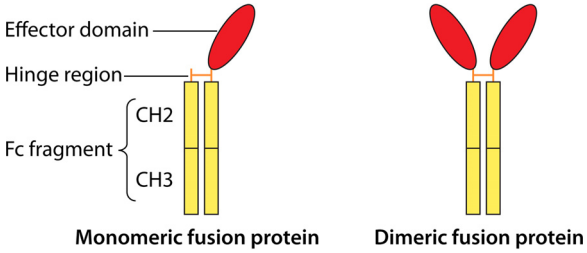


**FIG 5** Structure of fusion proteins.

Biologics have three major therapeutic mechanisms (Fig. 6). The first is soluble receptor antagonism. Antibodies function as decoy receptors that inhibit free cytokines in the serum. The second is surface receptor antagonism. Agents bind to a target receptor, preventing cytokine-mediated receptor activation (17). The third mechanism is a combination of soluble cytokine and bound receptor inhibition. Biologics with combination mechanisms seem to have higher affinities (18).

### Opportunistic Infection with Biological Agents

Biological therapy carries a theoretical advantage over traditional methods of immunosuppression. Corticosteroids act through downregulation of multiple proinflammatory pathways, inhibiting cytokines, chemokines, adhesion molecules, and arachidonic acid metabolites (19). This shotgun approach, while effective for autoimmune disease, causes a dose-dependent risk of infections from various pathogens (20, 21). Targeting specific cytokines and cells with biologics offers a more precise approach to the treatment of disease (22). The type of infectious complication is theoretically dependent on the immune cell or cytokine inhibited. Despite this, targeted immune interference from biologics often results in increased risk of infection from all microorganisms: viral, bacterial, fungal, and parasitic. Tumor necrosis factor alpha (TNF-$\alpha$) inhibitors reduce phagocytic function and heighten the risk of granulomatous infection. However, there is also an increased risk of invasive viral and parasitic disease (23, 24). B cell-depleting agents not only increase the rates of invasive bacterial infection but also lead to reactivation of chronic viral infections (25, 26). T cell inhibition worsens the risk of viral disease, but bacterial and fungal complications also occur (6). Ultimately, the immune system's response to every infection relies on the sum of its parts: a cohesive interplay of the innate and adaptive immune response (27). Inhibition of one part weakens the whole. As a result, the observed infectious complications often differ significantly from what would be predicted based on the mechanism of action (that is a key reason why collating the data together in this article is potentially useful). Combination immunosuppression results in a higher chance of infectious complications (28–30). Therefore, the combination of biologic therapy with other immunosuppressive agents should be used cautiously. In particular, the addition of corticosteroids to any immunosuppressive regimen increases the risk of infection (31). The term "serious infection" is widely used in published data describing the infectious risks of these agents and, thus, is used extensively in the rest of this article. This term generally means an infection which meets any of the following criteria: (i) required hospitaliza-

**TABLE 3** Comparative features of biologics and small molecule targeted therapies

| Characteristic | Biologics (MAbs and fusion proteins) | Small molecule targeted therapies (tyrosine kinase inhibitors) |
|---|---|---|
| Size | Large, complex | Small, simple |
| Site of action | Cell surface receptors or soluble cytokines | Intracellular second messengers |
| Mode of administration | Intravenous or subcutaneous | Usually oral |
| Half-life | Days to weeks | Hours |
| Production | Cell lines or animals | Often chemically synthesized |
| Specificity | Highly target specific | Many hard-to-predict off-target actions |
| Drug interactions | Rare | Common |

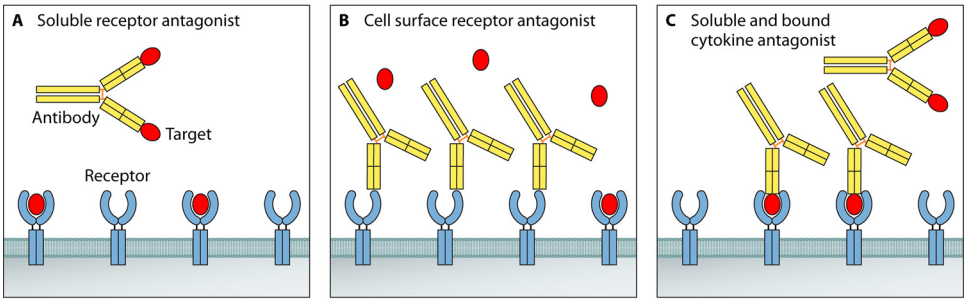


**FIG 6** Mechanisms of action of monoclonal antibodies.

tion, (ii) prolonged an existing hospitalization, (iii) was considered life threatening, or (iv) resulted in death or permanent disability. Some trials and reporting structures also include any infection which is considered a "medically important event" by the relevant site investigator. Some biological agents have been subject to "black box warnings" by the U.S. Food and Drug Administration (FDA). These are released when the FDA wishes to make prescribers aware of a potentially dangerous emerging adverse event (for example, hepatitis B virus [HBV] reactivation secondary to rituximab). The European Medicines Agency and Australia's Therapeutic Goods Administration also publish warnings to prescribers when serious new adverse events are recognized, but these are not generally known as black box warnings. Where warnings have been published for a biological agent, we have referred to the FDA's black box warning in the relevant section. The term "opportunistic infection" in this article is used to mean infections which are rare in those with normal immune function and are mainly recognized in those with iatrogenic, congenital, or human immunodeficiency virus (HIV)-induced immunosuppression. Classic examples include *Pneumocystis jirovecii* pneumonia (PJP) and progressive multifocal leukoencephalopathy caused by JC virus. The use of the term opportunistic infection can, however, be confusing. For example, tuberculosis is a very common infection in those with no evident immunosuppression but is much more common in those who are immunosuppressed. Bacterial and viral upper respiratory tract infections are common in all humans but are more common in those receiving certain biological agents (e.g., tocilizumab) than in healthy controls. In this article, we have primarily used the term in the first sense: infections which are rare in those with normal immune systems.

## TNF-$\alpha$ INHIBITORS

### Structure and Function of TNF-$\alpha$

Tumor necrosis factor alpha (TNF-$\alpha$) is a pleiotropic primary cytokine of the innate immune system. This cytokine has been shown to underlie the pathophysiology of many inflammatory disorders, including rheumatoid arthritis (RA), seronegative spondyloarthropathies, and inflammatory bowel disease (IBD) (32–34). TNF-$\alpha$ is produced by macrophages and T lymphocytes as a 233-amino-acid transmembrane precursor protein (35). Cleaving of the cytoplasmic portion of the protein by TNF-$\alpha$-converting enzyme (TACE) leads to the release of free TNF-$\alpha$ (157 amino acids) into the serum (36). The cytokine then activates a TNF receptor, TNF receptor 1 (p55 receptor) or TNF receptor 2 (p75 receptor). Activation results in the release of proinflammatory cytokines (interleukin-1$\beta$ [IL-1$\beta$], IL-6, IL-8, and granulocyte macrophage colony-stimulating factor [GM-CSF]), chemotactic molecules (MCP-1, MIP2, RANTES), and adhesion molecules (E-selectin, ICAM-1, and VCAM-1) (33). The net result is macrophage and neutrophil activation, promoting phagocytic function, chemotaxis, granuloma formation, and granuloma integrity (37).

TNF-$\alpha$ protects the host from pathogens in many ways (Fig. 7). TNF-$\alpha$ is an important cytokine against viral disease. For example, inhibition of TNF-$\alpha$ results in decreased hepatitis B virus (HBV) clearance in murine studies (38, 39). TNF-$\alpha$ promotes hepatitis B

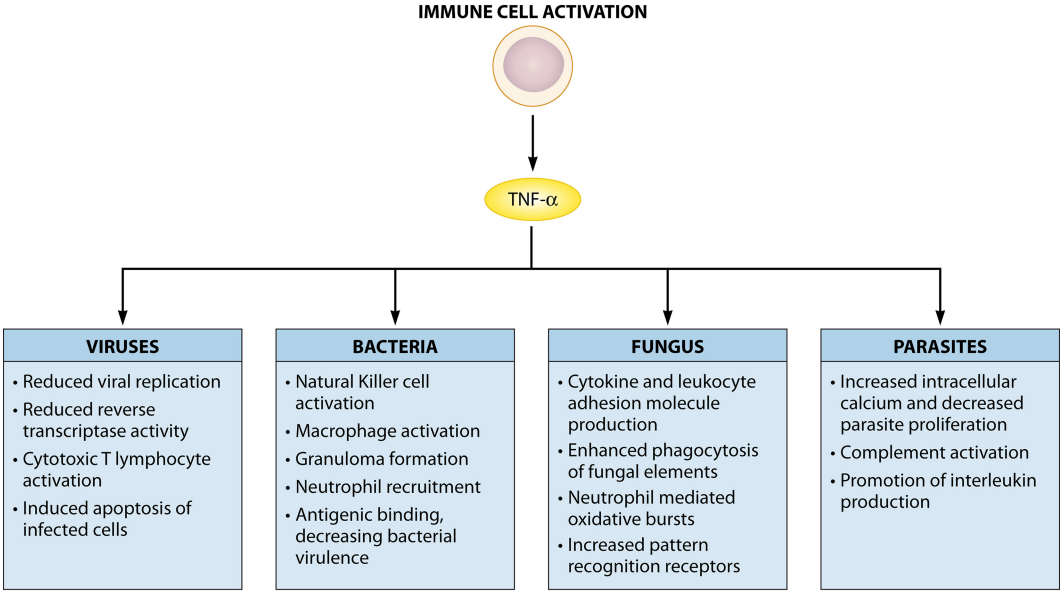


**FIG 7** Tumor necrosis factor alpha action against pathogens.

virus-specific cytotoxic T lymphocytes (40), and its concentration is inversely related to mortality in rodents infected with the Japanese encephalitis virus (41). TNF-$\alpha$ has a significant role in bacterial infection, particularly in regard to intracellular pathogens (42). Its action against bacterial organisms is complex, relating to natural killer (NK) cells and macrophage activation, allowing granuloma formation and prevention of pathogen dissemination (43–45). Animal studies have demonstrated the crucial role it plays in infections caused by mycobacteria, *Streptococcus pneumoniae*, salmonellae, and *Listeria monocytogenes* (46–50). Fungal infection is also inhibited by TNF-$\alpha$. Neutrophil-mediated oxidative bursts are directly promoted by the cytokine, increasing fungicidal capability (51, 52). Thus, TNF-$\alpha$ has been shown to be important in the host response against *Cryptococcus neoformans*, pulmonary histoplasmosis, and *Candida albicans* (53, 54). TNF-$\alpha$ likely also has a role in the response to parasitic infections; however, this has not been fully elucidated.

### Overview of TNF-$\alpha$ Inhibitors

There are five TNF-$\alpha$ inhibitors currently available for clinical use, with more in development (Table 4). Their original and still most common indication is for the treatment of rheumatoid arthritis (RA), a disease which has been revolutionized by the development of TNF inhibitor therapy.

All five agents are approved for use in rheumatoid arthritis, and all but etanercept are approved for use in inflammatory bowel disease. Some (e.g., infliximab) are also approved for use in psoriatic arthritis, plaque psoriasis, ankylosing spondylitis, hidradenitis suppurativa, and uveitis. In general, TNF-$\alpha$ inhibitors are highly effective treatments for inflammatory arthritides (55–57) and inflammatory bowel disease (58–60) compared to less targeted traditional treatments, such as methotrexate, azathioprine,

**TABLE 4** Biological TNF inhibitors in clinical use

| Drug | Yr approved | Nature | Mechanism |
|---|---|---|---|
| Infliximab | 1998 | Chimeric IgG1 MAb | Inhibits both soluble and membrane-bound TNF-$\alpha$ |
| Etanercept | 1998 | Dimeric fusion protein | Acts as a decoy soluble receptor to TNF-$\alpha$ and -$\beta$ |
| Adalimumab | 2003 | Human IgG1 MAb | Inhibits both soluble and membrane-bound TNF-$\alpha$ |
| Certolizumab | 2008 | Humanized Fab′ fragment conjugated to PEG[a] | Inhibits both soluble and membrane-bound TNF-$\alpha$ |
| Golimumab | 2009 | Human IgG1 MAb | Inhibits both soluble and membrane-bound TNF-$\alpha$ |

[a]PEG, polyethylene glycol.

or sulfasalazine. They share several potential adverse effects in addition to infection risk, including injection site reactions, exacerbation of heart failure, induction of autoimmunity, and increased risk of malignancy (55, 57, 61, 62). Etanercept differs from the other agents in that it is a dimeric fusion protein which is produced by the combination of the constant (Fc) portion of human IgG1 and the ligand binding portion of the tumor necrosis factor receptor (p75) (63). It functions as a decoy receptor to TNF-$\alpha$ and TNF-$\beta$, binding to these molecules in the serum. Because it acts as a soluble receptor inhibitor, it is a less potent inhibitor of TNF-$\alpha$ and, thus, appears to have lower rates of infectious sequelae (64–69). Certolizumab pegol is also structurally different from the other anti-TNF-$\alpha$ monoclonal antibodies; it comprises a Fab fragment produced from *Escherichia coli* and conjugated to polyethylene glycol (PEG2MAL40K) (70). Unlike other agents, it lacks a crystallizable fragment (Fc) region and, therefore, does not facilitate cell-mediated cytotoxicity (71, 72). Given the relatively recent introduction of certolizumab and golimumab, evidence on infectious complications of these agents is relatively scarce. One potential strategy for improving the risk/benefit ratio of TNF inhibitors is to only use them in patients with markers predictive of a therapeutic response. Using pharmacogenomics has been proposed as such a strategy, with preliminary evidence that certain polymorphisms in the TNF gene correlate with improved therapeutic responses in inflammatory arthritides (73, 74). However, other studies have had conflicting findings (75), and larger studies are needed before this strategy can be recommended in clinical practice (76).

### TNF-$\alpha$ Inhibitors: Infective Complications

**Overview.** TNF-$\alpha$ inhibitor therapy is associated with an increased risk of infection reported in multiple studies (Table 5) (77, 78). There appears to be a risk gradient, with the highest risk associated with the use of infliximab, lower in adalimumab, and lowest with etanercept, reflecting the decreased potency of soluble receptor antagonists (78–81). Most nontuberculous infectious complications are viral (40%), followed by bacterial (33%), fungal (22%), and parasitic infections (4%) (82). Independent risk factors for infection include malnutrition, diabetes, combination with other immunosuppressive agents, and older age (31).

**Viral infections.** Autoimmune disease and chronic viral infections (HBV, hepatitis C virus [HCV], and HIV) often coexist, raising questions about the safety of biological therapy in this setting. Reactivation of hepatitis B virus with TNF-$\alpha$ inhibitor therapy has been reported (83–86). There is a significantly higher risk of reactivation in patients who are HBV surface antigen positive ($HBsAg^+$) than in those who are HBV core antibody (Ab) positive (anti-$HBcAb^+$) alone (37% versus 5%, $P = 0.001$), a risk that is compounded by the concurrent use of corticosteroids (86, 87). There is limited literature on the use of anti-TNF-$\alpha$ agents in patients with HCV infection. Studies suggest safety with the short-term use of etanercept and adalimumab, with or without antiviral therapy (88–90). There is also a suggestion that etanercept therapy may improve HCV viral clearance (91). Insufficient data are available for infliximab, certolizumab pegol, and golimumab in the setting of chronic HCV infection.

Chronic HIV infection depresses immune function and increases the risk of life-threatening infections. Thus, prescribing TNF-$\alpha$ inhibitors to this population produces understandable anxiety in medical professionals. Initial case series show that the use of TNF-$\alpha$ blockers in patients with HIV may be a viable alternative to other disease-modifying therapies, provided there is adherence to an established and effective antiretroviral regimen (92–94).

Other viral opportunistic infections have been associated with TNF-$\alpha$ inhibitor therapy. Some studies suggest that infliximab and adalimumab increase rates of herpes simplex virus (HSV) reactivation (95, 96). The risk of herpes zoster also seems to increase with treatment and is occasionally associated with life-threatening complications (97–99). A prospective cohort study demonstrated an event rate of 10.9 per 1,000 patient years. This risk was confined to patients treated with adalimumab and infliximab and was not seen in those receiving etanercept (97). Several studies have demonstrated no

**TABLE 5** Infectious complications of TNF-$\alpha$ inhibitors

| Inhibitor, type of pathogen or infectious complication | Disease or pathogen | Differential factor | Frequency (% or no. of events/no. of PY)[a] |
|---|---|---|---|
| All inhibitors | | | |
| Viruses | Hepatitis B virus reactivation | $HBsAg^+$ | 12–39 (84, 86) |
| | | Anti-$HBcAb^+$, $HBsAg^-$ | 5 (86) |
| | Herpes zoster reactivation | | 1.01/100 (97) |
| Bacteria | Tuberculosis | | 116.7/100,000 (1227) |
| | Nocardiosis | | 8.66/100,000 (82) |
| | Listeriosis | | 6.93/100,000 (82) |
| Fungi | Invasive candidiasis | | |
| | Pneumocystosis | | 0.5 (1228) |
| Serious infections | | | 4.5–14.0/100 (1229, 1230) |
| Adalimumab | | | |
| Viruses | Cytomegalovirus | | <0.1/100 (1231) |
| | Herpes zoster | | 0.3–1.7/100 (97, 185, 1231) |
| Bacteria | Tuberculosis | | 0.29–0.44/100 (1231, 1232) |
| Fungi | Invasive candidiasis | | <0.1/100 (1231) |
| | Coccidioidomycosis | | <0.1/100 (1231) |
| | Histoplasmosis | | 0.03/100 (111) |
| Serious infections | | | 2.6/100 (1233) |
| | Cellulitis | | 0.3/100 (1231) |
| | Pneumonia | | 0.7/100 (1231) |
| | Urinary tract infection | | 0.4/100 (1231) |
| | Gastrointestinal tract abscess | | 1.6/100 (1231) |
| Infliximab | | | |
| Viruses | Herpes zoster | | 1.1–1.8/100 (97, 185) |
| Bacteria | Tuberculosis | | 144–188/100,000 (156, 1227, 1232) |
| | *L. monocytogenes* | | 15.5/100,000 (156) |
| Fungi | *Candida* | | 10.2/100,000 (1234) |
| | Aspergillosis | | 8.6/100,000 (1234) |
| Serious infections | | Age <65 yrs | 5.4/100 (1235) |
| | | Age >65 yrs | 16.0/100 (1235) |
| Etanercept | | | |
| Viruses | Herpes zoster | | 0.9–2.2/100 (97, 185) |
| Bacteria | Tuberculosis | | 9.3–35/100,000 (156, 1227) |
| | *L. monocytogenes* | | 1.8/100,000 (156) |
| Fungi | *Candida* | | 5.3/100,000 (1234) |
| | Aspergillosis | | 6.2/100,000 (1234) |
| Serious infections | | | 1.7–6.4/100 (1233) |
| Golimumab | | | |
| Viruses | Herpes zoster | | 1.6/100 (185) |
| Bacteria | *M. tuberculosis* | | 0.2–0.4/100 (192) |
| Serious infections | | | 3.0–5.1/100 (192) |
| Certolizumab pegol | | | |
| Viruses | Herpes zoster | | 0.9–2.5/100 (185, 1236) |
| Bacteria | *M. tuberculosis* | | 0.5/100 (201) |
| Fungi | | | 0.7/100 (1236) |
| Serious infections | | | 4.3/100 (201) |
| | Pneumonia | | 0.8/100 (201) |
| | Cellulitis | | 0.3/100 (201) |
| | Urinary tract infection | | 0.2/100 (201) |

[a]PY, patient years.

increase in Epstein-Barr virus (EBV) reactivation (100, 101). There have been reports of cytomegalovirus (CMV) reactivation in patients treated with infliximab and etanercept; however, these have generally occurred in the setting of combination immunosuppression (102). Since herpesvirus reactivations (e.g., cold sores and shingles) are common in the general population, it is unclear how much attributable risk increase occurs with TNF-$\alpha$ inhibitors.

***Mycobacterium tuberculosis*.** The role of TNF-$\alpha$ in the host response to *Mycobacterium tuberculosis* infection has been extensively documented. In the healthy host, TNF-$\alpha$

promotes granuloma formation, preventing the dissemination of bacilli and preserving latent disease (103). Fatal mycobacterial infections develop in murine models deficient in TNF-$\alpha$ (104–106). Unsurprisingly, TNF-$\alpha$ inhibitor use has been associated with an increased risk of active tuberculosis. The greatest risk is associated with infliximab use. The RATIO Registry reported odds ratios (ORs) of 17.6 for tuberculosis reactivation with infliximab, 10.0 for adalimumab, and 6.3 for etanercept (107–109) compared to those not receiving TNF inhibitors.

**Fungal infection.** The risk of disseminated fungal infection is also increased by anti-TNF-$\alpha$ treatment. This occurs most often in the setting of combination immunosuppression (110, 111). Life-threatening infections have been reported with *Histoplasma*, *Coccidioides*, *Cryptococcus*, *Pneumocystis*, and *Aspergillus*. These complications generally occur from 1 week to 6 months following commencement of therapy (112–114).

**Infectious complications of adalimumab.** Initial case series investigating adalimumab use in patients with hepatitis B and C virus infections have suggested safety, providing antiviral therapy is instituted (115–118). There have been three reports of hepatitis B virus reactivation (one fatal), all occurring in patients not on antiviral prophylaxis (119–121). Mori and Fujiyama report a hepatitis B virus reactivation rate of 0.6% for those taking adalimumab; one of the two cases did not receive antiviral treatment (122).

Adalimumab is frequently used in combination with other immunosuppressive therapies to induce rheumatoid arthritis remission. The PREMIER study demonstrated that the combination of adalimumab and methotrexate resulted in greater disease remission than adalimumab monotherapy. This was at the cost of an increase in severe infectious complications (2.9 versus 0.7 per 100 person years [PY]) (123). The ReAct Trial did not find an increase in infections comparing adalimumab monotherapy to adalimumab in combination with disease-modifying antirheumatic drugs (DMARDS) (methotrexate, lefluomide, sulfasalazine, azathioprine, hydroxychloroquine, and chloroquine) (124). CONCERTO demonstrated a dose-dependent increased rate of nonserious infectious complications with combination adalimumab and methotrexate compared to the rate with adalimumab alone. The rates of serious infections were similar between groups (125).

A recent review article examined the side effects of adalimumab therapy in patients with inflammatory bowel disease. Serious infectious complications occurred more often in patients with Crohn's disease than in patients with ulcerative colitis (6.7/100 PY versus 3.5/100 PY). Most of these complications were abdominal and anal abscesses (126). The rates of opportunistic infection (tuberculosis and esophageal candidiasis) were low, at 0.3/100 PY in Crohn's disease versus 0.2/100 PY in ulcerative colitis (126). One study showed that the first-line use of adalimumab in ulcerative colitis resulted in increased rates of hospitalization and serious infection over the rates in those treated with infliximab (78). Other studies have demonstrated similar rates of adverse events between adalimumab and infliximab in the treatment of IBD (127, 128).

Other reported adalimumab-associated infectious complications include gastroenteritis, CMV and EBV reactivation, bacterial pulmonary infections, *Mycobacterium chelonae*, *Mycobacterium fortuitum*, nocardiosis, toxoplasmosis, and visceral and cutaneous leishmaniasis (124, 129–135).

**Infectious complications of infliximab.** Among TNF-$\alpha$ inhibitors, the risk of infectious complications appears highest with infliximab, particularly bacterial infection (80, 136–138). The FDA drug label cites an infection rate of 36% in patients on therapy after a year compared to 25% of patients on placebo (98).

Carroll and Forgione published a review in 2010 suggesting infliximab has the highest rate of hepatitis B virus reactivation compared to other TNF-$\alpha$ inhibitors (40). Cooper et al. performed a randomized control trial (RCT) investigating the hepatitis C virus response in those treated with infliximab. The authors hypothesized that infliximab in combination with pegylated interferon alpha-2b and ribavirin would improve the virological response. Unfortunately, infliximab resulted in a nonsignificant decrease

in rapid virological response (19.5% versus 36.4%) and sustained virological response (34.1% versus 52.3%) (139). While there is a sparsity of data appraising infliximab in hepatitis C virus infection, small observational studies and case series suggest that worsening infection is unusual (140–144). Moreover, in the current era of potent direct-acting antiviral therapy for HCV, there is unlikely to be any effect on treatment efficacy with TNF-$\alpha$ inhibition. Even fewer data are available guiding the use of infliximab in those living with HIV. Case reports and series have suggested safety in those on established antiretroviral therapy (145–149).

Infections complicating the use of infliximab in rheumatoid arthritis most commonly occur within the first year of use (150). A review article studied the efficacy and safety of infliximab in rheumatoid arthritis. The most common sequela was respiratory tract infection. The risk of infectious events is greater with concomitant prednisone therapy, patient comorbidity, concurrent infection, and longer duration and severity of rheumatoid arthritis (151). The START trial demonstrated a dose-dependent increase in serious infectious complications, with a relative risk (RR) of 1 (95% confidence interval [95% CI], 0.3 to 3.1) in the 3-mg/kg-of-body-weight group and 3.1 (95% CI, 1.2 to 7.9) in the 10-mg/kg group (152, 153). Combination therapy with methotrexate also results in higher rates of serious infection of all kinds, particularly pneumonia (154). Wang et al. performed a large meta-analysis of tuberculosis risk with infliximab. The odds ratio for tuberculosis with infliximab compared to placebo was 3.93 (95% CI, 0.91 to 16.91), with an absolute rate of 0.70% (155). The rate of granulomatous infection is 3.25 times greater in patients on infliximab than in patients on etanercept (156).

ACCENT I and ACCENT II were randomized trials investigating infliximab for Crohn's disease. In both trials, around a third of patients had an infection requiring antimicrobial therapy within the first 54 weeks (157, 158). The serious infection rate was 4 to 5% in each study, and opportunistic infection was rare. Among the 879 patients, there were three opportunistic infections: a case of cutaneous nocardia, a case of CMV, and a successfully treated *M. tuberculosis* infection. The ACT 1 and ACT 2 trials were randomized placebo-controlled trials that assessed infliximab in ulcerative colitis. These trials compared placebo with 5-mg/kg and 10-mg/kg infliximab therapy. Results similar to those of ACCENT were demonstrated, with a serious infection rate of 4.1% and one episode of tuberculosis. While the numbers of serious infections were greater in the treated groups, the difference was not statistically significant. In ACT1, the rates of serious infection were 4.1% for placebo, 2.5% for infliximab at 5 mg/kg, and 6.6% for infliximab at 10 mg/kg. In ACT2, the rates of serious infection were 0.8% for placebo, 1.7% for infliximab at 5 mg/kg, and 2.5% for infliximab at 10 mg/kg ($P = 0.67$) (159).

Slifman et al. reported 14 cases of *Listeria monocytogenes* infection after treatment with infliximab (160), 6 of whom died as a result. Other studies have demonstrated that infliximab heightens the risk of non-*Candida* invasive fungal infections, including aspergillosis, zygomycosis, histoplasmosis, and *Pneumocystis jirovecii* pneumonia (112, 113, 161, 162).

Other notable infections reported in those receiving infliximab therapy include influenza virus A (H1N1), JC virus, herpes zoster, herpetic meningitis, *Salmonella*, *Legionella pneumophila* pneumonia, *Mycobacterium avium* complex, *Mycobacterium kansasii*, *Nocardia otitidiscaviarum*, and *Talaromyces* (formerly *Penicillium*) *marneffei* (163–172).

**Infectious complications of etanercept.** Similar to other TNF-$\alpha$ inhibitors, there are few data on etanercept in chronic viral infection. A recent review suggested etanercept has a significant rate of hepatitis B virus reactivation (2.4%); however, three of the seven cases did not receive antiviral prophylaxis (122). Early literature has suggested safety in patients with hepatitis C virus. One randomized placebo-controlled trial demonstrated that the use of adjuvant etanercept with interferon and ribavirin improved the virological response and reduced symptoms (91). The proposed mechanism is reversal of TNF-induced $CD4^+$ cell dysfunction (89). Pompili et al. identified 153 patients with hepatitis C virus receiving etanercept therapy, of whom 2 (1.3%) required drug withdrawal due to liver toxicity and 5 (3.3%) experienced an increase in viral load (89). There

are few data on etanercept use in the setting of HIV infection. Ting et al. performed a review on the subject, identifying one case report, one case series, and a clinical trial (173). Results from this review demonstrated that etanercept did not seem to increase mortality and may improve symptoms associated with HIV infection. There is one report of recurrent polymicrobial infection in an HIV-positive patient treated with etanercept for disabling psoriatic arthritis. The patient's $CD4^+$ cell count was 50 (174).

There have been several large randomized controlled trials looking at the use and safety of etanercept in rheumatoid arthritis. The Enbrel ERA trial demonstrated a 3.8% incidence of serious infection over 2 years of follow-up (175). The TEMPO trial in 2004 reported a 4.4% rate of serious infection in patients treated with etanercept or etanercept and methotrexate after 1 year (176). Serious infections during the ADORE trial were uncommon (1.3%), reflecting the shorter follow-up period of 16 weeks (177). Of the 1,184 patients included in these trials, there were no instances of opportunistic infection.

The rates of fungal infection appear to be low with etanercept, with infections occurring between 46 and 240 days after the initiation of therapy (111). Other infections reported with etanercept use include varicella zoster, herpes simplex virus, *Aspergillus*, zygomycetes, *Candida*, *Cryptococcus*, *Histoplasma*, mycobacteria, and *Pneumocystis jirovecii* (111, 178–183).

**Infectious complications of golimumab.** Due to the relatively recent approval of golimumab in 2009, there is limited literature informing the rates of infectious complications. It is unclear whether the use of golimumab causes reactivation or worsening of chronic viral infections. There has only been one report of its use in hepatitis B virus infection and none in the setting of hepatitis C virus or HIV (184). The risk of herpes zoster infection among TNF-$\alpha$ inhibitors appears to be lowest with golimumab, at 1.61 events per 100 person years (185). Liao et al. found a nonsignificant decrease in the HSV infection rate in those on golimumab compared to the rate in controls (5.5% versus 11.8%; OR = 0.30 [95% confidence interval, 0.07 to 1.26]; $P = 0.10$) (186).

Four major randomized control trials have examined golimumab therapy in rheumatoid arthritis (187–190). The serious infection rates from these studies range from 0.98% to 2.44% (4), with only one episode of tuberculosis out of 1,378 patients. The single occurrence of *M. tuberculosis* disease (spinal tuberculosis) was thought to predate the start of golimumab therapy (189). In the GO-FORWARD study, 92 patients with latent tuberculosis were treated with prophylactic isoniazid (190) and golimumab. At the 24-week follow-ups, there were no cases of tuberculosis reactivation. Hsia et al. found a 1.5% reactivation rate in patients with latent tuberculosis on prophylactic isoniazid treated with golimumab (191). Pooled analysis by Kay et al. using time-adjusted incidence rates yielded a serious infection incidence of 5.31 per 100 PY for placebo, 3.03 per 100 PY for golimumab at 50 mg, and 5.09 per 100 PY for golimumab at 100 mg (192). Higher doses of golimumab resulted in more episodes of tuberculosis (0.35 versus 0.17 events per 100 PY) and opportunistic infections (0.24 versus 0.13 events per 100 PY). The rates of infectious adverse events were higher in patients with underlying rheumatoid arthritis (9.1%) than in those with psoriatic arthritis (2.5%) or ankylosing spondylitis (4.8%).

A systematic review in 2016 found that golimumab in IBD did not increase serious infections (OR = 0.94; 95% CI, 0.19 to 4.63) or opportunistic infections (OR = 0.32; 95% CI, 0.05 to 1.99) (193). More recently, the PURSUIT-SC trial reported a serious infection rate of 4.5 per 100 PY with golimumab, similar to the rates of infection with other TNF inhibitors (194). Overall, the risk of serious infection with golimumab appears to be comparable with the risks with other TNF-$\alpha$ inhibitors, with combination therapy associated with heightened risk (4). Other documented infections associated with golimumab treatment include *Listeria*, syphilis, toxoplasmosis, *Nocardia*, leishmaniasis, and *Aspergillus* (195–199).

**Infectious complications of certolizumab pegol.** There are no data on the use of certolizumab in the setting of chronic viral infections (88). Upper respiratory tract infections are the most common nonserious infectious complication associated with

certolizumab pegol, with a relative risk of 1.34 compared to controls (95% CI, 1.15 to 1.57; $P = 0.0002$) (200). Urinary and gastrointestinal tract infections follow closely. Bykerk et al. published an analysis of the safety of certolizumab pegol in the setting of rheumatoid arthritis, combining data from 10 randomized trials and open-label extensions (201). Serious infectious complications occurred at 4.33 per 100 PY. Higher risk was seen in the first few months of treatment. The most frequent serious infectious complication was pneumonia (0.77 events per 100 PY), followed by cellulitis (0.31 events per 100 PY) and urinary tract infections (0.16 events per 100 PY). Forty-four cases of tuberculosis were identified, with an event rate of 0.47 events per 100 PY.

PRECISE 1 and PRECISE 2 examined the efficacy and safety of certolizumab in Crohn's disease. Patients with previous tuberculosis and latent *M. tuberculosis* infection were excluded. The rates of serious infection were low at around 2 to 3%, nonsignificantly higher than in the placebo groups (202, 203). One patient developed active pulmonary tuberculosis after five doses. The use of certolizumab for ulcerative colitis is still under investigation.

Marriette et al. reviewed the incidence of tuberculosis in patients treated with certolizumab, combining trials for all treatment indications. A total of 45 cases of tuberculosis were identified, 44 of which were associated with rheumatoid arthritis treatment. No one who received isoniazid therapy for latent *M. tuberculosis* developed active infection (204).

Other infections reported with certolizumab pegol include disseminated herpes zoster, soft tissue salmonella, esophageal candidiasis, bronchopulmonary aspergillosis, nocardiosis, histoplasmosis, and *Pneumocystis jirovecii* pneumonia (201, 205).

### TNF-$\alpha$ Inhibitors: Prevention of Infectious Complications

Initiation of TNF-$\alpha$ inhibitors should be preceded by a thorough history, examination, and investigations to assess infectious risk (Table 6) (206). Clinicians should elicit current and prior infectious history with attention for risk factors and symptoms of tuberculosis. History of chronic viral infections and vaccination status should be obtained. Tests recommended prior to therapy include interferon gamma (IFN-$\gamma$) release assay or tuberculin skin test, hepatitis B virus serology, HIV serology, and varicella zoster antibodies if prior infection is uncertain, and targeted hepatitis C screening (207). Chest radiography should be performed to screen for active and latent *M. tuberculosis* infection. In patients with inflammatory bowel disease, stool samples should be sent to screen for cytotoxic *Clostridioides difficile* (206). Serology and fecal microscopy for *Strongyloides* should be considered in those living in or returning from areas of high disease burden (208).

In patients with symptoms or chest X-ray findings suggestive of tuberculosis, exclusion of active disease with sputum culture and microscopy is needed. If active tuberculosis is diagnosed, TNF-$\alpha$ inhibitors should ideally be withheld until the completion of treatment. There are instances where anti-TNF-$\alpha$ therapy cannot be delayed. In such circumstances, national guidelines suggest at least 2 months of antituberculous medication prior to TNF-$\alpha$ inhibitor initiation (209).

Should latent *Mycobacterium tuberculosis* be identified, chemoprophylaxis should be considered. When considering prophylaxis, the risk of severe hepatitis must be weighed against the risk of *M. tuberculosis* reactivation. Drug-induced hepatitis from antituberculous therapy increases with age and occurs in around 0.15% of isoniazid-treated patients (208, 210). Prophylactic options include isoniazid for 6 to 9 months, rifapentine and isoniazid once weekly for 3 months, rifampin and isoniazid for 3 months, or rifampin alone for 4 months. The rifampin-pyrazinamide combination is no longer recommended due to high rates of serious hepatotoxicity (211). Rifapentine with isoniazid for 3 months has a low rate of serious hepatotoxicity (1%) (211). Moreover, the combination was noninferior to 9 months of isoniazid and associated with improved adherence (212). In another study, 4 months of rifampin had better completion rates (78.8% versus 63.2%; $P < 0.001$), lower rates of hepatotoxicity (0.3% versus 1.5%; $P <$

**TABLE 6** Screening and prophylaxis prior to initiating TNF-$\alpha$ inhibitor therapy

| Screening tool or type of intervention | Finding or type of examination, test, or intervention | Relevant/differential factor(s) or specific test or intervention |
|---|---|---|
| History | Active *M. tuberculosis* infection | Weight loss, fevers, cough, night sweats |
| | Risk for latent *M. tuberculosis* | Exposure to infected individuals |
| | | Previous travel or stay in endemic area |
| | History of infection | Prior hospitalization for infection |
| | | Prior fungal or parasitic infection |
| | | Prior varicella zoster infection |
| | Chronic viral infection | Hepatitis B virus, hepatitis C virus, HIV |
| | Vaccination status | Hepatitis B, diphtheria, tetanus, pertussis, poliomyelitis |
| Clinical examination | Cardiac | Stigmata of infectious endocarditis |
| | | Cardiac murmurs |
| | Respiratory | Active respiratory tract infection or signs of mycobacterial infection |
| | Lymph nodes | |
| | Skin | Current pyoderma or scabies |
| Laboratory investigation | Hepatitis B serology | |
| | IFN-$\gamma$ release assay for *M. tuberculosis* or Mantoux test | |
| | HIV serology | |
| | Stool testing (IBD patients) | *Clostridioides difficile* infection |
| | | Consider screening for *Strongyloides* if returned from area with high endemicity |
| Radiology | Chest radiography | Screen for latent tuberculosis infection |
| Prophylaxis | Latent *M. tuberculosis* | Referral to infectious diseases or respiratory specialist |
| | | Prophylactic therapy prior to treatment |
| | Hepatitis B | Referral to infectious diseases or hepatology specialist |
| | | Antiviral therapy prior to treatment |
| Vaccination | Influenza virus | Annual vaccination indicated |
| | Hepatitis B virus | Prior to therapy in those who are not immune |
| | 13-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal polysaccharide vaccine 8 wks later | Given prior to treatment with 23-valent vaccine repeated every 5 years |
| | Varicella zoster | Only administered in immunocompetent patients prior totemperatures) and characterized the roles of known treatment initiation |
| | Human papillomavirus | Indicated in females aged 11–26 yrs |

0.001), and fewer adverse events (2.8% versus 5.8%; $P < 0.001$) than 9 months of isoniazid (213).

While there are no data on the optimal timing of TNF-$\alpha$ therapy after starting prophylactic tuberculosis treatment, guidelines suggest a delay of 1 to 2 months (208). Occasionally, delaying TNF-$\alpha$ inhibitor treatment may cause patient morbidity and mortality. In such situations, a rapid tuberculosis risk assessment should be performed (history, examination, and chest radiography). If there is doubt about latent tuberculosis, prophylactic therapy should be initiated. Specialist guidance and laboratory investigations can be pursued subsequently. The patient should be followed with 3-monthly reviews, liver function tests, and chest radiography (209). If respiratory symptoms develop, prompt investigation for active tuberculosis should follow.

Hepatitis B virus reactivation is an established risk with TNF-$\alpha$ inhibitors. The incidence rate approaches 50% in HBsAg-positive patients not on prophylaxis and is lower for those who are only HBcAg positive (208, 214). Current guidelines advise prophylaxis with antiviral agents in HBsAg-positive patients, starting 2 to 4 weeks before commencement (215). Prophylaxis should be continued for 3 to 12 months following TNF-$\alpha$ inhibitor cessation. In those with isolated HBcAb positivity, monitoring is an alternative to preemptive antiviral treatment.

Hepatitis C virus infection is not a contraindication to TNF-$\alpha$ therapy but needs careful consideration in the presence of cirrhosis (84). The HCV reactivation risk with

anti-TNF-$\alpha$ therapy is controversial. While TNF-$\alpha$ inhibition theoretically may worsen the course of HCV infection, a review demonstrated that worsening HCV infection with anti-TNF-$\alpha$ therapy is rare and may not be attributable to anti-TNF therapy. Of 216 patients followed over 1.2 years, only 3 required cessation of their monoclonal antibody due to suspicion of HCV progression (89). In areas with low prevalence, given a low risk of reactivation, most experts would advise against the universal screening of patients for HCV (207, 216).

Vaccination status should be considered before starting TNF-$\alpha$ inhibitors. It is recommended that all patients should receive the influenza vaccination annually and the 23-valent pneumococcal vaccine (repeated every 5 years), and the hepatitis B virus vaccine should be given to seronegative patients who are not immune (217). To increase immunogenicity and improve protective efficacy, more recent guidelines recommend giving the 13-valent conjugate pneumococcal vaccine prior to a boost with the 23-valent polysaccharide vaccine at least 8 weeks later (218). Vaccination should be given before TNF inhibitor therapy starts if possible, because patients on anti-TNF therapy have a poor response to many vaccinations (219). Current guidelines recommend the varicella-zoster virus (VZV) vaccination be provided in immunocompetent patients who are not immune prior to initiation of therapy. Once started on treatment, live attenuated vaccinations are contraindicated (220). Human papillomavirus (HPV) vaccination is strongly suggested in female patients of the ages of 11 through 26 (221).

### TNF-$\alpha$ Inhibitors: Summary

TNF-$\alpha$ inhibition is associated with modest but definite increases in the risk of infection, principally tuberculosis, common bacterial infections, and invasive fungal infections. The exact attributable risks are not clear, as most data sources report the incidence of infection in those treated with TNF-$\alpha$ inhibitors without comparators or compare them with patients treated with nonbiological immunosuppressive therapies. Furthermore, TNF-$\alpha$ inhibition is generally used following or in combination with other immunosuppressive therapies, such as corticosteroids, making exact risk estimates difficult. There is a risk gradient, with etanercept associated with the lowest risk of infection and infliximab the highest. Cofactors which have been consistently shown to be important across the spectrum of TNF-$\alpha$ inhibitors include age (older age leading to higher risk), dose of the TNF-$\alpha$ inhibitor, and combination with other immunosuppressive agents. Due to their proven efficacy in inducing remission of inflammatory arthritis and inflammatory bowel disease, most people treated with TNF-$\alpha$ inhibitors derive a large net benefit, particularly if active measures are taken to minimize the risk of infectious complications.

## ANTI-T LYMPHOCYTE THERAPIES

### Function of T Lymphocytes

T lymphocytes originate from progenitors in the bone marrow, moving to the thymus for maturation and selection (222). T lymphocytes are responsible for coordinating and regulating cell-mediated adaptive immunity. They regulate the activities of B cells, T cells, and other immune effector cells. T cells are characterized by having a T cell receptor (TCR) associated with a CD3 molecule on the cell surface. The TCR/CD3 is the key element which recognizes pathogens and abnormal cells, leading to T cell activation and signaling to recruit other immune effector cells. A detailed review of the many and complex functions of T cells is beyond the scope of this article. In short, T lymphocytes are the key cell type responsible for cell-mediated immunity, and they are thus pivotal in the immune response to intracellular organisms like viruses, mycobacteria, and fungi. T cells can be roughly divided into T helper cells ($CD4^+$) and cytotoxic T cells ($CD8^+$). T helper cells are then further divided into multiple subtypes (e.g., Th1, Th17, Treg, and Tfh), each of which is triggered by and expresses particular cytokines and other signaling molecules. $CD8^+$ cells recognize infected cells through antigen presentation on major histocompatibility complex (MHC) class 1 molecules.

Interleukin-2 is the major cytokine promoting $CD8^+$ cell activation (223). This leads to calcium mobilization and the release of cytotoxic granules that contain perforins and granzymes (224, 225). Perforins form transmembrane pores that promote cell lysis and the passage of granzymes intracellularly (226). After an infectious insult, a portion of responding cells differentiate into memory T cells, ready to reactivate should a repeat insult occur (227).

As an example of the role of T cells in fighting intracellular viruses, T cells are key to the clearance of HBV during acute infection. $CD4^+$ T cell activation results in the sustained recruitment of $CD8^+$ T lymphocytes and a Th1 immune response (228). $CD8^+$ cells have both cytotoxic and noncytotoxic mechanisms to promote HBV clearance. These cells lead to apoptosis of hepatocytes infected with HBV, though only a small proportion of infected cells are killed. Secretion of viral inhibitory cytokines, interferon gamma (IFN-$\gamma$), and TNF-$\alpha$ appears to be the major action of $CD8^+$ T lymphocytes against HBV (229). Patients with chronic HBV infection commonly exhibit T cell function impairment and exhaustion (230).

Similarly, T cells are important in the immune response to *M. tuberculosis*. Individuals deficient in T lymphocytes have a clear increased risk of invasive *M. tuberculosis* infection. This is seen in HIV infection, where rates of active tuberculosis are dramatically higher (231). $CD4^+$ lymphocytes dominate in the setting of acute tuberculosis (232). Intravascular *M. tuberculosis*-specific $CD4^+$ cells produce greater amounts of interferon gamma than their organ-based counterparts (233). This $CD4^+$ response is critical in macrophage activation and infection containment through granuloma formation (234). The $CD8^+$ T cell response to *M. tuberculosis* is complex and essential. After exposure to the *M. tuberculosis* epitope, $CD8^+$ T cells release cytolytic granules against *M. tuberculosis*-infected cells (235). Secreted granulysin causes direct bacillus destruction through cell membrane disruption (236). In murine models, depletion of $CD8^+$ cells in latent infection results in higher bacterial proliferation, indicating that $CD8^+$ cells have a role in the maintenance of immune control (237).

### Anti-T Cell Biological Therapies

**Basiliximab.** Basiliximab is the only specific T cell-targeted therapy currently marketed as an immunosuppressive agent. Basiliximab is a chimeric monoclonal antibody composed of human IgG Fc and a murine variable region (RFT5 antibody) directed against CD25, the alpha subunit of the IL-2 receptor (238). By binding to the IL-2 receptor, basiliximab prevents the activation of T lymphocytes (239). Prophylaxis against acute rejection as part of induction immunosuppression in patients undergoing renal transplant is the only on-label indication. Off-label use includes prophylaxis for acute rejection in liver, heart, and lung transplantation, as well as the treatment of refractory acute graft-versus-host disease (GVHD) (240–242).

**Abatacept.** Abatacept is a fusion molecule consisting of cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and the Fc portion of IgG1. Its mechanism of action is much less direct than that of basiliximab; abatacept prevents the activation of T cells by blocking the "second signal" or costimulatory signal, in the communication between antigen-presenting cells and T cells. Abatacept prevents CD28 from binding to its receptor CD80/CD86, thus inhibiting T cell costimulation and preventing the suppression of Treg activity, blocking the activation of T effector cells (243). It is registered for use in rheumatoid arthritis, psoriatic arthritis, and juvenile idiopathic arthritis, including for those in whom TNF antagonists have failed. Abatacept appears to have efficacy similar to that of the TNF inhibitors in RA (244, 245), but better tolerability (245, 246). In a meta-analysis of seven trials that included 2,908 patients, a 50% improvement in RA activity (ACR50 [50% improvement according to the American College of Rheumatology criteria]) was 2.2 times more likely in those treated with abatacept than in those treated with placebo (247). Abatacept appears less effective for ankylosing spondylitis (248), but preliminary data suggest it may have a place in the treatment of Sjogren's syndrome (249), systemic lupus erythematosus (SLE) (250), and Wegener's syndrome (251).

**Other and withdrawn anti-T cell antibodies.** Brentuximab vedotin is a chimeric monoclonal antibody drug conjugate directed against CD30 (252). It is not covered in detail in this article since it is indicated only as an antitumor agent, not as an immunomodulatory one. The antimitotic agent monomethyl auristatin E (MMAE) is attached to the antibody. When bound to CD30, MMAE enters the T lymphocyte, disrupting microtubules and leading to cell death. On-label indications for use include Hodgkin lymphoma, cutaneous and systemic anaplastic large cell lymphoma, and mycosis fungoides. The key infectious risks derive from the tendency for the drug to cause neutropenia (253, 254). Less common but more serious are reports of increased risk of progressive multifocal leukoencephalopathy (PML) due to JC virus reactivation (255) and of CMV disease (256).

There have been a few biological agents in this class withdrawn from the market due to adverse events and reduced market viability. Daclizumab (a CD25 inhibitor, like basiliximab) was previously approved for the treatment of multiple sclerosis (257) and was also used as induction therapy in solid organ transplantation. The drug was withdrawn from the market in 2018 due to reports of immune-mediated meningoencephalitis (258). Alefacept is a fusion protein of human leukocyte functional antigen 3 (LFA3) with an IgG1 Fc component and targets CD2 on T lymphocytes. It was FDA approved for moderate to severe chronic plaque psoriasis (259) but was voluntarily withdrawn from the market in 2011 due to decreased utilization (260). Muromonab (CD3 inhibitor) was previously used in the setting of transplant immunosuppression. This drug was withdrawn from the market due to falling sales (261). More specific T cell-depleting agents (anti-CD25 agents basiliximab and daclizumab) have largely displaced OKT3 because of lower rates of infusion reactions and reduced development of neutralizing antibodies. Rabbit and equine antithymocyte globulin (ATG) is still used as a T cell-depleting agent in transplantation medicine but is not covered in the present article since it is a polyclonal antibody and not strictly a biological agent.

## Infectious Complications of Anti-T Cell Therapies

In a meta-analysis of basiliximab in addition to cyclosporine-based immunosuppression for induction immunosuppression in renal transplant, basiliximab did not increase the rates of all-cause infection (OR = 0.97; 95% CI, 0.77 to 1.24) or CMV infection (OR = 0.81; 95% CI, 0.62 to 1.04) (262). These results were confirmed in two further meta-analyses (263, 264). Sun et al. performed a meta-analysis comparing basiliximab and daclizumab in renal transplant, finding no difference in infection rate (95% CI, 0.66 to 1.01) or CMV (95% CI, 0.45 to 1.14) (239). Compared to antithymocyte globulin, basiliximab has a lower rate of infectious complications (relative risk [RR] = 0.87; 95% CI, 0.78 to 0.97; $P = 0.02$) (265). Pathogen types were similar between placebo- and basiliximab-treated groups. Urinary tract infections from *E. coli* were the most common bacterial infections, while CMV and *Candida albicans* were the most common viral and fungal infections, respectively (266, 267). The frequency of invasive fungal infections with basiliximab in renal transplant is around 1.2% (268).

Similar findings are seen with basiliximab use in liver transplant. A meta-analysis by Wang et al. in 2010 found no increase in rates of infection with basiliximab compared to the usual background with immunosuppressive regimens (269). Neuhaus et al. performed a double-blind randomized placebo-controlled trial which showed no increase in infection rate with basiliximab (270). In that study, there was a statistically significant decrease in invasive fungal infections in those treated with basiliximab compared to the rate in those treated with placebo (16.5% versus 25.4%).

A double-blind randomized control trial compared basiliximab to placebo as an adjunctive agent for induction immunosuppression in heart transplantation. There was no difference in infection rate after 1 year (271). Other trials have compared antithymocyte globulin (ATG) to basiliximab. Basiliximab is associated with higher rates of rejection and graft failure but no increase in infectious complications (272, 273). Butts et al. found a lower rate of infection in patients treated with basiliximab than in those treated with ATG (274).

There is limited evidence for basiliximab in lung transplant. A small retrospective analysis of 28 patients showed basiliximab to nonsignificantly prolong survival and decrease acute rejection compared to these parameters in controls. No increased infection risk was found (275). Another prospective study of 37 patients by Clinckart et al. found that basiliximab was associated with an increase in CMV infection compared to the rate seen with ATG. This occurred in CMV-positive recipients who received a CMV-negative donor transplant (242). Compared to alemtuzumab, basiliximab does not seem to increase the risk of infection (276, 277). The rate of CMV infection with basiliximab in lung transplant is around 0.3% (277).

A systematic review combining data for patients treated with brentuximab for all indications demonstrated that neutropenia occurred in 8% of patients, sepsis in 7%, and other infections in 3% (278). Another single-center analysis reviewed the drug in 53 patients with Hodgkin and anaplastic large cell lymphoma (279). No hematological or infectious complications were reported with a median follow-up of 36.8 months.

Most early trial data on the safety of abatacept are confounded by the fact that patients must have failed prior treatment with TNF inhibitors, as well as disease-modifying antirheumatic drugs (DMARDS). The initial phase III randomized control trial comparing abatacept to placebo (ATTAIN) randomized 391 patients with RA refractory to TNF inhibitors to abatacept at 10 mg/kg or placebo (280). The incidence of serious infections in the abatacept group (2.3%) did not differ from that in the placebo group (2.3%), and infections were mostly skin and soft tissue or respiratory tract infections with common pathogens. In another phase III RCT of abatacept at 10 mg/kg, serious infections (mostly respiratory tract infections) occurred in 2.9% of the abatacept group and 1.9% of the placebo group. Serious adverse events (SAEs) were more common in those receiving a combination of abatacept and other biologics (22.3%) than in those receiving abatacept plus DMARDs (12.5%) (281). A subsequent trial randomized patients with RA receiving etanercept to have abatacept added or not. Adding abatacept to etanercept did not improve efficacy but did significantly increase the risk of SAEs (282), including infections. Hence, this combination is not recommended.

Meta-analyses report findings similar to those of these phase III RCTs. In a meta-analysis that included seven trials enrolling 2,908 patients with RA, serious infections were more common in the abatacept group (OR = 2.2; 95% CI, 1.07 to 3.42) (247). A subsequent meta-analysis that included eight trials with long-term follow-up data of up to 7 years in RA patients treated with abatacept after failing TNF therapy found no new safety concerns. Rates of serious infection were 3.0% in the abatacept group versus 1.9% in placebo recipients (283). A postmarketing population-based cohort study reported data from 5,752 patients who initiated treatment with abatacept and 78,556 treated with other biologic DMARDs; the incidence of serious infections was 4.45 per 100 person years for abatacept and 3.62 for other biologics. There was no significant difference in the risk of serious infections in those treated with abatacept versus other biologics (hazard ratio [HR] = 1.08; 95% CI, 0.77 to 1.52) (284).

Several case reports have raised concerns about reactivation of hepatitis B virus infection in those taking abatacept, including those with occult HBV (HBcAb positive but HBsAg negative) (285–287). However, a study following 72 patients with HBV being treated with abatacept reported no episodes of HBV flare or reactivation (288). It is important to note that 47 of these patients were isolated HBcAb positive (i.e., at very low risk) and 17 were receiving antiviral agents against HBV. The results of a second small study are more concerning: eight patients with chronic HBV (HBsAg positive) were treated with abatacept for RA (289). Four of them were receiving lamivudine prophylaxis, none of whom experienced a hepatitis flare. However, all four of those not receiving antiviral prophylaxis experienced HBV reactivation.

The strong association of anti-TNF therapy with tuberculosis reactivation raises questions about abatacept and tuberculosis, but it appears that there is very low, if any, attributable risk of tuberculosis reactivation. A study in mice experimentally infected with tuberculosis found no effect of abatacept compared with placebo but 100% mortality from disease progression in those exposed to TNF inhibitors (290). Two

systematic reviews compiling over 15 years of population-based data and case reports of tuberculosis reactivation in those treated with biologic agents found no cases in those treated with abatacept but multiple cases in those on TNF inhibitors (291, 292).

Reactivation of EBV (293, 294) and other herpesviruses (295) has been reported rarely with abatacept, but it is unclear if these cases are due to previous or concomitant immunosuppression. An observational study suggests that long-term use of abatacept does not affect immunological control of EBV infection (296).

### Prevention of Infectious Complications of Anti-T Cell Therapies

Since basiliximab is not used in isolation, strategies for prevention of infection (e.g., chemoprophylaxis for *Pneumocystis jirovecii* pneumonia [PJP] and CMV) should already be in place and generally do not need to be altered with the addition of basiliximab to induction immunosuppression. In those receiving abatacept, general measures to decrease the risk of common bacterial infections should be instituted prior to therapy, including vaccination against pneumococcus and influenza and optimization of skin and lung health. All patients should have HBV serology done, and those who are HBsAg positive should be offered antiviral prophylaxis with tenofovir, entecavir, or lamivudine. Those who are isolated HBcAb positive should be monitored for liver enzymes at 1- to 3-month intervals and HBV viral load at 6-month intervals, and earlier if transaminases increase. There are no data to support testing or treating for latent tuberculosis infection (LTBI) prior to abatacept treatment.

### Anti-T Cell Therapies: Summary

Overall, the clinical data suggest there is no difference in the rates of viral, bacterial, fungal, or other opportunistic infections with basiliximab compared to the rates with placebo (238, 297). However, this would not be likely to be the finding if one were to run a trial of basiliximab versus no immunosuppression at all. This is a good example of the fact that we are limited by the type of clinical data available to us: in this case, basiliximab has generally been used against a background of potent combination immunosuppression (e.g., with corticosteroids, mycophenolate, and ciclosporin/tacrolimus) and of protocolized infection prevention strategies (e.g., co-trimoxazole for all and valganciclovir for most patients). Abatacept is associated with a small risk of serious infection, approximately 2 to 3%, generally skin or respiratory tract infections with common organisms. While there are no data to suggest tuberculosis reactivation in those on abatacept, the risk of HBV reactivation does appear to be increased.

## ANTI-B LYMPHOCYTE ANTIBODIES

### Function of B Lymphocytes

After their discovery in the 1960s, researchers identified the pivotal role of B lymphocytes in adaptive immunity (298). While B cells are classically described as regulating humoral immunity (by producing antibodies), the interaction between B lymphocytes and cellular immunity is increasingly recognized (299). B lymphocyte function can be divided into immunoglobulin production, antigen presentation, and T cell activation/regulation (Fig. 8).

Plasma cells are an activated form of B cells and produce targeted antibodies against invading organisms. Antibodies have four major functions: neutralization, opsonization, antibody-dependent cell-mediated cytotoxicity (ADCC), and complement activation (300).

B lymphocytes also have a role as professional antigen-presenting cells (APC) (301). Phagocytosis of pathogens allows the expression of antigens on major histocompatibility complex (MHC) class 2 molecules. B cells then present the antigen to $CD4^+$ T cells and, with costimulatory molecules, cause T lymphocyte activation (302). $CD4^+$ T cells then release cytokines, which mediate the activation of cytotoxic T cells. Studies have revealed that B cell depletion results in impaired $CD4^+$ T cell proliferation (303).

**The role of B cells in key viral infections.** B cells have an important role in the immune response against viral infection. Antibody production leads to neutralization

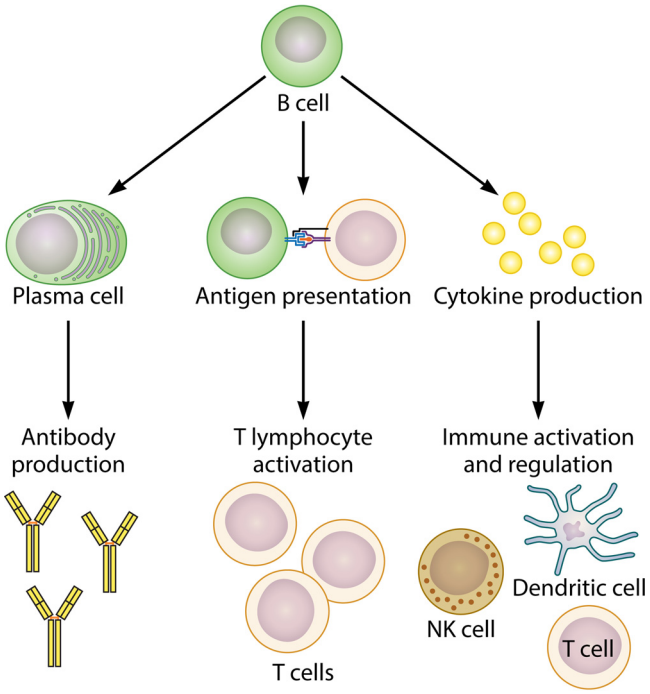


**FIG 8** B cell function.

and opsonization of antigens, promoting viral clearance. Polyreactive IgM and IgD antibodies are produced initially, some of which will inactivate the invading organism. Class switching to a specific IgG immunoglobulin occurs through activation-induced cytidine deaminase and class switch recombination (304). B cells also provide significant support to the cellular immune response. T lymphocytes, both $CD4^+$ and $CD8^+$, are markedly reduced in rodents depleted of B cells (305).

B cell depletion results in increased risk of disseminated viral infection (306). During influenza infection, neutralizing antibodies have a major role in reducing viral transmission. Polyreactive B cells produce IgM, 10% of which will inactivate the influenza virus antigen. At day 7 of infection, germinal center responses have fully matured with the production of both memory B cells and plasma cells. Influenza virus IgA antibodies enter host cells to combat the pathogen intracellularly (307, 308). This provides lifelong protection from the offending strain of influenza (309).

Immunity to hepatitis B virus after chronic infection is determined by the presence of hepatitis B virus surface antibody in the serum. Patients with chronic HBV are characterized by B cell hyperactivation with impairment of HBsAg-specific B cells. Functional impairment of HBsAg-specific B cells is hypothesized to be mediated by the HBsAg itself. B cell CD80 expression is also reduced in HBV infection, reflecting impaired antigen presentation (310). An increase in B regulatory cells is seen during the immune activation phase of HBV infection, associated with higher levels of interleukin-10. The production of this anti-inflammatory cytokine is directly associated with higher AST and ALT levels (311). HBV may increase B regulatory cells to dampen the immune response in acute infection.

The B cell response in hepatitis C virus infection is an area of active research. Hepatitis C virus infection is characterized by polyclonal B cell activation and increased immunoglobulin production, leading to complications of lymphoproliferative disorders and cryoglobulinemia (312, 313). Increased B cell receptor signaling has been demonstrated with HCV protein NS3/4A, a potential mechanism underlying B cell proliferation (314). B cell subset alteration is promoted through the increased expression of BclII, a B cell antiapoptotic marker more common in HCV-infected subjects (312). Studies of the natural history of HCV infection demonstrate that the presence of HCV-specific anti-

bodies reduces viremia, promotes clearance of HCV, and enhances infection resolution (315–317).

B cell function has been found to be crucial in the immune response against HIV. Production of nonneutralizing antibodies (anti-gp41) can be detected within 1 week of HIV infection, but this has little impact on viremia (318). Neutralizing antibodies begin to appear a few months after infection, resulting in the rapid production of viral escape mutants to avoid neutralization (319, 320). About 20% of patients infected can produce cross-reactive antibodies that can neutralize multiple viral antigen epitopes; however, this takes 2 to 4 years to develop (321–323). Around 1% of infected individuals are "elite neutralizers," able to produce broadly neutralizing antibodies active against hundreds of viral antigen epitopes (324, 325). Production of these antibodies capable of ADCC is linked to decreased rates of maternal-fetal transmission of HIV (326), increased frequencies of long-term nonprogressors, and reduction in viral reservoirs in murine models (327, 328). The administration of polyclonal broad neutralizing antibodies to infant macaques led to a significant reduction in plasma viral load (329).

**The role of B cells in key bacterial infections.** B cells play a pivotal role in producing antibodies (via differentiation to plasma cells) directed against bacterial pathogens, leading to opsonization, complement activation, and enhanced phagocytosis. This is underlined by the fact that patients with genetic deficiencies of antibody production (e.g., X-linked agammaglobulinemia) are at high risk of infection with encapsulated bacteria, such as *S. pneumoniae* and *H. influenzae*, for which opsonization is a primary host defense (330). Contrary to the traditional view, the humoral B cell response also plays a critical role in intracellular bacterial infection (331). B cells influence the host response through antigen presentation, enhancement of T cell effector function via cytokine production, and production of pathogen-specific antibodies (332). B cell-activating factor (BAFF) is central in maintaining a T cell-independent IgM response in acute infection. Growing evidence supports the role of the B lymphocyte in *M. tuberculosis* infection. After acute infection with *M. tuberculosis*, B cells mediate the Th1 response. This reduces the inoculum burden through antibody-directed opsonization and promotes the granulomatous containment of infection through T cell and macrophage activation (333). Interleukin-10 production by B cells countering intracellular infection is another essential regulator of the inflammatory response (333, 334). In summary, protection of the host from intracellular pathogens is dependent on both B and T cell function (331).

**The role of B cells in other infections.** Fungal infection is countered directly and indirectly by B cell activity. The direct mechanisms include inhibition of biofilm formation, iron starvation, and prevention of replication (335–337). The indirect mechanisms include complement activation, opsonization for phagocytosis, and antibody-directed cellular cytotoxicity (338–340). In *Candida albicans* infection, antibodies to the *C. albicans* mannoprotein prevent adherence to HEp-2 cells and halt pathogen germination while also starving the organism of iron (337, 341). In murine models of *Cryptococcus neoformans* infection, B cell deficiency is associated with uncontrolled disease (342, 343). The host response to helminthic infection is dependent on B cells. The T-helper 2 immune response is reliant on B cell antigen presentation (344). B cell release of IL-4R mediates antibody class switching to an IgG and IgE response (345). IgE then activates mast cells and basophils, crucial for countering helminthic infections (346). Antigen-bound IgE leads to degranulation of mast cells and basophils, releasing cytokines, chemokines, proteases, and enzymes directed against the invading organism (347, 348).

## Available Anti-B Cell Agents

There are six monoclonal antibodies directed against B cells currently marketed, of which four work in the same way, against the B cell surface marker CD20, one, inebilizumab, works against CD19, which is found primarily on B cell precursors, and one, belimumab, works against the B cell survival molecule BLySS (Table 7).

**TABLE 7** Overview of available anti-B cell agents

| Agent | Type of agent | Cellular target | Key approved indication(s)[b] |
|---|---|---|---|
| Rituximab | Chimeric MAb | CD20 | CLL, various lymphomas, RA, pemphigus vulgaris |
| Ocrelizumab | Humanized MAb | CD20 | Multiple sclerosis |
| Ofatumumab | Human MAb | CD20 | Refractory CLL |
| Obinutuzumab | Humanized MAb | CD20 | CLL, follicular lymphoma |
| Inebilizumab | Humanized MAb | CD19 | Neuromyelitis optica spectrum disorders |
| Belimumab | Human MAb | BlySS/BAFF[a] | Refractory SLE |

[a]BLySS, B lymphocyte-specific stimulator; BAFF, B cell-activating factor.
[b]CLL, chronic lymphocytic leukemia; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

**Rituximab.** Rituximab is a chimeric monoclonal antibody directed against the B cell CD20 antigen. The CD20 antigen is pivotal in regulating B cell development and activation through its role in transmembrane calcium transport (349, 350). Binding of the Fab portion of rituximab leads to complement and antibody-mediated B cell lysis (351). Immunoglobulin levels rarely decline with rituximab therapy, as plasma cells do not express the CD20 antigen (352, 353). On-label indications for use in malignant disease include chronic lymphocytic leukemia (CLL) and Hodgkin and non-Hodgkin lymphoma. Off-label use for malignant disease includes Burkitt's lymphoma (354), central nervous system (CNS) lymphoma (355), splenic marginal zone lymphoma (MZL) (356), mucosa-associated lymphoid tissue lymphoma (357), posttransplant lymphoproliferative disorder (358), and Waldenstrom's macroglobulinemia (359). On-label indications for autoimmune disease include rheumatoid arthritis, pemphigus vulgaris, granulomatosis with polyangiitis (GPA), and microscopic polyangiitis (MPA). Off-label use in autoimmune disease includes multiple sclerosis (360, 361), thrombotic thrombocytopenic purpura (362, 363), immune thrombocytopenia (ITP) (364), myasthenia gravis (365), neuromyelitis optica (366), lupus nephritis (367), idiopathic membranous nephropathy (368), autoimmune hemolytic anemia (369), and chronic graft-versus-host disease (370). Decreased B cell numbers are seen for at least 6 to 9 months after administration (371), and impaired memory B cell maturation may continue for years (372).

**Ofatumumab.** Ofatumumab is an anti-CD20 human monoclonal antibody (373). After binding to CD20, the Fc portion induces antibody-, complement-, and cell-mediated cytolysis of B cells. The on-label indication for use is CD20-positive chronic lymphocytic leukemia refractory to alemtuzumab and fludarabine.

**Ocrelizumab.** Ocrelizumab is a humanized IgG monoclonal antibody that acts against CD20. After binding, ocrelizumab mediates antibody- and complement-dependent cytolysis of B cells (374). B cell levels reach a nadir at day 14 after therapy and return to baseline in a median of 72 weeks (27 to 175 weeks). On-label indications for use include relapsing or progressive multiple sclerosis. Off-label indications include rheumatoid arthritis (375) and systemic lupus erythematosus (376).

**Obinutuzumab.** Obinutuzumab is a humanized monoclonal antibody directed against CD20. When bound to CD20, obinutuzumab causes B cell cytolysis through activation of complement and intracellular apoptotic pathways (377). On-label indications for obinutuzumab use include untreated chronic lymphocytic leukemia and untreated or refractory/relapsed follicular lymphoma (FL).

**Belimumab.** Belimumab is a human IgG1 monoclonal antibody (378). Unlike the other anti-B cell agents, which are directed against CD20, belimumab binds to and inactivates soluble B lymphocyte stimulator-specific protein (BLyS, also known as B cell-activating factor, or BAFF), reducing B cell differentiation and survival. BLyS is a B cell survival factor that promotes the formation and survival of memory B cells and plasma cells. Hence, rather than depleting B cell numbers, belimumab has a subtler action, which may explain its lower risk of infectious complications. After administration, reductions in IgG and anti-double-stranded DNA (dsDNA) occurred by week 8 and

**TABLE 8** Infectious complications of rituximab therapy based on treatment indication

| Disease, infectious complication | Disease, pathogen, or differential factor | Frequency (% or no. of events/no. of person yrs, unless otherwise stated) (reference[s]) |
|---|---|---|
| Non-Hodgkin lymphoma | | |
| Serious infections | | 31.8/100 (1237) |
| Viral reactivation | Herpes zoster | 6.9/100 (453) |
| | Hepatitis B virus | 52–67 (406, 410–412) |
| | $HBsAg^+$ patients without prophylaxis | 4–42 (402, 413, 414) |
| | Anti-$HBcAb^+$ without prophylaxis | 2.9/1,000 (1238) |
| | PML[a] | 0.72/100 (1237) |
| Bacteria | *M. tuberculosis* | 2–10.6 with R-CHOP (1239–1241) |
| Rheumatoid arthritis | | |
| Serious infections | | 3.8–5.0/100 (396, 473) |
| Opportunistic infections | | 0.05/100 (396) |
| Respiratory tract infections | | 6.1/100 (1242) |
| Urinary tract infections | | 2.6/100 (1242) |
| Viruses | Herpes zoster | 0.8–2.3/100 (185, 476, 1243) |
| | PML | 1/25,000 patients (1244) |
| Systemic lupus erythematosus | | |
| Serious infections | | 6.6–16.6/100 (454, 1245, 1246)[b] |
| Glomerular disease | | |
| Serious infections | | 16.6–43/100 (466, 1247) |

[a]PML, progressive multifocal leukoencephalopathy.
[b]Higher rates are associated with renal involvement.

were maintained to week 52. Belimumab is indicated for the treatment of active, autoantibody-positive systemic lupus erythematosus already on standard treatment. This monoclona antibodyl has not been assessed in severe active CNS lupus or lupus nephritis and is not recommended in these settings. Moreover, combination with cyclophosphamide and other biologics has not been investigated.

**Inebilizumab.** Inebilizumab is a humanized monoclonal antibody directed against CD19, found primarily on B cell precursors. It leads to substantial depletion of a range of lymphocytes derived from the B cell lineage (379). Inebilizumab has been granted FDA breakthrough therapy designation for accelerated assessment for use in neuromyelitis optica spectrum disorders (NMOSDs) but at the time of writing is not yet approved for use. In a recent phase II/III RCT, inebilizumab was more effective than placebo, with 12% of treated NMOSD patients having an attack during the study compared with 39% in the placebo group (380). Safety in this trial was similar to that of placebo, but there is currently insufficient information to assess the risk of infection with this agent. Its use has also been reported for the treatment of multiple sclerosis (381) and B cell lymphoma (382).

**Withdrawn anti-B cell agents.** Tositumomab is an IgG2a monoclonal antibody directed against the CD20 antigen (383). It was initially approved for the treatment of relapsed or refractory CD20-positive non-Hodgkin lymphoma. Despite its efficacy, with a cited 75% complete response rate (384), it was withdrawn from the market due to a decline in market viability.

### Anti-B Cell Agents: Infectious Complications

Apart from belimumab, the risk and type of infectious complications are very similar across this group of drugs, as one would expect given their common target and mechanism of action. Because it has been available for the longest, there is substantially more clinical data about the infectious risk of rituximab than about the infectious risks of the other agents, and hence, this section will focus primarily on rituximab. The observed risks of infectious complications of rituximab therapy, according to indication, are summarized in Table 8.

In the setting of hematological malignancy, systematic reviews indicate that rituximab therapy is associated with increased risk of infectious complications (385, 386).

Infections in this setting are most commonly bacterial (63%) and viral (34%) in origin (387). Serious infections occur in <5% of patients in single-arm studies of rituximab in non-Hodgkin lymphoma (351). Increased rates of infections are also noted in the setting of solid organ transplant (388–390). In contrast, infections in rituximab therapy for autoimmune disease are uncommon. Serious infections in rheumatoid arthritis (RA) patients treated with rituximab range from 1 to 3.3% (391–395). The lower rates of infection likely relate to smaller cumulative doses of rituximab and less concomitant immunosuppressive therapy. Long-term safety data from 3,595 patients over 11 years confirmed a similar incidence of serious infections compared to the incidence with placebo (3.76 events per 100 PY versus 3.79 events per 100 PY, respectively) (396). Pneumonia was the most common serious infection (2%). The serious opportunistic infection rate was also similar to the rate with placebo (0.05 events/100 PY versus 0.09 events/100 PY).

In 2011, rituximab's label was updated with a black box warning for hepatitis B virus reactivation. There is an established risk of HBV reactivation with rituximab therapy, with fatal cases reported (397, 398). The rates of reactivation vary as reported in the literature and depend on host-, virus-, treatment-, and disease-related factors. Reactivation generally occurs between 3 months after starting and 1 month after completion. Occasionally, reactivation can manifest more than 2 years after cessation (399–401). The risk of HBV reactivation with rituximab is increased in males, those with HBV surface antigen positivity, precore mutant HBV, high HBV DNA levels, transplant recipients, patients with lymphoma, and those receiving concomitant combination chemotherapy or steroids (402–409). HBV reactivation is less common in those with autoimmune disease treated with rituximab (395, 396). The highest rates of reactivation are seen in those with surface antigen positivity who are on combination chemotherapy and not given prophylaxis. In this setting, reactivation is seen in 52 to 67%, with mortality rates as high as 22 to 52% (406, 410–412). In those who are surface antigen negative but core antibody positive on combination chemotherapy with rituximab, reactivation rates are lower, reported in 4 to 42% of patients (402, 413, 414).

Compared to the general population, chronic hepatitis C carriers have a 20 to 30% increased risk of non-Hodgkin lymphoma and a 3-fold risk of Waldenstrom's macroglobulinemia (415). Though data are sparse, HCV flares can occur in those with chronic HCV treated for malignancy with rituximab-based regimes. Sagnelli et al. reviewed five studies examining HCV reactivation with rituximab for non-Hodgkin lymphoma. The pooled incidence of life-threatening liver failure was around 10% (416). An observational study by Torres et al. found that in the setting of malignancy, rituximab was highly associated with hepatitis C reactivation (44% versus 9%; $P < 0.0001$) (417). The largest study was a multicenter retrospective analysis on 553 patients, 131 of whom were HCV positive, treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) for diffuse large B cell lymphoma. This study reported a high rate of severe hepatotoxicity (grade 3/4 elevations in liver transaminases) in patients with HCV, 27%, compared to 3% in the noninfected population (418). Six HCV-infected patients died due to hepatic failure (4.6%), but four of these had underlying hepatocellular carcinoma known prior to therapy. Progression-free and overall survival were similar in those with and without HCV.

There are no published data on the use of rituximab in the HIV-positive patient outside the setting of hematological malignancy (419). Immunosuppression associated with HIV-associated lymphoma makes rituximab therapy challenging in this cohort. A study performed by Kaplan et al. in 2005 was disheartening. This multicenter AIDS-Malignancies Consortium trial (AMC) compared rituximab and CHOP to CHOP alone in HIV-associated non-Hodgkin lymphoma (420). All patients included were treated with antiretroviral therapy and *Pneumocystis jirovecii* prophylaxis with co-trimoxazole, dapsone, or pentamidine. There was no difference in time to progression, progression-free survival, or overall survival in those treated with rituximab versus those who were not. There were more adverse events in the rituximab-treated group, mostly in those with CD4 counts of <50. Fourteen percent of patients in the rituximab group died of

infection-related complications, compared to 2% in the control group ($P = 0.04$). Thirty-six percent of patients treated with rituximab with baseline CD4 counts of <50 died from infection. Bacteremia was the most common infectious complication leading to death (50%). Another phase II trial of rituximab in HIV-positive patients with lymphomas revealed an infection-related death rate of 8.6%, most commonly due to bacterial infection (421). Sparano et al. confirmed the AMC trial findings with a 38% mortality rate in patients with CD4 levels of <50 (422). While infectious complications appear common, a pooled analysis showed that rituximab therapy was associated with higher rates of complete remission (odds ratio = 2.89; $P < 0.001$) and overall survival (HR, 0.51; $P < 0.0001$) (423). Current guidelines recommend the addition of rituximab to anti-lymphoma chemotherapy if the CD4 count is >50 (424). The use of rituximab in those with CD4 counts of <50 must be individualized, and caution is warranted.

An FDA black box warning for progressive multifocal leukoencephalopathy from rituximab was released in 2007. Carson et al. described 57 cases of progressive multifocal leukoencephalopathy after rituximab therapy (425). Disease onset occurred at around 5.5 months into treatment, with a median survival of 2 months. While the incidence of PML in rituximab-treated patients is lower than that reported with natalizumab, the mortality rate is significantly higher, at 90% (426). In a report summarizing all confirmed cases of PML with rituximab in rheumatoid arthritis, granulomatosis with polyangiitis, and microscopic polyangiitis patients, the incidence of PML in RA patients treated with rituximab was 2.56 per 100,000 patients, and the incidences in GPA/MPA were <1 per 10,000 patients (427). All events occurred in patients with other risk factors, including high-dose corticosteroids and combination immunosuppressive therapy. A high index of suspicion is required for the diagnosis, as many patients present with subacute and nonspecific neurological deterioration (428). The diagnosis is made with brain MRI and lumbar puncture identifying JC virus in a compatible clinical context. Management involves cessation of the offending agent, supportive care, and specialist neurology involvement (429). A recent report provides hope that immune system activation using checkpoint inhibitors may reverse the disease process in patients with immunosuppression-related PML (430).

Cytomegalovirus (CMV) infection complicating rituximab use can affect many organ systems, with reports of CMV pneumonitis, esophagitis, gastritis, enterocolitis, meningitis, encephalitis, and retinitis in this setting (25, 431–442). CMV case reports have most often been associated with lymphoproliferative malignancy and transplant, both stem cell and solid organ. Patients are often on combination immunotherapy or chemotherapy, making it challenging to establish rituximab as the causative agent. Aksoy et al. found that CMV was the second most common viral infection (following hepatitis B virus) in lymphoma patients treated with rituximab (23.4%) (406). A case series identified 17 patients with hematological malignancy whose course was complicated by CMV infection (443). Sixteen of the 17 cases were associated with the combination of rituximab and steroids. Ganciclovir treatment, which remains the first line (444), was successful in most episodes (18 of 20). A review by Lanini et al. discussed infection risk in lymphoma patients receiving rituximab (445). Of the 17 RCTs included, only one examined the rate of complicating CMV infection. This trial compared ESHAP (etoposide, methylprednisolone, cytosine arabinoside, and platinum) to rituximab and ESHAP in frail patients with refractory B cell lymphoma (446). The rate of CMV infection complicating treatment cycles was higher in the rituximab-treated group (9.9% versus 0.9%). Lee et al. performed a retrospective analysis on 48 patients with non-Hodgkin lymphoma undergoing allogeneic stem cell transplant treated with rituximab (447). The rate of CMV infection was significantly higher in the rituximab-treated group (17.6% versus 0%; $P = 0.045$). Currently there is no evidence of an increased risk of CMV infection with rituximab in solid organ transplant (428, 448, 449). This may be explained by the widespread use of CMV prophylaxis.

The rates of varicella zoster infection seem to be increased with rituximab, and there are reports of fatal infections (450–452). It is the third most common viral infection complicating rituximab use in lymphoma (9.4%) (406). Cho et al. performed a longitu-

dinal study investigating the rates of herpes zoster in non-Hodgkin lymphoma patients receiving chemotherapy over 7 years (453). There was no difference in the overall incidence of herpes zoster with the addition of rituximab ($P = 0.16$), but over the first year, the rituximab group did have an increased risk (OR = 1.38; $P = 0.02$). Herpes zoster also appears more common in renal transplant (7.3% versus 0.26%) and systemic lupus erythematosus (SLE) patients (9.5% versus 3.4%) treated with rituximab (454, 455).

Other viral infections reported with rituximab use include herpes simplex virus (456, 457), parvovirus B19 (458–461), and West Nile virus. There have been four reported episodes of fatal West Nile virus infection, three associated with lymphoma and one in a lung transplant patient (462–464).

Bacterial infections are the most common infectious complication of rituximab in patients being treated for a hematological malignancy (32% to 43.4%) (387, 465). *Escherichia coli* and coagulase-negative staphylococci were the two most common organisms reported. Higher rates of infection were seen in the first 6 months of treatment (466). Kamar et al. found no difference in the rates of bacterial infection in renal transplant patients with and without rituximab (36.3% versus 31.6%; $P$ = nonsignificant [NS]) (388). In the setting of patients being treated with rituximab for autoimmune diseases, a single-center study found that 17.4% of patients developed a serious infection, all of which were bacterial (467). Causative organisms included *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Staphylococcus aureus*, and infection-related mortality was high, at 42%. Notably, those who had received pneumococcal vaccination had a lower risk of serious infection (OR = 0.11; $P = 0.0009$).

While there have been reports of *Mycobacterium tuberculosis* infections with rituximab (390, 468, 469), this appears to be a rare complication. Cantini et al. reviewed nine RCTs and nine open-label studies investigating rituximab in RA (470). Among the 4,814 patients included, there were no reports of tuberculosis. Relapse in patients with previously treated tuberculosis is also uncommon (471–474). Tuberculosis in lymphoma patients treated with rituximab also appears rare (25, 475–477).

Patients on rituximab monotherapy have a low incidence of fungal infection at around 1% (475). Fungal infection complicating treatment of hematological malignancy is uncommon given the widespread use of antifungal prophylaxis, with only one episode among 113 treated patients in one cohort study (387). The risk of invasive fungal infections also appears low in solid organ transplant recipients treated with rituximab. Scemla et al. found no difference in fungal infection rates in those with and without rituximab treatment for renal transplant (7.9% versus 7.7%, $P$ = NS) (478). Other studies have yielded similar results, with no difference in fungal infections (479–481). In contrast, Patel et al. performed a retrospective study of kidney and kidney/pancreas transplants comparing infectious complications between those who did and did not receive rituximab (455). Fungal infections in the rituximab group were significantly more likely, occurring in 11% versus 3% ($P = 0.009$). However, in this study, patients treated with rituximab received more ATG ($P = 0.001$), a potential confounder given its association with fungal complications (388).

Although the attributable risk is small, *Pneumocystis jirovecii* infection is increasingly recognized as a complication of rituximab therapy, with mortality rates of 30% to 33% (482, 483). Murine models show that anti-CD20 therapy reduces the host response to *Pneumocystis* infection (484). A case series published in 2013 reviewed 30 cases of *Pneumocystis* pneumonia associated with rituximab therapy (482). Only one patient received antimicrobial prophylaxis, 90% of cases occurred in those with hematological malignancy, and 73% were associated with concurrent steroid use. Jiang et al. performed a systematic review on *Pneumocystis jirovecii* pneumonia in rituximab-treated lymphoma patients (485). Rituximab was associated with an increased risk of *Pneumocystis* infection (2.9% versus 0.5%; $P = 0.001$). Prescribing prophylaxis to such patients significantly reduced the risk of infection (0% versus 2.6%; $P = 0.04$).

Other infections reported with rituximab include babesiosis (486), enteroviral meningoencephalitis, staphylococcal pericarditis, *Pasteurella multocida*, atypical mycobacteria, *Listeria*, cryptococcal meningitis, strongyloidiasis, and tick-borne encephalitis virus (487–496).

Other anti-CD20-directed therapies have risks and types of infectious complications similar to those of rituximab, albeit with fewer data available. A review of ocrelizumab for rheumatoid arthritis combining data from four RCTs found that serious infections were more frequent in those in the group receiving ocrelizumab at 500 mg (2.4 events per 100 patient years) than in placebo recipients (375). The most common serious infections included pneumonia, urinary tract infections, and cellulitis. Mysler et al. performed a randomized study investigating ocrelizumab in the setting of proliferative lupus nephritis (376). Three hundred eighty-one patients were randomized to three arms of the study: placebo, ocrelizumab at 400 mg, and ocrelizumab at 1,000 mg. The study was terminated early due to the increased rates of serious infection seen in those treated with ocrelizumab, with rates of serious infections in the placebo, ocrelizumab at 400 mg, and ocrelizumab at 1,000 mg groups of 18.7, 28.8, and 25.1 events per 100 patient years, respectively. In 2011, Kappos et al. reported an RCT of ocrelizumab versus placebo or interferon in 218 MS patients (497). The rates of serious infection were similar at 3.8, 3.4, and 3.5 events per 100 patient years for patients receiving placebo, ocrelizumab at 600 mg, and ocrelizumab at 2,000 mg, respectively. No opportunistic infections were reported during the 48-week follow-up period. Despite these reassuring results, there was still concern from clinicians (498). The OPERA I and OPERA II trial results were published in 2017, comparing ocrelizumab to interferon beta-1$\alpha$ in relapsing MS (499). In this analysis, there was a lower rate of serious infection in the ocrelizumab group (1.3% verse 2.9%). Mild upper respiratory tract infections and nasopharyngitis were more common with ocrelizumab. No opportunistic infections were identified with 96 weeks of follow-up. An ongoing open-label extension assessing safety and efficacy is continuing with the same cohort (500). The overall rates of serious and opportunistic infection appear low in ocrelizumab-treated MS patients; however, long-term data are needed to confirm these findings. Ocrelizumab does seem to increase the risk of mild and moderate herpesvirus infections. The rates of herpes zoster (2.1% versus 1.0%) and herpes simplex virus infection (0.7% versus 0.1%) are higher in those on ocrelizumab than in those on placebo (374).

There have been two major studies investigating ofatumumab for refractory CLL. In a phase I/II study, Coiffier et al. reported an overall infection rate of 51% with ofatumumab in patients with refractory or relapsed B cell CLL (501). Most of these were mild to moderate in severity, with nasopharyngitis being the most common. Wierda et al. investigated ofatumumab as a single agent in the treatment of fludarabine-resistant CLL (502). Infections were common, with 189 events in 92 patients, 13 of which led to death, including one episode of *Fusarium* infection and one of PML. The RESONATE study compared ibrutinib to ofatumumab in relapsed/refractory CLL (503). The overall rates of infection were lower in the ofatumumab group (54% versus 70%); however, severe infection rates were similar (22% versus 24%). Bacterial infections were much less common in a phase II trial of treatment-naive CLL patients being treated with ofatumumab, with serious infections occurring in 8% of patients and no opportunistic infections reported (504). This likely reflects the fact that treatment-refractory CLL patients have a high risk of infection with or without ofatumumab, due to previous treatments and the underlying disease.

In a randomized controlled trial, Goede et al. investigated the efficacy of obinutuzumab in untreated CLL (505). Seven hundred eighty-one patients were randomized to one of three groups: chlorambucil alone, obinutuzumab and chlorambucil, or rituximab and chlorambucil. Patients treated with anti-CD20 therapy had significantly longer progression-free survival. The rates of grade 3 to 5 infections ranged from 11 to 14% and were similar between the groups. Bacterial pneumonias were the most common serious infection, and no opportunistic infections were reported. In a retrospective single-center analysis of infectious complications in CLL, obinutuzumab was associated

with a lower relative risk of infection than alemtuzumab (RR = 0.63 [range, 0.48 to 0.82]; $P = 0.0001$) (506). Overall, the rate of infection with obinutuzumab was similar to the rate with rituximab in the treatment of CLL (38% versus 37%) (377). The largest trial of obinutuzumab in follicular lymphoma, GALLIUM, compared obinutuzumab to rituximab in previously untreated advanced disease (507). Obinutuzumab led to longer progression-free survival but did not alter overall survival. Obinutuzumab and rituximab were associated with similar rates of overall infectious events (77.3% versus 70.0%) and serious infections (20.0% versus 15.6%).

Belimumab has a different mechanism of action than the other anti-B cell agents and consequently appears to be associated with a lower risk of infectious complications. The overall rates of serious infection reported with belimumab are similar to the rates with placebo (378). Pooled data confirmed the low rates of serious infections with belimumab. The rates of serious infection in placebo and in belimumab at 1 mg/kg, 4 mg/kg, and 10 mg/kg were 5.5%, 7.1%, 6.3%, and 5.3%, respectively (508). A systematic review assessed the safety of biological therapy in SLE (509). Of four randomized controlled trials included, no significant difference in safety was noted with belimumab compared to placebo. BLISS-52 and BLISS-72 were multicenter, phase III, randomized placebo-controlled trials assessing the efficacy and safety of belimumab in SLE patients (510, 511). These two studies randomized 1,686 patients to belimumab at 1 mg/kg, beliumumab at 10 mg/kg, or placebo. Both trials reported a reduction in SLE disease activity. The rates of infection were comparable between the different groups. In BLISS-52, infection events were comparable between belimumab at 1 mg/kg and 10 mg/kg and placebo: 68% versus 67% versus 64%. Similar results were seen in BLISS-72, with equivalent severe infection rates (3.0% versus 2.6% versus 4.0%). Upper respiratory tract and urinary tract infections were the most common infectious complications. Two of 1,122 belimumab-treated patients had opportunistic infections (0.2%). There were no reports of tuberculosis. In a subsequent RCT of belimumab in SLE (512), serious infection was more common in the belimumab-treated group (4.5 versus 7.2 events per 100 patient years), with cellulitis and pneumonia (0.8 events per 100 patient years) accounting for most infectious events. Concurrent use of mycophenolate mofetil (MMF) and corticosteroids increased the risk of severe infections. A 7-year follow-up study of patients enrolled in this RCT reported that serious infections were rare, at $<2$ events per 100 patient years (513). A more recent RCT of belimumab in SLE had similar findings, with the risk of serious infection no different in the belimumab and placebo groups (4.1% versus 5.4%).

### Anti-B Cell Agents: Prevention of Infections

The key recommendations prior to using an anti-CD20 monoclonal antibody are similar to the recommendations for most potent immunosuppressive agents, but with more emphasis on HBV and less on tuberculosis.

Screening for HBsAg and anti-HBc antibody is recommended for all patients (514, 515). Nonimmunized, unexposed patients should be vaccinated against HBV. In those who have evidence of past exposure (HBcAb positivity) or chronic infection (HBsAg positivity), HBV DNA and liver transaminases should be tested and antiviral prophylaxis initiated (516). A 100-fold increase in HBV DNA often occurs in patients 12 to 28 weeks prior to reactivation of hepatitis (517). Entecavir or tenofovir prophylaxis is favored over lamivudine due to high rates of resistance with lamivudine, up to 20% within a year (412, 518, 519). A randomized control trial in 2014 compared entecavir to lamivudine in the setting of R-CHOP chemotherapy for the prevention of HBV reactivation (520). This study randomized 121 HBsAg-positive patients to lamivudine or entecavir. The entecavir group had lower rates of HBV hepatitis (0% versus 13.3%; $P = 0.003$), reactivation (6.6% versus 30%; $P = 0.001$), and chemotherapy disruption (1.6% versus 18.3%; $P = 0.002$) (521). Consensus guidelines recommend continuing antiviral prophylaxis for 12 to 18 months after cessation of rituximab (514, 515). Routine adult vaccinations are recommended to be up to date. In addition, pneumococcal vaccination should be given 3 to 4 weeks prior to therapy commencing, as it is less likely to elicit an immune

**TABLE 9** Combination lymphocyte-depleting agents

| Agent | Target | Cell type(s) affected | Main approved indication |
|---|---|---|---|
| Alemtuzumab | CD52 | T and B cells, NK cells, macrophages | Multiple sclerosis |
| Blinatumomab | CD19/CD3 | T and B cells | B cell precursor acute lymphocytic leukemia |
| Daratumumab | CD38 | MDSC,[b] Treg, B cells | Multiple myeloma |
| Elotuzumab | SLAMF7[a] | Plasma cells | Multiple myeloma |

[a]SLAMF7, signaling lymphocytic activation molecule family member 7.
[b]MDSC, myeloid-derived suppressor cells.

response afterwards (522, 523). Routine screening for tuberculosis is not recommended. Zoster vaccination should also be given if it can be achieved at least 6 weeks prior to therapy initiation, since live vaccines are contraindicated during anti-CD20 therapy. An alternative is to use recombinant zoster vaccine, but its immunogenicity is decreased following immunosuppression and it requires a 2-dose schedule, so it also needs to be given well in advance of immunosuppression if possible. While *Pneumocystis* pneumonia has been reported as a complication of these agents, the risk does not appear higher than that with background chemotherapy or combination immunosuppression, and thus, prophylaxis for PJP is not recommended for anti-CD20 therapy unless it is used along with or following other potent immunosuppression. Recommendations for belimumab are less clear, given the lack of a strong signal for an increased infection risk with this agent.

### Anti-B Cell Agents: Summary

Anti-CD20 therapies lead to major and durable depletion of B cells, but not of B cell precursors or plasma cells. Anti-CD20 therapies pose a moderate risk of serious bacterial infections (particularly respiratory tract infections), as well as HCV and herpes zoster reactivation, and a high risk of HBV reactivation. The risk of infectious complications is largely determined by cofactors, including concomitant immunosuppressive therapy, the underlying condition, and the patient's age. Belimumab appears to be associated with little additional infection risk, but the available data are limited to patients with SLE, who have a lower risk of infectious complications than those with hematological malignancies.

## COMBINATION LYMPHOCYTE-DEPLETING AGENTS

### Functions of Target Molecules of Combination Lymphocyte-Depleting Agents

The agents discussed in this section work by a variety of mechanisms, and thus, their mechanisms of action, the functions of their targets, and the infectious complications will be discussed for each individual agent. These agents all share the fact that they target lymphocytes but affect more than one type of cell.

### Available Lymphocyte-Depleting Biological Agents and the Epidemiology and Prevention of Their Infectious Complications

Lymphocyte-depleting agents approved for use in the United States and/or Europe are listed in Table 9.

**Alemtuzumab.** Alemtuzumab is a humanized IgG1($\kappa$) monoclonal antibody directed against the CD52 receptor present on B lymphocytes, T lymphocytes, natural killer cells, and macrophages (524). Alemtuzumab causes antibody- and complement-mediated cytolysis, profoundly depleting lymphocytes. Low circulating CD4 T lymphocyte counts persist for 1 to 2 years after administration (525). The on-label indication for use is relapsing remitting multiple sclerosis in those with inadequate response to two or more alternative drugs (526). Off-label use includes B cell chronic lymphocytic leukemia (527), T cell promyelocytic leukemia (528), Sézary syndrome (529), refractory autoimmune cytopenia (530, 531), acute graft-verse-host disease (532), hemophagocytic lymphohistiocytosis (533), and solid organ transplantation (276, 534, 535). Alemtuzumab is contraindicated in the setting of HIV infection given the prolonged and severe decline in $CD4^+$ lymphocytes. The treatment protocol for alemtuzumab is once-daily infusions

for 5 days in the first year, followed by once-daily infusions for 3 days in the second year. Premedication with 1 g of intravenous methylprednisone is required before each dose, potentiating the immunosuppressive effect of the regimen. Vaccinations should be provided 6 weeks prior to starting alemtuzumab and should not be administered during and for 6 months after cessation of treatment (536).

There are scant data on the risk of HBV reactivation with alemtuzumab therapy. Hepatitis B infection was an exclusion criterion in investigative trials. Those with chronic or past HBV infection are likely at high risk of reactivation (537). A retrospective analysis identified three episodes of HBV reactivation in HBsAg-negative (but HBcAb-positive) patients with lymphoma (538). Another group reported two episodes of HBV reactivation with alemtuzumab in chronic lymphocytic leukemia. Current evidence supports the routine screening of patients for past or chronic HBV infection (536). In those with past or chronic HBV infection, careful consideration should be made for alternative treatment options. If alemtuzumab is still required, antiviral prophylaxis should be started 1 to 2 weeks prior to treatment and continue for 12 to 18 months after cessation (539). Prophylaxis is warranted in HBsAg-negative/anti-HBcAb-positive patients to prevent reactivation (540).

Alemtuzumab is contraindicated in the setting of HIV infection. Despite this, there is interest in using alemtuzumab as a CD4 cell-depleting agent to assist in the eradication of HIV. Ruxrungtham et al. showed that HIV-infected CD4 cells retain functional CD52 (541). These CD4 cells are depleted when exposed to alemtuzumab. This theory was tested in a patient with cutaneous T cell lymphoma and concurrent HIV and HBV (542). Ultimately, treatment with low-dose alemtuzumab resulted in depletion but not elimination of HIV-infected CD4 cells. While he responded well initially, with a resolution of cutaneous symptoms, impairment of liver function and subsequent multiorgan failure resulted in death 6 weeks after treatment initiation.

The risk of reactivation of herpesvirus infections is increased among those treated with alemtuzumab. High rates of herpes simplex virus and herpes zoster infections were seen in the CAMMS223, CARE-MS I, and CARE-MS II trials (526, 543, 544). As such, the routine use of antiviral prophylaxis (with acyclovir, famciclovir, or valacyclovir) is recommended on the day of treatment initiation (537). Currently, the drug label advises continuing prophylaxis for 2 months after completion of therapy or until CD4 counts improve to $>$200, whichever occurs later (524). CMV infection, while rare, has been known to complicate alemtuzumab use (545, 546). Given the relative sparsity of these infections, prophylaxis and routine testing for CMV are not recommended in the multiple sclerosis population (537). This is different in the setting of underlying hematological malignancy, with rates of reactivation between 20 and 50% (538, 547, 548). O'Brien et al. performed an analysis assessing the routine use of valganciclovir prophylaxis in patients with hematological malignancy treated with alemtuzumab (547). The study was terminated early due to the efficacy of valganciclovir. Seven of 20 patients (35%) without prophylaxis had CMV reactivation, compared to 0% in the treated group. Patients being treated for hematological malignancy with alemtuzumab should receive valganciclovir prophylaxis with monitoring of CMV by PCR (549).

Several episodes of JC virus reactivation have been reported with alemtuzumab treatment. In a review by Raisch et al., 15 episodes of PML were noted (255). This equated to a proportional reporting ratio of 0.49%. Of the 15 patients included, 10 were associated with hematological malignancy, 4 were in the setting of transplant, and 1 patient had multiple sclerosis (550). Close monitoring programs are warranted to facilitate the early identification of JC virus reactivation in patients receiving alemtuzumab (551).

*Mycobacterium tuberculosis* infection has been described with alemtuzumab therapy. As for PML, tuberculosis appears uncommon in the MS population. In the three major trials, including 1,194 patients, only two episodes of tuberculosis occurred (526, 543, 544). This was in the context of compulsory screening for all involved. *M. tuberculosis* reactivation is more commonly reported in alemtuzumab-treated patients with hematological malignancy and solid organ transplant (552, 553). In a region of ende-

micity, the Asian Lymphoma Group reported an incidence of 8.8% (16 events in 182 patients) in those treated for hematological malignancy (538). In a retrospective single-center analysis, Walsh et al. reviewed 477 renal transplant patients who were treated with alemtuzumab (554). Two patients (0.4%) developed active tuberculosis. Both patients eventually succumbed to disseminated disease. Screening for latent *M. tuberculosis* infection should be performed in all patients prior to alemtuzumab therapy, and therapy with rifampin for 4 months (noting drug interactions) or isoniazid for 9 months should be initiated as soon as possible, ideally prior to commencement of therapy (537).

Ordinary bacterial infections are increased in patients treated with alemtuzumab with multiple sclerosis, most commonly respiratory and urinary tract infections (555). The three landmark trials establishing its role in multiple sclerosis were CAMMS223, CARE-MS I, and CARE-MS II (526, 543, 544). CAMMS223 randomized 334 patients to interferon beta-1a or alemtuzumab. The rates of infection were higher in the alemtuzumab-treated group, 65.7% versus 46.7%. Most events were respiratory and urinary tract infections. Serious infections were also higher in the alemtuzumab group, 4.2% versus 1.9%. Herpes simplex virus (8.3% versus 2.8%) and herpes zoster (3.7% versus 0.9%) infections were both more common in those receiving alemtuzumab. In the CARE-MS I trial, 581 patients were randomized to interferon beta-1a or alemtuzumab in a ratio of 1:2. Overall infection rates were higher for those receiving alemtuzumab (67% versus 45%). This was primarily driven by nasopharyngitis and respiratory tract and urinary tract infections. As in CAMMS223, herpes simplex virus (13% versus 2%) and herpes zoster (3% versus 0%) infections were also more common. One patient in a country of endemicity developed disseminated tuberculosis which resolved with treatment. The CARE-MS II trial compared alemtuzumab to interferon beta-1a in the setting of relapsed MS (526). Once again, infections were more common in the alemtuzumab group. Herpesvirus infection remained significantly higher than in the interferon beta-1a cohort. Serious infections occurred in 1% of those on interferon beta-1a and 4% of patients on alemtuzumab. While alemtuzumab is associated with lower rates of relapse and disability than is interferon beta-1a, serious and nonserious infectious complications are more common.

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) has provided guidelines on infection prevention for patients on alemtuzumab (540). Routine screening for past or resolved HBV, HCV, CMV, and *M. tuberculosis* is recommended prior to initiation. Females receiving alemtuzumab are advised to have yearly human papillomavirus screening. PJP and CMV prophylaxis should be offered to all patients on alemtuzumab for hematological malignancy. In order to reduce the risk of listeriosis and toxoplasmosis, all patients should be advised to avoid unpasteurized milk, soft cheeses, undercooked meat, and contact with cat feces. If possible, routine vaccinations should be up to date prior to commencing alemtuzumab and patients should be vaccinated for hepatitis B virus, pneumococcus, and influenza according to the guidelines for immunocompromised patients in general (556). Other infections reported with alemtuzumab therapy include CMV pneumonia, *Legionella longbeacheae* pneumonia, *Listeria monocytogenes*, and disseminated nocardiosis (557–561).

**Blinatumomab.** Blinatumomab is a human monoclonal antibody directed against CD19 and CD3. It functions to activate T cells through binding to the CD3 receptor and forming a complex with CD19 on the surface of B cells (562). This synapse results in T cell activation and proliferation and the release of cytolytic proteins, which causes lysis of CD19 B cells. Both T lymphocyte and B lymphocyte numbers decline following administration. T cell numbers improve to baseline in 7 to 14 days, while B cell numbers remain low throughout treatment. As such, it causes hypogammaglobinemia, which can persist for over a year after treatment (540, 563). The on-label indication for use is B cell precursor acute lymphoblastic leukemia (ALL) for both minimal residual disease and relapsed/refractory ALL. Serious infections are reported in 25% of patients receiving blinatumomab (562). Live vaccines are contraindicated during treatment and for 6 to 12 months after cessation.

In a randomized trial where 405 patients with B precursor ALL (b-ALL) were allocated to adjunctive blinatumomab or conventional chemotherapy, the blinatumomab group had higher rates of complete remission and longer overall survival, with less neutropenia and a lower risk of severe infection (34.1% versus 52.3%) (564). Cytokine release syndrome (presenting as fevers, tachypnoea, tachycardia, and hypotension) occurred in 4.9% of patients with blinatumomab. Presenting days to weeks after therapy administration, this syndrome is often indistinguishable from sepsis (565).

In a single-center review of 20 patients treated with blinatumomab for b-ALL (566), 14 patients had 26 infectious events. Pneumonia and bacteremia were common (occurring in 35% and 19%, respectively), and suspected fungal pneumonia occurred in four patients. The authors recommend monitoring neutrophils and beginning antifungal prophylaxis when neutrophil counts are $<500/\mu$l. ESCMID's guidelines on infection prevention with CD19-targeted therapies concluded that the overall rates of infection were comparable to the rates in other patients undergoing treatment for relapsed or refractory ALL (540). Hence, prevention protocols for b-ALL patients undergoing combination chemotherapy should follow institutional guidelines.

**Daratumumab.** Daratumumab is an IgG1($\kappa$) human monoclonal antibody directed against CD38. After binding to CD38, daratumumab induces Fc-mediated cell lysis through antibody-dependent cellular phagocytosis, cell-mediated toxicity, and complement activation (567). Positive CD38 myeloid-derived suppressor cells, regulatory T cells, and B cells are all depleted. On-label indications are combination treatment of newly diagnosed multiple myeloma (MM) and combination or single-agent therapy in the relapsed/refractory setting. Methylprednisolone at 100 mg intravenously is required as premedication with each dose.

Two large phase III trials assessed the role of daratumumab for multiple myeloma. In CASTOR, 498 patients with relapsed or refractory multiple myeloma were randomized to bortezomib and prednisone or daratumumab, bortezomib, and prednisone (568). The addition of daratumumab resulted in significantly longer progression-free survival, more neutropenia (12.8% versus 4.2%), and a similar risk of serious infection (21.4% versus 19.0%). In the POLLUX trial, 569 patients with previously treated multiple myeloma were randomized to daratumumab, dexamethasone, and lenalidomide or dexamethasone and lenalidomide alone (569). As in CASTOR, the daratumumab group had longer progression-free survival, a higher rate of neutropenia (5.7% versus 2.5%), and a similar rate of serious pneumonia (8.1% versus 8.5%). In both trials combined, there were relatively high herpes zoster rates of 2 to 5%. Overall, daratumumab does not appear to increase the risk of infection over those of alternative treatment regimens (570), with the possible exception of herpes zoster reactivation. Hence, antiviral prophylaxis for VZV is recommended with this agent.

**Elotuzumab.** Elotuzumab is a humanized IgG1 monoclonal antibody directed against the signaling lymphocytic activation molecule family member 7 (SLAMF7) protein. The Fc portion of elotuzumab binds to SLAMF7/CD16 receptors on natural killer cells, promoting NK cell activation (571). Elotuzumab also binds to SLAMF7 receptors on the surface of plasma cells, tagging them for NK-plasma cell interaction. NK cells then cause antibody-dependent cellular cytotoxicity, leading to plasma cell death (572). Myeloma cells express SLAMF7 at all stages of differentiation, making elotuzumab a theoretically effective agent in the treatment of multiple myeloma (573). SLAMF7 is also expressed on CD8 T lymphocytes, monocytes, and dendritic cells, and thus, elotuzumab may result in declines in these cell types (574). The on-label indication is in combination with lenalidomide and dexamethasone in the treatment of relapsed or refractory multiple myeloma. The only phase III trial of elotuzumab was ELOQUENT-2 (575), in which 646 patients with refractory multiple myeloma were randomized to receive elotuzumab, lenalidomide, and dexamethasone or lenalidomide and dexamethasone alone. Significantly lower risks of disease progression and death were seen in the intervention group. Overall infections were more common in both groups (81% versus 74%), with higher rates of severe lymphopenia (77% versus 49%) and herpes zoster (4.1 versus 2.2 events per 100 patient years) in the elotuzumab group. At the 3-year

**TABLE 10** Available IL-1 pathway inhibitors

| Agent | Nature | Indication(s)[a] |
|---|---|---|
| Anakinra | Chemically altered version of IL-1 receptor antagonist (IL-1Ra) that inhibits binding of IL-1R$\alpha$ and IL-1$\beta$ to IL-1R | Rheumatoid arthritis, CAPS, systemic juvenile idiopathic arthritis, adult-onset Still's disease |
| Canakinumab | Human monoclonal antibody binds to IL-1$\beta$, thus blocking its activation of IL-R1 | CAPS, TRAPS, hyper-IgD syndrome, adult-onset Still's disease, systemic juvenile idiopathic arthritis, recalcitrant gout |
| Rilonacept | Fusion protein of ligand binding domain of IL-1R1 and receptor accessory protein IL-1RAcP, linked via Fc portion of IgG1 that acts as a decoy receptor, binding to IL-1$\alpha$ and IL-1$\beta$ and blocking their binding to IL-1R | CAPS |

[a]CAPS, cryopyrin-associated periodic syndromes; TRAPS, TNF receptor-associated periodic syndrome.

follow-up, no new safety signals were identified (576). Observational data suggest that elotuzumab does appear to increase infection risk (570), with opportunistic infections occurring in 22% of patients, compared with 13% in comparator groups (572). Anti-herpesvirus prophylaxis should be prescribed to patients who have positive herpes zoster serology.

### Lymphocyte-Depleting Agents: Summary

Alemtuzumab appears to carry the highest risk of infectious complications among these agents. Alemtuzumab leads to profound CD4 lymphocyte depletion and a high risk of both ordinary bacterial infections and opportunistic infections, particularly tuberculosis and herpesvirus reactivation. Given that alemtuzumab is indicated for a condition which is not immediately life-threatening (MS), the high risk of infection needs to be balanced carefully against the potential benefits and the severity of the underlying disease. Blinatumomab, daratumumab, and elotumumab are all used in hematological malignancies; they each lead to depletion of important populations of immune cells but do not appear to increase the risk of infectious complications over the risk in those treated with conventional therapies.

## IL-1 PATHWAY INHIBITORS

### The Role of the IL-1 Pathway in the Human Immune Response

The interleukin-1 (IL-1) pathway is an 11-member family of closely related cytokines and 10 receptors (IL-1Rs). Members of the IL-1R and Toll-like receptor (TLR) family share sequence homology in their cytoplasmic tails and are involved in activating and regulating a complex inflammatory cascade that yields similar effects of increased chemokine production, enhanced adhesion molecule expression, nuclear factor kappa B (NK-$\kappa$B) expression, inflammatory cytokine production, neutrophil activation, and fever. IL-1$\alpha$ and IL-1$\beta$ act as proinflammatory cytokines upon binding to IL-1R1 and the accessory protein IL-1RAcP. There are also inhibitory cytokines, in particular IL-1R antagonist (IL-1Ra), that bind to IL-1R1 and block the proinflammatory effects of IL-1$\alpha$ and IL-1$\beta$ by competitive inhibition. The IL-1 response is thought to play an important role in inflammation, host defense against infection, and autoinflammatory/autoimmune conditions (577–580). The main cellular source of IL-1 is activated mononuclear phagocytes, but it is also produced by neutrophils, epithelial cells, and endothelial cells. Increased production of IL-1 typically requires two signals, one to increase production of the pro-IL-1$\beta$ precursor protein and the other to activate the inflammasome that proteolytically cleaves the precursor to generate active IL-1$\beta$, the most active of the IL-1 molecules. Gene transcription of the pro-IL-1$\beta$ is stimulated via NK-$\kappa$B activation by Toll-like and NOD-like receptors responding to pathogen-associated molecular patterns (PAMPS) and tissue damage-associated molecular patterns (DAMPs) (577, 581, 582).

### Available Drugs Which Inhibit the IL-1 Pathway

There are three molecules that block the IL-1 pathway in clinical use (Table 10).

Anakinra is a recombinant, nonglycosylated IL-1Ra that only differs from native IL-1Ra in having an extra methionine residue at the N terminus. It acts by direct inhibition of IL-1$\alpha$ and IL-1$\beta$ binding to IL-1R1, mirroring the action of endogenous

IL-1Ra (580, 583, 584). Anakinra is given once daily by subcutaneous injection. In contrast, canakinumab is a fully human IgG1 monoclonal antibody that binds to IL-1$\beta$ to block its interaction with IL-1R1 (585, 586). Canakinumab is given by subcutaneous injection every 4 to 8 weeks. Rilonacept is a fusion protein of the ligand binding domains of IL-1R1 and the receptor accessory protein IL-1RAcP, linked together via the Fc portion of IgG1. Rilonacept acts as a decoy receptor, binding to IL-1$\alpha$ and IL-1$\beta$ and blocking binding to IL-1R1 and the accessory protein needed for activation of the inflammatory cascade. It is given by weekly injection (587–589).

Inhibitors of the IL-1 pathway are effective and approved for the treatment of rheumatoid arthritis, Still's disease, juvenile rheumatoid arthritis, and many of the autoinflammatory syndromes, including cryopyrin-associated periodic fever syndromes, familial Mediterranean fever, TNF receptor-associated periodic fever, and hyper-IgD syndrome (mevalonate kinase deficiency) (586, 590–596). Therapy with IL-1 antagonism is also approved for treatment-resistant gout, or gout when colchicine and nonsteroidal anti-inflammatory drugs (NSAIDs) are contraindicated or not tolerated (597–600). The IL-1 blockers have also been used off label in the treatment of Behcet's disease (601, 602), calcium pyrophosphate crystal arthritis (603), refractory pericarditis (604, 605), and neutrophilic dermatoses (606, 607). Recent studies in atherosclerosis have suggested a potential benefit of canakinumab therapy in patients with evidence of inflammation, evidenced by high-sensitivity C-reactive protein (CRP) elevation, with most benefit for those whose CRP falls to $<$2.0 with therapy (608, 609). Gevokizumab is a humanized monoclonal antibody which targets IL-1$\beta$, but it has not yet been approved for clinical use (610).

### Infectious Complications of IL-1 Pathway Inhibitors

The role of the IL-1 pathway in host responses to infection raises concerns about infection risk. Despite this, short-term therapy trials of anakinra, canakinumab, and rilonacept for acute gout were not associated with a major increase in infection, though there was a slightly higher rate of side effects, including headache, back pain, and hypertension (597, 600, 611, 612). Short- and long-term studies of anakinra in rheumatoid arthritis, often combined with other immunosuppressive agents, including corticosteroids, showed increased rates of infection, most commonly upper respiratory tract infections. However, infections did not usually require treatment cessation, which was largely driven by injection site reactions and lack of therapeutic efficacy (583, 613–615). In 1,346 patients treated with anakinra for RA for a mean of 3 years, the cumulative incidence of serious infection was 5.4 episodes per 100 patient years (614). In a network meta-analysis of RCTs of anakinra therapy in rheumatoid arthritis, the rates of serious infections were higher, at 98 per 1,000 patient years, versus 26 per 1,000 patient years for control (OR = 4.05; 95% CI, 1.22 to 16.84) (78, 616). Studies of canakinumab in juvenile rheumatoid arthritis found higher rates of infection than with placebo, but canakinumab facilitated reduced requirements for corticosteroid therapy and improved quality of life and disease control for this difficult-to-manage condition (617, 618). In a meta-analysis of anakinra use in adult-onset Still's disease, the rate of infection was likely reduced overall by the use of anakinra, as it allowed dose reduction of steroid therapy (619). Anti-IL-1 therapy has also been extensively studied in the autoinflammatory conditions. These studies have employed novel design strategies due to the rarity of these conditions and the ethical difficulties of a prolonged placebo control period (620–625). As in the RA studies, the most common adverse events were injection site reactions and upper respiratory tract infections. Serious adverse events did occur but were infrequent and typically judged to be not associated with the study medication (586, 623, 625–628). The recent CANTOS study of canakinumab in atherosclerosis presents a relatively unusual opportunity to observe the infection risks of a biological therapy in the absence of any preceding or concomitant immunosuppression. The CANTOS trial noted a small but statistically significant excess of deaths attributed to infection in those who received canakinumab compared to those who received placebo (incidence of 0.31 versus 0.18 per 100 person years; $P = 0.02$) (608). The patients who

died from infection tended to be older and more likely to have diabetes. While there was no difference in rates of opportunistic infection between the placebo and canakinumab arms, there were six confirmed cases of tuberculosis during the trial. Tuberculosis has not been highlighted as a risk in trials of IL-1 pathway therapy. Neutropenia and thrombocytopenia occurred more frequently in those who received canakinumab. There was no difference in all-cause mortality between placebo and canakinumab therapy in the CANTOS trial (608).

### IL-1 Pathway Inhibitors: Prevention of Infectious Complications

Patients should be screened for latent tuberculosis prior to IL-1 pathway inhibition therapy, as there is a theoretical risk of tuberculosis due to IL-1 physiology and there are case reports of tuberculosis reactivation. It should be noted that anti-TNF and anti-IL-6 therapies are alternatives to IL-1 blockade in several conditions for which IL-1 pathway inhibition is indicated, and latent tuberculosis screening and appropriate therapy facilitates treatment changes if needed. Age-appropriate vaccination should be given according to guidelines (556, 629, 630), though higher rates of febrile and adverse reactions have been suggested in patients with autoinflammatory disease receiving the polysaccharide pneumococcal vaccine (631).

### IL-1 Pathway Inhibitors: Summary

In summary, IL-1-targeted therapy is associated with small to moderate increases in infection risk. The risk of more serious life-threatening infection is increased in older patients with comorbidity, such as diabetes, and who are receiving combination immunosuppressive therapy, including corticosteroids (608). Where immunosuppression can be tapered by the addition of IL-1 pathway blockade, that infection risk may be mitigated but not eliminated.

## DRUGS TARGETING IL-4

### The Role of the IL-4 Pathway in the Human Immune Response

There are two types of IL-4 receptor: type 1 consists of an $\alpha$ subunit (IL-4R$\alpha$) and the common $\gamma$ chain (a receptor component common to IL-2, -4, -7, -9, -15, and -21 receptors), and a type 2 receptor consisting of the IL-4R$\alpha$ subunit stabilized by the IL-13R$\alpha$1 subunit. The type 1 receptor can be activated by IL-4, whereas the type 2 receptor can be activated by either IL-4 or IL-13. These receptors are present on B lymphocytes, eosinophils, airway smooth muscle cells, dendritic cells, monocytes, macrophages, basophils, bronchial epithelial cells, keratinocytes, endothelial cells, and fibroblasts. Binding of IL-4 and/or IL-13 to these receptors leads to modulation of the genes involved in IgE class switching, Th2, B, and plasma cell differentiation, and M2 macrophage polarization (632–636). Taken together, the key result of activation of the IL-4 receptor is upregulation of the allergic response to antigens.

### Available Drugs Targeting the IL-4 Pathway

Dupilumab is the only currently approved drug targeting the IL-4 pathway. It is a fully humanized recombinant IgG4 monoclonal antibody produced in Chinese hamster ovary cell cultures that targets the IL-4R$\alpha$ subunit. Dupilumab has been shown in multiple clinical trials to be effective in the management of moderate to severe atopic eczema (637–641). Complete or almost complete resolution of moderate to severe eczema was reported in 36 to 39% of those receiving dupilumab at doses of 300 mg once or twice weekly combined with topical therapy, compared with rates of 8 to 12% in topical therapy and placebo groups, over 16 to 52 weeks of therapy in a number of landmark trials (632–636). The FDA and the European Medicines Agency have approved dupilumab for use in moderate to severe atopic dermatitis. Placebo-controlled trials of dupilumab in steroid-dependent severe asthma have also shown substantial benefit, both by reducing steroid requirements and by improving lung function (642–646). Comparative trials in severe steroid-dependent asthma are awaited between the key biological approaches to asthma therapy, those targeting the IL-5, IgE, or IL-4/IL-13

pathways (647). Early studies have also suggested a benefit for dupilumab in allergic rhinitis, nasal polyposis (633, 648–650), and eosinophilic esophagitis (633, 652).

### IL-4 Pathway Inhibitors: Infectious Complications

Dupilumab has been well tolerated in the clinical trials, and infectious complications have rarely been reported. Longer-term studies suggested a possible higher rate of herpes simplex virus infections in dupilumab-treated subjects (637, 638), but recent meta-analyses of adverse events in eight of the RCTs assessing dupilumab for atopic dermatitis concluded that the incidences of nasopharyngitis, urinary tract infection, upper respiratory tract infection, and herpesvirus infections were no different from those in placebo groups (653, 654). In the meta-analyses, patients on dupilumab had a lower risk of skin infection (RR = 0.54; 95% CI, 0.42 to 0.69) and higher risks of injection site reaction (noninfectious) (RR = 2.24; 95% CI, 1.68 to 2.99), headache (RR = 1.47; 95% CI, 1.05 to 2.06), and conjunctivitis (RR = 2.64; 95% CI, 1.79 to 3.89) than did placebo patients (653, 654). In contrast to the atopic dermatitis trials, conjunctivitis did not occur at higher frequencies than in placebo recipients in the asthma and rhinitis trials, suggesting that this complication of dupilumab is specific to atopic dermatitis (633, 655). Ocular lubrication with artificial tears has not been found to be helpful for the conjunctivitis, whereas topical steroid and tacrolimus have proved effective in managing the inflammation and limbic hyperemia in this noninfectious conjunctival condition (656).

Long-term asthma studies have found that the overall rates of adverse events, deaths, infections, conjunctivitis, herpes infections, and discontinuations were comparable between dupilumab and placebo. Injection site reactions were more common than in placebo recipients (17% versus 8%), and some patients had transient rises in eosinophil levels (643, 644). One case of hypereosinophilia was previously noted in an earlier study, which resulted in withdrawal of dupilumab, but this was not associated with an infection (645).

### IL-4 Pathway Inhibitors: Summary

In summary, studies of dupilumab to date suggest the drug is safe and effective. Further long-term data will be needed to confirm these findings, particularly in children and older patients.

## AGENTS TARGETING IL-5 AND IgE

### The Roles of IL-5 and IgE in the Human Immune Response

Interleukin-5 (IL-5) is a 115-amino-acid homodimer expressed by Th2 cells, innate lymphocyte cells expressing Th2 cytokines (ICL2 cells), $CD34^+$ progenitor cells, invariant NK-T cells, mast cells, and eosinophils (657–659). The gene encoding this cytokine is located on chromosome 5 in close association with IL-3, IL-4, IL-13, and GM-CSF. The actions of IL-5 are mediated by IL-5 binding to its receptor (IL-5R), a dimeric molecule with alpha (CD125) and beta (CD131) subunits. Cell signaling occurs via the beta chain, which IL-5R shares with the receptors for GM-CSF and IL-3, while IL-5-specific binding to the receptor is mediated by the alpha subunit. The DNA encoding the IL-5R alpha chain is located on chromosome 3p26 and is expressed in eosinophils, basophils, and mast cells (660, 661). IL-5's key function is regulation of eosinophil growth and differentiation, maturation, activation, and survival, though it also plays a role in mast cell, B cell, and basophil biology (657, 662, 663). IL-5R activation leads to intracellular signaling via the Janus kinase (JAK)-STAT signaling pathway. IL-3 and GM-CSF are also involved in eosinophil growth, protein translation, and cell survival (660, 664, 665).

Eosinophil activation and cellular degranulation release a variety of proinflammatory and regulatory cytokines, including IL-4, IL-5, IL-13, transforming growth factor $\beta$ (TGF-$\beta$), interferon gamma, and proteins that can cause local tissue damage and cytotoxicity, including major basic protein, eosinophil cationic protein (ECP), eosinophil peroxidase, eosinophil-derived neurotoxin, leukotrienes, platelet-activating factor (PAF), and prostaglandins. Eosinophils are understood to be important mediators of

**TABLE 11** Available agents targeting IL-5 or IgE

| Agent | Nature | Target/mechanism | Indication(s) |
|---|---|---|---|
| Mepolizumab | Humanized IgG1 MAb | IL-5 | Add-on maintenance treatment of severe eosinophilic asthma, eosinophilic granulomatosis and polyangiitis |
| Reslizumab | Humanized IgG4 MAb | IL-5 | Add-on maintenance treatment of severe eosinophilic asthma |
| Benralizumab | Humanized IgG1 MAb | IL-5 receptor, alpha subunit | Add-on maintenance treatment of severe eosinophilic asthma |
| Omalizumab | Humanized IgG1 MAb | IgE (Fc region) | Moderate to severe allergic asthma, chronic idiopathic urticaria |

tissue inflammation, remodeling, and repair, clearance of helminthic infection, angiogenesis, and homeostasis (663, 666, 667). Eosinophils also play a central role in the pathophysiology of a number of diseases, including severe eosinophilic asthma (668, 669), eosinophilic chronic obstructive pulmonary disease (670), eosinophilic granulomatous vasculitis (EGPA) (671, 672), and hypereosinophilic disorders (663, 673).

IgE is an antibody that functions as an antigen receptor on the surface of cells that express the high-affinity IgE receptor (Fc$\varepsilon$RI). High-level expression of Fc$\varepsilon$RI is limited to mast cells and basophils, though eosinophils, epidermal Langerhans cells, activated monocytes, and some dermal macrophages express Fc$\varepsilon$RI to a lesser extent. Binding of IgE to Fc$\varepsilon$RI occurs at very high affinity (dissociation constant, $\sim 10^{-10}$ M), ensuring that mast cells and basophils are always coated with IgE, even in nonatopic individuals (674, 675). Fc$\varepsilon$RI is made up of an $\alpha$ chain that binds to the Fc region of IgE and a $\beta$ chain associated with two $\gamma$ chains. A second IgE receptor, Fc$\varepsilon$RII (CD23), binds IgE at lower affinity and is expressed on B and T cells, follicular dendritic cells, and tissue macrophages. CD23 is important in the regulation of IgE production and the transport of IgE and antigen across epithelium (676–679). To activate mast cells and basophils, cross-linking of multiple Fc$\varepsilon$RIs is typically required. In classic mast cell activation in an atopic individual, a large number of the Fc$\varepsilon$RIs are occupied by IgEs specific for an allergen, facilitating Fc$\varepsilon$RI cross-linkage and mast cell activation. In nonatopic individuals, the IgEs that occupy Fc$\varepsilon$RI have a broad range of specificities, so cell activation via a cross-linking antigen is unlikely to occur (680, 681). In contrast, chronic idiopathic urticaria (CIU) is not linked to specific IgE-allergen interaction, and mast cell activation occurs via other mechanisms, including autoimmune activation (IgE to autoallergens and IgG autoantibodies to IgE or its receptor), coagulation pathway factors, and physical stimuli (674, 675, 682–684).

Mast cell and basophil activation leads to an allergic response via immediate cellular degranulation and synthesis of inflammatory mediators. Mast cell degranulation immediately releases histamine, tryptase, acid hydrolases, cathepsin G, and carboxypeptidase that increase vascular permeability and smooth muscle contraction, promote degradation of microbial structures, and start the process of tissue damage and repair. Prostaglandins, leukotrienes, PAF, IL-3, IL-4, IL-5, IL-13, TNF, and MIP-1$\alpha$ are produced and released over the 18 to 24 h following activation, promoting further vasodilation, bronchoconstriction, leukocyte chemotaxis, mucous secretion, IgE production, and eosinophil production, recruitment, and activation (685). Mast cells and basophils are key drivers of not only acute asthma episodes and CIU but also the chronic pulmonary changes and remodeling that occur in asthma (674).

### Available Agents Targeting IL-5 or IgE

Several agents are available to target IL-5 or IgE, all of which were primarily developed for severe eosinophilic asthma (Table 11).

Blocking IL-5 (mepolizumab and reslizumab) or the alpha subunit of its receptor (benralizumab) significantly reduces blood and tissue eosinophilia. Benralizumab is more potent in eosinophil depletion, as it has a direct cytotoxic effect on eosinophils via antibody-mediated cellular cytotoxicity acting on IL-5R (686). The reduction in airway eosinophils is approximately 50% to 90% with anti-IL-5 therapy (687, 688). Mepolizumab is a humanized anti-IL-5 monoclonal antibody produced in Chinese hamster ovary cells. It is indicated as add-on maintenance therapy in patients aged 12 or older with severe eosinophilic asthma at a dose of 100 mg given subcutaneously

every 4 weeks. It is also approved for use in some countries for eosinophilic granulomatosis and polyangiitis (formerly known as Wegener's granulomatosis) at a dose of 300 mg every 4 weeks. Reslizumab is a humanized IgG4($\kappa$) monoclonal antibody produced in murine nonsecretory myeloma cells. Reslizumab at 3 mg/kg is given as add-on therapy in patients 18 years and older with eosinophilic asthma by intravenous infusion over 20 to 50 min every 4 weeks, but not in acute bronchospasm or status asthmaticus. Benralizumab is a humanized cytolytic IgG1 monoclonal antibody with a molecular weight of 150 kDa raised in Chinese hamster ovary cells. It is indicated as add-on therapy in the chronic management of eosinophilic asthma in patients aged 12 years and older. Benralizumab at 30 mg is given by subcutaneous injection every 4 weeks for three doses and then every 8 weeks. Studies of anti-IL-5 therapy in eosinophilic asthma (689–692), eosinophilic chronic obstructive pulmonary disease (670, 693), and eosinophilic granulomatosis and polyangiitis (671) have demonstrated that the therapy has significant benefit under these conditions at these doses, with reduced frequency of disease relapse and requirement for steroid therapy. Randomized placebo-controlled trials in eosinophilic asthma with reslizumab (694–697), benralizumab (692, 698–701), and mepolizumab have shown similar efficacies (702). These therapies have also been trialed to a more limited extent in other hypereosinophilic disorders, including eosinophilic esophagitis and carditis, allergic bronchopulmonary aspergillosis, and severe rhinosinusitis. It has proven effective for disease control, allowing reductions in steroid requirements without major toxicity (673, 703–706).

Omalizumab is a humanized IgG1 monoclonal antibody produced in Chinese hamster ovary cells that binds to the constant Fc region of IgE in the same location as Fc$\varepsilon$RI. Omalizumab is licensed for use in moderate to severe atopic asthma, typically defined as patients with positive skin tests or serum IgE tests for allergen sensitization, failure to control asthma with combined inhalant steroid, beta agonist, and antimuscarinic therapy, and a total serum IgE level of $>$30 IU/ml (668, 707–712). Omalizumab is also licensed for use in chronic idiopathic urticaria uncontrolled by maximal antihistaminic therapy. Omalizumab acts to prevent IgE from binding to both Fc$\varepsilon$RI- and Fc$\varepsilon$RII-expressing cells, including B cells, dendritic cells, and eosinophils. This reduces IgE production and its function mediated through both these receptors. Omalizumab has also been shown to reduce Fc$\varepsilon$RI density on mast cells and basophils, to reduce the density of mast cells in pulmonary and skin tissues, and to reduce circulating free IgE, though there may be a paradoxical increase in measured serum IgE due to immune complex formation (675, 713). Subcutaneous dosing of omalizumab in asthma is calculated based on baseline IgE level and body weight, whereas dosing in chronic idiopathic urticaria is given as 300 mg subcutaneously each month, reflecting the distinct pathogenesis of each condition.

### Agents Targeting IL-5 or IgE: Infectious Complications

Treatment with both anti-IL-5 and anti-IgE therapies has proven remarkably safe to date, with rates of influenza, lower respiratory tract infection, pharyngitis, gastroenteritis, and viral infection matching the rates in the placebo population. There have been few reports of herpes zoster in patients receiving mepolizumab (689, 714). Considering the number of patients and the length of follow-up in patients treated with this medication, it is too early to judge the significance of these reports. It is also noteworthy that the patients who receive anti-IL-5 therapy typically are receiving steroid therapy when the drug is started. As steroid dose reduction is one of the aims of treatment, the possibility is raised that these herpes zoster cases occurred in the context of substantial steroid reduction and may represent an immune reconstitution phenomenon.

Although eosinophils play an important role in the immune response to parasites and fungi, genetic eosinophil deficiency, antibody-mediated destruction of eosinophil precursors, and animal models with engineered eosinophil deficiency have no characteristic ill effects or infectious complications (715–717). Cynomolgus monkeys given mepolizumab showed no ill effects over 6 months during intravenous and subcutane-

ous toxicity studies (718). The monkey studies showed dose-dependent reductions in peripheral blood eosinophil counts, of up to 95% at doses of 5 mg/kg or greater (718). However, eosinophil precursors in the bone marrow of these monkeys were preserved, and there was persistence of low levels of eosinophils in blood and tissues. It is known that IL-3 and GM-CSF also have a role in eosinophil ontogeny and survival, and it is likely that these cytokines preserve the precursor population (660, 687, 719) and the low-level residual eosinophil populations in tissues of treated subjects. This observation, which has also been made in humans, may explain why IL-5 neutralization by anti-IL-5 therapy is not completely effective in eosinophilic asthma and, potentially, why there is no clear rise in infectious risk with these medications (660, 663).

There has always been concern that anti-IL-5 and anti-IgE therapy may be deleterious in helminthic and parasitic disease (587). This concern has been particularly strong for tissue-invasive helminths. Studies where eosinophil-deficient mice were infected with either *Schistosoma mansoni* (720), *Strongyloides stercoralis* (721), or *Trichinella spiralis* (722) showed no defect in the animal's host defense. Indeed, in Fabre's mouse model, depletion of eosinophils was associated with enhanced nematode clearance, and in this model, Th1 cytokine responses rather than eosinophil activation were associated with nematode clearance (722).

Prolonged therapy with anti-IL-5 in humans also appears to be well tolerated. In an extension study of a previous randomized control trial in hypereosinophilic patients (673), 78 asthmatic adults received mepolizumab at 750 mg every 4 weeks for a mean of 251 weeks (range, 4 to 302) (723). The rate of side effects decreased over time, and the rates of infection and toxicity in the treated group were similar to those in the placebo group during the double-blind period of study. In another post-RCT (724) follow-on study (725), mepolizumab at 100 mg every 4 weeks was continued for a further 52 weeks in 651 patients, of whom 414 patients had previously received mepolizumab and 237 had received placebo. Across the whole study population, the incidences of adverse events were no different in the mepolizumab and placebo groups. The other anti-IL-5 therapies have shown a similar lack of adverse effects. A recent meta-analysis of 13 human randomized trials of anti-IL-5 therapy (4 mepolizumab, 4 reslizumab, and 5 benralizumab trials) in 6,000 participants found no excess serious adverse events with any of the anti-IL-5 therapies, with some evidence for a reduction in adverse events, perhaps related to reductions in asthma-related serious adverse events, hospitalization, and corticosteroid use (688). Serious adverse events leading to therapy discontinuation were fewer in patients receiving therapy (mepolizumab at 19/1,000 versus placebo at 26/1,000, and reslizumab at 38/1,000 versus placebo at 58/1,000). Benralizumab also had a lower rate of serious adverse events than placebo (109/1,000 versus 139/1,000) but had a slightly higher rate of withdrawal from therapy (19/1,000 versus 9/1,000).

Reliable assessment of the long-term safety of eosinophil depletion will require a much longer period of observation, as these therapies will be used long term in severe asthmatics, and our current safety and toxicity data are of limited duration.

Early trials of omalizumab noted immunological issues, including anaphylaxis (~0.2%), the potential for immune complex disease, and the risk of loss of efficacy due to blocking antibodies (726, 727). Concern has also been expressed regarding the risk for parasitic disease. A reported case of *Echinococcus multilocularis* infection occurring after prolonged therapy with omalizumab in a high-prevalence area highlights this concern (728). Most clinical trial and postmarketing surveillance data of anti-IL-5 and anti-IgE therapy have been obtained in resource-rich countries where the background prevalence of intestinal helminth disease is low. This concern was addressed in a double-blind, placebo-controlled randomized trial in 137 subjects with asthma and/or rhinitis at high risk of geohelminth infection in Brazil (729). "High risk" was defined as having at least one of the following characteristics: documented history of a geohelminth infection in the last year, or a household member with current or a history of such an infection within the last year, or a positive specific IgE to *Ascaris lumbricoides* at trial screening and a self-reported geohelminth infection within the last year. Patients

with very high IgE (>1,300 IU/ml) or who required oral corticosteroids for their asthma were excluded from the study, and all patients were treated to clear helminthic infections prior to the commencement of the trial (729). There was no significant difference in the incidence of new helminth infections in the omalizumab recipients compared with the placebo subjects after 1 year of therapy (50% versus 41%; OR = 1.47; 95% CI, 0.74 to 2.95). When adjusted for baseline helminthic infection, which was higher in the placebo group, the risk of new helminth infection was numerically higher in the omalizumab group, but again, this was not statistically significant (adjusted OR = 2.2; 95% CI, 0.94 to 5.15). There was no difference between the groups in maximal helminth infection intensity, time to infection, morbidity, mortality, or response to helminthic therapy (729). A subsequent editorial points out the lack of evidence from animal models and observational studies in humans that IgE plays a critical role in mediating protection from helminths (730).

No consistent risk of helminthic, parasitic, or opportunistic infection was apparent during the licensing trials for omalizumab, and none has become apparent in follow-up studies. Indeed, omalizumab has been trialed in allergic bronchopulmonary aspergillosis patients (including those with comorbid cystic fibrosis) without invasive disease developing, and it allowed reduction in steroid use (731–734). There are no reports of *Strongyloides* hyperinfection syndrome associated with omalizumab. Severe *Strongyloides* infection is most strongly associated with broad host immune compromise affecting cell-mediated immune responses, with broad immune-suppressive medications (steroids, methotrexate, vinca alkaloids, and cyclophosphamide), techniques (total body irradiation), and conditions (bone marrow transplant, solid organ transplant, diabetes, HIV infection, and human T cell leukemia virus 1 [HTLV-1] infection) most strongly associated (735–737).

Clinical trials have not suggested a significantly increased risk of infection in omalizumab-treated patients versus placebo subjects, be this in asthma or urticarial or seasonal rhinitis (710, 726, 738–743). Postmarketing surveillance efforts have not demonstrated a substantial safety issue, including for infectious diseases (726).

### Agents Targeting IL-5 or IgE: Prevention of Infection

Since all the available data suggest no attributable risk of infection in those treated with anti-IL-5 or anti-IgE therapies, one could argue that no special prevention measures are needed. However, because of the mechanistic presumed risk of parasitic infection combined with a lack of long-term data from areas with a high prevalence of intestinal helminth infection, most authors recommend baseline testing for and treatment of intestinal helminths prior to therapy, especially for those with an epidemiological risk (587). This should include patients residing in or who have immigrated from resource-poor countries, particularly in the tropics. Baseline testing should include stool microscopy for ova, cysts, and parasites, as well as serology for strongyloidiasis. Any detected helminth infection should be treated prior to or coincident with the commencement of omalizumab.

### Agents Targeting IL-5 or IgE: Summary

Despite an extensive literature on the role of eosinophils in parasitic and helminthic disease, there do not appear to be any adverse effects from their absence, perhaps due to redundancy in the host immune response to these pathogens. The data on drugs designed to inhibit these targets are similar: no evidence of increased infection risk, with the possible exception of a small risk of intestinal geohelminth infection. Longer-term studies in more widespread geographical areas are needed before definitive conclusions can be drawn.

## IL-6-TARGETED AGENTS

### Function of the IL-6 Pathway

Interleukin-6 (IL-6) is a key proinflammatory cytokine in the mammalian adaptive immune response. It is produced by a range of cell types, including fibroblasts,

macrophages, and lymphocytes (744), and is an important driver of the acute-phase inflammatory response (745). The acute-phase response induces systemic changes, such as fever, leukocytosis, and rapid release of over 40 different proteins into the circulation. Other downstream effects of IL-6 include the activation of endothelial cells, the recruitment of circulating lymphocytes, the induction of antibody production by B cells, and differentiation of T cells. IL-6 has been shown to be important in the pathophysiology of rheumatoid arthritis (746, 747), sepsis (748, 749), and multiple other acute and chronic inflammatory conditions (750–754). Indeed, the importance of IL-6 to many aspects of the human immune response is underlined by its utility as a prognostic marker in sepsis (755), malignancy (756), and several other conditions (752, 757, 758). The IL-6 pathway can be inhibited by blockade of the IL-6 receptor as a cell-bound molecule or as circulating soluble receptors or by the binding and inactivation of circulating IL-6 itself. Downstream effects of IL-6 can also be constrained by small molecule inhibitors of Janus kinase (JAK) (759, 760), a group of important chemical messengers transducing the signaling of IL-6, discussed below (see JAK Inhibitors).

The IL-6 receptor (IL-6R) is also known as CD126. After IL-6 binds, an IL-6/IL-6R dimer causes homodimerization of glycoprotein 130, which then leads to signal transduction via the JAK/STAT pathway (761). It is important to note that, as in most aspects of the human immune system, IL-6 is part of a group of similar cytokines which have overlapping roles and result in a degree of redundancy. These include IL-11, IL-27, IL-31, and cardiotrophin-1 (762). This explains why blocking IL-6 does not lead to a complete inability to respond effectively to acute challenges from pathogens or to mount an acute-phase response to such challenges. Without such redundancy, the risk of inhibiting IL-6 would be high and would likely far outweigh any benefit.

### Available Anti-IL-6 Agents

IL-6 pathway inhibitors that have reached the market include tocilizumab and sarilumab (monoclonal antibodies directed against the IL-6 receptor) and siltuximab, an antibody directed against circulating IL-6 itself. Several other IL-6 inhibitors are in clinical trials currently, including satralizumab, clazakizumab, sirukumab, and olokizumab.

Tocilizumab is a humanized IgG1 monoclonal antibody (763); the complementarity-determining regions of these antibodies are produced in mice and then grafted onto human IgG1 to make them less immunologically foreign. Tocilizumab binds to the 80-kDa component of the IL-6R, which prevents dimerization with gp130 and, hence, signal transduction. IL-6 receptors can circulate in a soluble form, as well as be membrane bound, and tocilizumab can bind to both forms. Sarilumab is also a humanized monoclonal antibody, and siltuximab is a mouse-human chimeric IgG1 monoclonal antibody. Sarilumab has the same mechanism of action as tocilizumab, but siltuximab works by binding to IL-6 itself, thus preventing it from activating the IL-6R.

Tocilizumab is approved for the treatment of rheumatoid arthritis (RA) resistant to first-line nonbiological disease-modifying antirheumatoid drugs (DMARDs), such as methotrexate or leflunomide. It is often reserved for those who have not responded to TNF inhibitors (i.e., as second-line biological therapy) but is approved for use as first-line biological therapy if clinicians choose to do so. Multiple RCTs have shown that tocilizumab is effective in reducing the activity of RA (764, 765). A meta-analysis including data from RCTs enrolling 3,334 patients found that RA patients receiving tocilizumab at 8 mg/kg intravenously every 4 weeks were more likely to show a 50% improvement in disease activity on the ACR50 score than those receiving placebo, with both groups also receiving methotrexate (39% versus 10% response rates, respectively) (766). It is given as an intravenous infusion every 4 weeks or as a subcutaneous injection every 1 or 2 weeks. Tocilizumab is also approved for use in giant cell arteritis, juvenile idiopathic arthritis, and CAR-T cell-induced cytokine release syndrome, although there are fewer supportive data under these conditions. Sarilumab is approved for use in adults with RA resistant to DMARDs. Siltuximab is FDA approved for use in the rare

condition multicentric Castleman's disease without HIV or human herpesvirus 8 (HHV-8) infection.

Successful off-label use of tocilizumab has been reported in neuromyelitis optica spectrum disorders (767), Crohn's disease (768), systemic lupus erythematosus (769), and adult-onset Still's disease (770). Siltuximab appears to have an emerging role in the treatment of multiple myeloma (771–773).

### IL-6 Pathway Inhibitors: Infectious Complications

The great majority of data examining the risk of infectious complications following IL-6 blockade relate to tocilizumab, since it has been on the market for longer than the others. What data do exist for other IL-6 inhibitors suggest that their infectious risks are very similar to that of tocilizumab (774–776); hence, the remainder of this section will deal principally with tocilizumab.

Most RCTs comparing tocilizumab with placebo, on a background of methotrexate with or without prednisone use, have shown a small but significant excess of infections in those receiving tocilizumab. These are mostly common viral and bacterial infections, principally upper and lower respiratory tract infections. A meta-analysis including data from six RCTs in 3,501 patients showed the odds ratio for any infection in the tocilizumab group compared with the placebo group to be 1.30 (95% CI, 1.07 to 1.58) for 8 mg/kg/dose and 1.20 (95% CI, 0.81 to 1.46) for 4 mg/kg but the risk of serious infection to be not significantly different from the risk with placebo (OR = 0.83 [95% CI, 0.28 to 2.50] for 4-mg/kg dose; OR = 2.33 [95% CI, 0.88 to 6.13] for 8 mg/kg dose) (777). In the largest component RCT, the TOWARD trial, 1,220 patients were randomized to tocilizumab at 8 mg/kg or placebo every 4 weeks for 24 weeks, with a stable background DMARD regimen (mostly methotrexate) (764). "Any infections" occurred in 37% of the tocilizumab group and 32% of the control group; these were mostly upper respiratory tract infections or cellulitis and resolved with antibiotics and continuation of tocilizumab. "Serious infections" (defined as above) occurred in 2.7% of the tocilizumab group and 1.9% of the placebo-plus-DMARD group. These serious infections were mostly cellulitis ($n = 5$), pneumonia ($n = 3$), and shingles ($n = 3$). There were no cases of tuberculosis. Of note, none of these infections were with organisms usually considered "opportunistic."

Longer-term follow-up and postregistration data tell a similar story. A meta-analysis including data from five RCTs of tocilizumab and their open-label extension phases examined adverse effects in 4,211 patients with approximately 5 years of follow-up. The rate of serious infections was 4.5 per 100 patient years in over 12,000 patient years of data (778). A more recent postmarketing study analyzed data from U.S. Medicare claims from 2010 to 2015 and the MarketScan database from 2011 to 2015 (779) to examine the relative risk of infection with tocilizumab compared with TNF inhibitors. In this study, 16,074 patients receiving tocilizumab were matched using propensity scores with 33,109 receiving TNF inhibitors. The risk of any serious infection (defined as one requiring hospitalization) was no different, but tocilizumab was associated with higher risks of serious bacterial infection (HR = 1.19), skin and soft tissue infection (HR = 2.38), and diverticulitis (HR = 2.34). The actual risk of any serious bacterial infection in those taking tocilizumab was 3.95 events per 100 person years (779).

In contrast to other biological agents, such as rituximab or TNF inhibitors, flares of chronic viral hepatitis do not seem to be increased with tocilizumab use. Moreover, case reports suggest it may be safe to treat patients with chronic hepatitis B infection (780), hepatitis C infection (781), and isolated HBcAb positivity (782) without previous or concomitant antiviral therapy. Reactivation of latent tuberculosis also does not appear to be associated with tocilizumab use (783). An *in vitro* study provides a potential explanation for this observation: when human whole blood was incubated with tuberculosis antigens in the presence of various biologic agents, the production of interferon gamma by lymphocytes was inhibited by etanercept and infliximab, but tocilizumab had no effect (784). Reactivation of latent herpesvirus infections also appears to be rare in those receiving tocilizumab and probably not attributable to it.

While there are occasional case reports (785, 786), there is no evidence the risk is higher than that in the background population (185). In fact, tocilizumab use in adults with RA either has no effect or leads to a decrease in plasma viral loads of herpesviruses, including EBV and CMV (296, 787).

### IL-6 Pathway Inhibitors: Prevention of Infectious Complications

Given the documented risk of common bacterial infections (especially respiratory and skin), the skin and lung health of the patient should be optimized prior to beginning therapy with IL-6 pathway inhibitors. This includes evaluating and treating for any current skin infections (e.g., furunculosis and scabies) or comorbid conditions (e.g., xerodermatitis and eczema). If there is a history of previous recurrent skin abscesses, decolonization for *Staphylococcus aureus* should be undertaken (1 week of nasal mupirocin plus chlorhexidine body washes). Vaccinations should be up to date, especially for influenza, pneumococcus, and *Haemophilus influenzae*. Live vaccines should be avoided once IL-6 antagonists have been initiated. Upper respiratory tract infectious syndromes like pharyngitis, mucopurulent bronchitis, and sinusitis are usually not recommended to be treated with antibiotic therapy due to the minimal benefit. However, in those receiving IL-6R inhibitors, these syndromes should be treated early with antibiotic therapy to avoid progression to severe or complicated infection. The European Society for Clinical Microbiology and Infectious Diseases guidelines (587) recommend testing for latent tuberculosis infection (LTBI) and hepatitis B virus (HBV) infection prior to IL-6 pathway inhibitor therapy (as for TNF inhibitors). The existing data do not support this recommendation; however, since IL-6 inhibitors are generally used in combination with other immunosuppressive agents, it is reasonable to recommend LTBI and HBV testing, but it is probably not justified prior to IL-6 pathway inhibitor monotherapy. It is important to alert the patient and their caring doctors that the usual inflammatory response may be blunted if there is an invasive bacterial infection (for example, fever may be low or absent, and CRP may be normal). This, along with the fact that rare infectious complications may not have been detected with existing data, means that a high index of suspicion for infection should be maintained in those on anti-IL-6 therapy.

### IL-6 Pathway Inhibitors: Summary

In summary, IL-6 pathway inhibitors are associated with a moderately increased risk of common bacterial and viral infections, particularly of the respiratory tract and skin. The risk of such infections in postmarketing surveillance is approximately 4 per 100 patient years. The risk of opportunistic infections (fungal, mycobacterial, and viral) appears to either be not increased at all or increased by such a small margin that the effect has not been detected thus far.

## IL-12/IL-23 PATHWAY INHIBITORS

### Role of the IL-12/IL-23 Pathway

IL-12 and IL-23 are key cytokines in adaptive immunity, driving T cell differentiation and immune response. These two cytokines are primarily produced by activated antigen-presenting cells, including dendritic cells, monocytes, and macrophages, and IL-12 is also produced by neutrophils (788). They selectively drive immune responses affecting NK cell, Th17 cell, and Th1 cell activation, typically in concert with other cytokines, including TGF-$\beta$ (788, 789). NK, Th17, and Th1 cell activation mediates a nuanced response with downstream effects on vasodilation, neovascularization, endothelial cell activation, lymphocyte recruitment, and tissue remodeling and specific proinflammatory effects with production of inflammatory cytokines, including IL-17, IFN-$\gamma$, GM-CSF, and TNF-$\alpha$ (788, 789). Cytokines in this pathway share a heterodimeric structure and have common elements. IL-12 and IL-23 share a p40 element. IL-12 and IL-35 share a p35 element. IL-23 and IL-39 share a p19 element. Activation of this pathway is pivotal in the pathogenesis of psoriasis and inflammatory bowel disease.

**TABLE 12** Available agents inhibiting the IL-12/IL-23 pathway

| Agent | Nature | Target/mechanism | Indication(s) |
|---|---|---|---|
| Ustekinumab | Human IgG1 MAb | P40 subunit of IL-12 and IL-23 | Moderate to severe plaque psoriasis, active psoriatic arthritis, treatment-resistant Crohn's disease |
| Risankizumab | Humanized IgG1 MAb | P19 subunit of IL-23 | Moderate to severe plaque psoriasis |
| Tildrakizumab | Humanized IgG1 MAb | P19 subunit of IL-23 | Moderate to severe plaque psoriasis |
| Guselkumab | Human IgG1 MAb | P19 subunit of IL-23 | Moderate to severe plaque psoriasis |

### Available Inhibitors of the IL-12/IL-23 Pathway

Ustekinumab targets the p40 subunit of IL-12 and IL-23, whereas risankizumab, tildrakizumab, and guselkumab target the p19 subunit of IL-23 (Table 12) (790, 791). Of note, these anticytokine antibodies block receptor binding and do not bind to interleukin after it is bound to the receptor. The antibodies therefore cannot contribute to complement- or cell-mediated cytotoxicity of cells expressing these receptors.

Targeting the IL-12 and IL-23 pathway has proven an effective strategy in the management of psoriasis, psoriatic arthritis, and Crohn's disease and is being studied for effectiveness in ankylosing spondylitis (792). Off-label indications have included pyoderma gangrenosum and hidradenitis suppurativa (793–795).

Ustekinumab, the first agent in this group, is a human IgG1($\kappa$) monoclonal antibody that targets the common p40 subunit of IL-23 and IL-12. Ustekinumab blocks the binding of human IL-12 and IL-23 to their specific receptor complex on the surface of NK cells and T cells, hence neutralizing IL-12 and IL-23 cell signaling and activation. Studies inhibiting specifically the IL-12 p35 subunit and the IL-23 p19 subunit have suggested that IL-23 mediates most of the disease pathology attributed to the IL-12/IL-23 pathway. Highlighting this issue, the IL-23R R381Q gene variant (encoding a change of R to Q at position 381) that protects against psoriasis, Crohn's disease, and ankylosing spondylitis exerts its protective effect by selectively attenuating the IL-23-induced Th17 effector cell function (796, 797).

Guselkumab is a fully human immunoglobulin G1-lambda monoclonal antibody that binds the p19 subunit of human IL-23. Early dose-finding and phase II studies showed guselkumab to have promising safety and efficacy in plaque psoriasis, with a trend to superior efficacy compared to that of adalimumab (798, 799). Subsequently, the Voyage 1 and 2 trials also suggested superior efficacy for guselkumab over adalimumab in psoriasis. The two antibodies had similar side effect profiles (800, 801).

Risankizumab is a fully human IgG monoclonal antibody to the p19 subunit of IL-23. Early studies have suggested a side effect profile similar to those of other agents targeting the IL-12/IL-23 pathway in plaque psoriasis, though the data and follow-up are more limited (802–807). In the UltIMMa-1 and -2 drug licensing trials, risankizumab was compared with placebo and ustekinumab in plaque psoriasis. Risankizumab proved significantly more effective than ustekinumab and placebo, with comparable rates of adverse events.

Tildrakizumab is a humanized IgG1 monoclonal antibody to the p19 subunit of IL-23. Two phase III trials in chronic plaque psoriasis were reported in 2017 (reSURFACE 1 and 2), in which tildrakizumab was compared to placebo and etanercept therapy (808). The most common adverse event in both trials was nasopharyngitis. Tildrakizumab led to at least a 75% improvement in 64% of patients after 12 weeks, compared with 48% treated with etanercept and 6% treated with placebo (808).

### IL-12/IL-23 Pathway: Risk of Infectious Complications

Because the IL-12/IL-23 pathway is important in the activation of T cells and NK cells, inhibiting the IL-12 and IL-23 pathways would be expected to increase the risk of infection from intracellular pathogens. However, to date, mycobacterial and other infections with intracellular organisms have not been seen at higher frequencies in those treated with IL-12/IL-23 inhibitors. This will need to be monitored long term, since such infections have been reported in individuals congenitally deficient in the

IL-12 P40 subunit and IL-12R$\beta$1 (809–812). Also, the indirect effects of these agents on the IL-17 pathway theoretically could be expected to increase the risk for fungal infection, as inherited deficiency and antibody-mediated IL-17 blockade are associated with chronic mucocutaneous candidiasis and increased fungal infection (813–815).

The safety and efficacy of ustekinumab in moderate to severe plaque psoriasis have been explored in three large randomized controlled trials (816–818) and a number of smaller phase II trials (819–822). Studies in psoriatic arthritis (823–826) and Crohn's disease (827–830) have also been conducted. Of note, pretreatment screening for latent tuberculosis infection (LTBI) was included in most of these trials, and patients diagnosed with LTBI were either treated with chemoprophylaxis or excluded. Those with active tuberculosis were excluded. A study of 167 patients diagnosed with LTBI and then started on ustekinumab showed no breakthrough infections on therapy and no increase in the rate of toxicity from isoniazid prophylaxis (831). Serious and opportunistic infections were rare in these trials and mainly occurred in those that included patients on standard immunosuppressive regimens. To summarize, adverse events with ustekinumab therapy were generally mild and nonserious and did not require treatment adjustment across these trials. There was no significant difference between patients and controls in terms of serious infection or malignancy. The most common adverse incidents were upper respiratory tract infection, nasopharyngitis, headache, and arthralgia. Three- and 5-year follow-up studies of the safety and efficacy of ustekinumab have been reported, and to date, no major safety or serious infection issues have been identified compared to their occurrence in patients on conventional immunosuppressive regimens (832–836). Indeed, some suggest that ustekinumab has a lower rate of serious infections than adalimumab and infliximab therapy (836). However, viral and other intracellular pathogens remain a potential concern. Hepatitis B virus screening is recommended before therapy, as reactivation of hepatitis B virus has been reported in HBsAg-positive but not HBcAb-positive HBsAg-negative patients (837, 838). A few cases of herpes zoster have been reported in ustekinumab-treated subjects; however, the significance of this is unclear given frequent concomitant immunosuppressive therapy and the lack of a control cohort (839–842). A more recent longitudinal analysis of 10,000 patients in the psoriasis longitudinal registry showed no association between ustekinumab therapy and herpes zoster (842).

Trials of guselkumab had similar findings. Nasopharyngitis and upper respiratory tract infection were the most commonly reported adverse events and occurred at comparable frequencies across adalimumab, guselkumab, and placebo groups (800, 801, 843). The serious infection rate was low in both trials, and there was no difference between groups. Again, it is worth noting that those with a history or evidence of active tuberculosis were excluded from these trials, and there were no incident cases of tuberculosis reported in the trial. A later trial of guselkumab in patients failing therapy with ustekinumab showed similar rates of adverse events, with nasopharyngitis and upper respiratory tract infections being the most common (844). More recent trials have focused on patients with pustular and erythrodermic psoriasis and psoriatic arthritis and have had safety and infection risk results similar to those of trials in plaque psoriasis (843, 845, 846).

Risankizumab has been assessed for treatment of plaque psoriasis in two phase III registrational trials (804, 807). Across the two studies, infectious events were more frequently reported in patients receiving risankizumab and ustekinumab than in controls, mainly viral upper respiratory tract infection, upper respiratory tract infection, and diarrhea (804). A trial by Feagan et al. studied 121 patients with moderate to severe Crohn's disease, 93% of whom had been previously treated with anti-TNF therapy. Conventional therapy for Crohn's disease was continued through the study. No dose-related increase of adverse events was noted for subjects treated with risankizumab, and the most common adverse events were nausea and worsening of Crohn's disease (803).

In the two phase III registrational trials of tildrakizumab (RESURFACE 1 and 2), severe adverse events were no different between the placebo, tildrakizumab, and etanercept

groups (808). The incidences of severe infection, malignancy, and cardiovascular events were low and similar across patient groups (808). In a follow-up study specifically addressing safety issues in the phase II and III trials, exposure-adjusted infection frequency rates were lower for tildrakizumab than for placebo or etanercept (847). Candida skin infection occurred in the patient cohorts at frequencies of 0.1%, 0.3%, 0.0%, and 0.0% for tildrakizumab at 100 mg and 200 mg, placebo, and etanercept, respectively (847). Long-term extension studies after 148 weeks of use in the RESURFACE 1 and 2 cohorts revealed an ongoing low risk of severe infections of 1.1 per 100 patient years (848).

### IL-12/IL-23 Pathway Inhibitors: Prevention of Infectious Complications

Antiviral prophylaxis is recommended in hepatitis B virus surface antigen-positive patients (587, 837, 838, 849–851). Screening for latent and active tuberculosis prior to therapy is also recommended; if patients are at high risk of *M. tuberculosis* exposure during treatment, further tuberculosis screening may be appropriate. Standard guideline-based vaccinations should be provided to patients prior to therapy. Though live virus vaccines are relatively contraindicated during therapy on theoretical grounds, data addressing the question are needed before clear guidance can be offered (587).

### IL-12/IL-23 Pathway Inhibitors: Summary

In summary, the agents that target the IL-12/IL-23 pathway have similar side effect profiles and theoretically share similar risks for infectious complications from therapy. To date, the available data do not suggest an increased risk of serious infection, but there does appear to be a modest risk of upper respiratory tract infections. The risks of reactivation of tuberculosis and chronic HBV infection have not been fully characterized, and it is possible that the risk of these events is also modestly increased in patients treated with IL-12/IL-23 pathway inhibitors.

## IL-17-TARGETED AGENTS

### Role of the IL-17 Pathway

The IL-17 family consists of six cytokines (IL-17A through IL-17F). IL-17A and IL-17F, the best studied of these cytokines, form homo- and heterodimers that signal through a dimeric IL-17 receptor, IL-17RA/IL-17RC (852–855). Subsequent studies have shown that IL-17A, the most potent of the cytokines, is also produced by CD8 T cells, natural killer T cells, mast cells, and neutrophils. Other IL-17 family members are also expressed by Th2 cells and epithelial cells and bind to other IL-17 receptor species to mediate their actions (856, 857). IL-17 is an important mediator of inflammation, having roles in both host immune defense from extracellular pathogens and autoimmune disease pathogenesis. During infection, IL-17 enhances bacterial and fungal clearance through inducing antimicrobial peptides, such as defensins, and by enhancing chemokine and proinflammatory cytokine expression to promote local activation of phagocytic cells (856, 858). The importance of the IL-17 pathway in *Candida* infection was first suggested by the presence of chronic mucocutaneous candidiasis in patients with high titers of IL-17 neutralizing antibodies (859, 860). Subsequent genetic studies revealed that patients with functional deficiencies in the IL-17 activation pathway, including autosomal recessive IL-17RA and autosomal dominant IL-17F mutations, develop chronic mucocutaneous candidiasis (861–866). However, such patients do not develop systemic infections, disseminated or invasive candidiasis, or *Mycobacterium tuberculosis* infections at higher than background rates (867, 868). Despite the potent capacity of Th17 cells and the IL-17 pathway, blockade of IL-17A by genetic mutation or broad neutralizing antibodies does not appear to have infectious consequences beyond chronic mucocutaneous candidiasis (868).

IL-17 plays a central role in psoriasis pathogenesis, driving keratinocyte activation and proliferation, local chemokine expression, and recruitment of inflammatory cells to the psoriatic lesion. IL-17 is also highly expressed in the synovium of patients with

**TABLE 13** Available agents inhibiting the IL-17 pathway

| Agent | Nature | Target/mechanism | Indication(s) |
|---|---|---|---|
| Secukinumab | Human IgG1 MAb | IL-17A | Moderate to severe plaque psoriasis, active psoriatic arthritis, ankylosing spondylitis |
| Ixekizumab | Humanized IgG4 MAb | IL-17A | Moderate to severe plaque psoriasis, active psoriatic arthritis |
| Brodalumab | Human IgG2 MAb | IL-17 receptor | Moderate to severe plaque psoriasis |

rheumatoid arthritis and is likely an important driver of the inflammatory cascade (869, 870).

### Available Anti-IL-17 Agents

Available anti-IL-17 agents are shown in Table 13. In general, IL-17 blockade has proved effective in the management of plaque psoriasis, and studies continue in psoriatic arthritis and spondyloarthritides (871–873). In contrast, IL-17 blockade has proven ineffective in Crohn's disease and may even worsen the condition (814). In rheumatoid arthritis, blockade of IL-17 has shown modest benefits compared to those of other biologics, such as TNF inhibitors, tofacitinib, and abatacept (874–876).

Secukinumab, a fully humanized IgG1($\kappa$) antibody, and ixekizumab, a humanized IgG4 antibody, both target IL-17A, blocking the actions of IL-17A and IL-17A/F heterodimers. Brodalumab, a fully human IgG2 antibody, targets the IL-17RA molecule. By targeting the receptor, brodalumab blocks not only IL-17A and IL-17A/F heterodimer action but also IL-17F and IL-17E, which also bind to IL-17RA. All three antibodies are given by subcutaneous injection. All three have shown efficacy in plaque psoriasis and have been approved for use, with secukinumab and ixekizumab (873, 877–879) receiving further licensure for use in psoriatic arthritis and secukinumab the further indication of therapy for ankylosing spondylitis (871, 872, 880–886). Secukinumab has been the most extensively studied therapy, though the efficacy and safety profiles of all three agents are similar. Suicides among participants in the early trials of brodalumab were above the expected number, resulting in a black box warning, though subsequent study has suggested the association is random rather than causal (887–889).

### IL-17 Inhibitors: Infectious Complications

Specific issues that have been explored across most trials of IL-17 pathway inhibitors include the potential for the development of Crohn's disease, candidiasis, neutropenia, cardiovascular disease, and malignancy (890–892). No significant infectious safety signal was identified in early placebo-controlled trials, with common side effects of nasopharyngitis, headache, arthralgia, bronchitis, injection site reaction, and upper respiratory tract infection occurring in at least 5% of patients (873, 877, 879, 893). Three- to 5-year follow-up studies have not suggested any newly recognized toxicities, and withdrawal from therapy was relatively rare, with most side effects mild to moderate in severity and similar in frequency and character to those seen in short-term trials (871, 877, 880, 894, 895). Candidiasis has been shown to occur at a higher frequency, but this has not resulted in therapy discontinuation, resistant candidiasis, or significant morbidity. In a recent review of the published trials, the rates of mucocutaneous candidiasis were reported as 4.0% for brodalumab, 1.7% for secukinumab, and 3.3% for ixekizumab, contrasting with rates of 0.3% for placebo, 2.3% for ustekinumab, and 0.8% for etanercept (896). The *Candida* infections in these trials have typically been mucosal and of mild severity, resolving spontaneously or with simple therapy (896–899). The development of inflammatory bowel disease remains a concern in patients on anti-IL-17 therapy, after early reports of exacerbation of Crohn's disease with these drugs (814, 900). A recent analysis of 4,209 patients (6,480 exposure years of therapy) from seven trials of ixekizumab therapy showed that inflammatory bowel disease was rare, developing in $<$1% of patients (901).

The recent COAST-V trial enrolled 341 patients with spondyloarthritis to receive either ixekizumab (dosing at 2- or 4-week intervals), adalimumab, or placebo in a 1:1:1:1 ratio for 16 weeks. Mild neutropenia was noted in all three active therapy arms, though

there were no associated infectious complications (rates of 24% for adalimumab, 14% for ixekizumab at 2-week intervals, 11% for ixekizumab at 4-week intervals, and 3% for placebo). There were no opportunistic infections, no deaths, and only one case of candidiasis occurring in a patient receiving adalimumab (873). Data from longer-term treatment studies are similar. In the 3-year study UNCOVER-3, 156 patients with plaque psoriasis received continuous ixekizumab after a 16-week introductory randomized period of therapy with ixekizumab (50%), etanercept (25%), or placebo (25%). The most common infectious complication over this time was viral upper respiratory tract infection. Grade 3 and 4 neutropenia was noted in 0.8% of subjects. No opportunistic infections or cases of tuberculosis were noted (877). The SCULPTURE extension study assessed continuous secukinumab therapy over 5 years in moderate to severe psoriasis and showed low but consistent rates of around 5% per annum for headache, nasopharyngitis, upper respiratory tract infection, and back pain, as in previous short-term studies. Among the 126 participants who remained on therapy for 5 years (75% of the initial cohort), there were nine cases of *Candida* infection among five subjects, none serious or persistent. There were no episodes of opportunistic infection or tuberculosis (880). Brodalumab is the least studied of the three antibodies targeting the IL-17 pathway. In short-term trials, it has shown a similar side effect profile, with headache, nasopharyngitis, and upper respiratory tract infections the most common side effects, with a low rate of neutropenia again noted. Neutropenia resolved without incident in these studies but is an issue to watch as the use of these agents increases (902–907).

### IL-17 Inhibitors: Prevention of Infection

Because patients with active tuberculosis were excluded from trials and those with latent tuberculosis were usually treated for it, screening for and treatment of latent tuberculosis infection is recommended prior to anti-IL-17 therapy. History and physical examination should seek current or recent oral, genital, or cutaneous *Candida* infections, and if present, these should be treated prior to beginning anti-IL-17 therapy. In view of the slightly increased risk of upper respiratory tract infections, respiratory health should be optimized and annual influenza vaccine given.

### IL-17 Inhibitors: Summary

In summary, IL-17 therapy appears to be associated with a low risk of serious infections. Mucocutaneous candidiasis (but not invasive candidiasis), upper respiratory tract infections, and mild neutropenia occur at higher rates than with placebo. Current data are limited to 5 years of follow-up, so uncommon toxicities may yet become apparent.

## TYROSINE KINASE INHIBITOR OVERVIEW

Tyrosine kinases are a family of enzymes involved in the initial steps of intracellular signaling cascades in response to an extracellular messenger, such as an interleukin or an immune effector cell (Fig. 3). Their role is to phosphorylate their target protein and initiate or perpetuate a signaling cascade within the cell, leading to cell growth, transformation, activation, or apoptosis. Inhibitors of these enzymes are generally small molecules (that are capable of entering cells) and are also known as "targeted therapies" because of their specific mechanisms of action (908). Tyrosine kinases are often selectively overexpressed in malignancies due to point mutations or chromosomal rearrangements. Hence, tyrosine kinase inhibitors (TKIs) have mostly been developed for the treatment of malignancies. Unlike monoclonal antibodies, TKIs have good oral bioavailability and so can be administered orally (usually at least daily) rather than subcutaneously or intravenously, as the monoclonal antibodies are (2-week to yearly intervals) (909). Drug-drug interactions (due partially to cytochrome P450 interactions) are also an issue for TKIs that most monoclonal antibodies do not share (910). Over 20 TKIs have reached the market for the treatment of malignancies. Those which have the potential to lead to infectious complications are discussed in the following sections, and their indications are summarized in Table 14.

**TABLE 14** Individual and class overview of tyrosine kinase inhibitor drugs

| Class | Drug | Approved indication(s) |
|---|---|---|
| JAK inhibitors | Tofacitinib | Rheumatoid arthritis, psoriatic arthritis, ulcerative colitis |
| | Baricitinib | Rheumatoid arthritis |
| | Ruxolitinib | Myelofibrosis, polycythemia rubra vera |
| BTK inhibitors | Ibrutinib | Chronic lymphocytic leukemia, small lymphocytic lymphoma, mantle cell lymphoma, Waldenstrom's macroglobulinemia, marginal zone lymphoma, chronic graft-versus-host disease |
| | Acalabrutinib | Mantle cell lymphoma |
| PI3K inhibitors | Idelalisib | Chronic lymphocytic leukemia, small lymphocytic lymphoma, follicular lymphoma |
| | Copanlisib | Follicular lymphoma |
| BCR-ABL inhibitors | Imatinib | $Ph^+$ chronic myeloid leukemia, $Ph^+$ acute lymphoblastic leukemia, $PDGFR^+$ myelodysplasia or myeloproliferative disorder, chronic eosinophilic leukemia, hypereosinophilic syndrome, aggressive systemic mastocytosis with eosinophilia, gastrointestinal stromal tumor |
| | Dasatinib | $Ph^+$ chronic myeloid leukemia, $Ph^+$ acute lymphoblastic leukemia |
| | Nilotinib | $Ph^+$ chronic myeloid leukemia |
| | Ponatinib | $Ph^+$ or T3151 mutant chronic myeloid leukemia or acute lymphoblastic leukemia |
| | Bosutinib | $Ph^+$ chronic myeloid leukemia |
| Spleen TKIs | Fostamatinib | Chronic immune thrombocytopenia |
| ALK inhibitors | Crizotinib | $ALK^+$ or $ROS1^+$ advanced non-small cell lung cancer |
| | Ceritinib | $ALK^+$ advanced non-small cell lung cancer |
| | Alectinib | $ALK^+$ advanced non-small cell lung cancer |
| | Brigatinib | $ALK^+$ advanced non-small cell lung cancer |

## JAK INHIBITORS

### JAKs: Structure and Mechanism of Action

Janus-associated kinases (JAKs) are a family of four non-receptor protein tyrosine kinases, JAK1, JAK2, JAK3, and tyrosine kinase-2 (760), which mediate downstream signaling of cytokine receptors (759). JAK pathways are involved in the growth, survival, development, and differentiation of a variety of cells but are crucial to the function of immune and hematopoietic cells (911). Each JAK protein has specificity for a different set of cytokine receptors, and cytokine signaling via JAK pathways leads to further induction of inflammatory gene expression, continuing the loop of inflammatory signaling (911).

### JAK Inhibitors: Available Agents

The currently available JAK inhibitors and their indications are summarized in Table 14. Tofacitinib is a reversible competitive inhibitor of JAK1, JAK2, and JAK3 that has been shown to inhibit lymphocyte proliferation and the production of cytokines and to affect the maturation of human monocyte-derived dendritic cells and their capacity to stimulate T cells (912, 913). Data suggest that tofacitinib inhibits the survival of plasmacytoid dendritic cells and interferon alpha production and also suppresses antiviral effects of interferon alpha signaling, possibly contributing to an increased risk of viral infections in patients receiving tofacitinib (914). Tofacitinib has also been shown to inhibit IL-4-dependent Th2 cell differentiation and interfere with Th17 cell differentiation, as well as to prevent the activation of STAT-1 and subsequent generation of Th1 cells and to modulate innate immune responses (915). Tofacitinib is approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of rheumatoid arthritis (RA) and psoriatic arthritis (916, 917). It has also been used off-label for plaque psoriasis (918, 919).

Baricitinib is a selective and reversible inhibitor of JAK1 and JAK2 (920) that has been shown to suppress the differentiation of plasmablasts, Th1, and Th17 cells, in addition to affecting innate immunity, such as the T cell stimulatory capacity of dendritic cells (921). It is currently approved for use in RA (922–924). It has also been investigated for

**TABLE 15** Summary of the risk of infectious complications of JAK inhibitors

| Drug | Type of infection | No. of events/100 PY (reference[s]) with: | | % of patients (reference[s]) receiving: | |
|---|---|---|---|---|---|
| | | Drug | Placebo | Drug | Placebo |
| Tofacitinib | All serious infections | 3.1 (937), 2.7 (1248), 3.0 (1249), 2.6 (1250) | | | |
| | Herpes zoster | 2.6 (1251), 4.3 (937), 3.9 (1248), 3.9 (1252) | | 3.6 (1251) | |
| | Tuberculosis | 0.2 (1253), 0.2 (1254), 0.2 (1248) | | 0.2 (1253), 0.2 (1254), 0.2 (1248) | |
| Baricitinib | All serious infections | | | 3 (1255), 1–2 (1256), 2 (1257) | 3 (1255), 1 (1257) |
| | Herpes zoster | 2.5 (1258) | | 4 (1255), 1–2 (1256), 2 (1257) | 1 (1255), 0.4 (1257) |
| Ruxolitinib | All serious infections | | | 2–6 (1258), 4–6 (1259) | |
| | Herpes zoster | 3.5 (1260), 5.3 (1261) | 1.0 (1260) | 6.4 (1261) | 0 (1261) |
| | Tuberculosis | | | 1 (1262) | |

off-label use in systemic lupus erythematosus (SLE) (925) and autoinflammatory interferonopathies (926). Ruxolitinib is an inhibitor of JAK1 and JAK2 and is approved for the treatment of myelofibrosis and polycythemia vera (PCRV) (927–929). The gain-of-function JAK2 V617F mutation, leading to increased signal transduction and activator of transcription STAT-3 and STAT-5 activity, is present in more than 95% of patients with PCRV and in 50 to 60% of patients with myelofibrosis (930, 931).

Several more JAK inhibitors are under development. Filgotinib is a JAK inhibitor that is selective for JAK1, as opposed to tofacitinib (JAK1, JAK3, and to a lesser extent JAK2) and baricitinib (JAK1 and JAK2). It has recently completed a phase III trial for rheumatoid arthritis (932), with several more under way, but it is not yet approved for clinical use. Filgotinib is also being investigated for use in ankylosing spondylitis (933), psoriatic arthritis (934), and inflammatory bowel disease (935). Peficitinib and upadacitinib are other selective JAK inhibitors in early-phase clinical trials for the treatment of rheumatoid arthritis. It is hoped that the narrower specificities of these newer agents will be associated with lower risks of infectious complications, but this remains to be seen and will need postmarketing data and head-to-head RCTs against other JAK inhibitors to determine.

### JAK Inhibitors: Infectious Complications

JAK inhibitors have been shown to exert effects on T cells, natural killer (NK) cells, and dendritic cells. Reductions in helper T cell number and function, inhibition of T cell proliferation, impairment of NK cell maturation, and interference with dendritic cell function have been observed in patients receiving JAK inhibitors and may be responsible for infectious complications (760). However, data investigating changes in lymphocyte subsets in patients with rheumatoid arthritis (RA) receiving baricitinib suggest that changes in B and T cell numbers during treatment are modest and are not the primary cause for the observed increased risk of serious infections (936). The risks of infectious complications of available JAK inhibitors are summarized in Table 15.

**Tofacitinib.** A review of pooled data from phase II/III and long-term extension studies of tofacitinib in 4,789 patients with RA (8,460 patient years of exposure) reported an overall rate of serious infection of 3.1 events per 100 patient years (937). The most common serious infection was pneumonia, but skin and soft tissue infections were also frequently reported. Independent risk factors for serious infection included age $\geq$65 years, prednisolone dose $\geq$7.5 mg, presence of diabetes, and tofacitinib dose of 10 mg twice daily. The risk of serious infection did not increase over time. Long-term follow-up (up to 8.5 years) of this clinical trial cohort reported a serious infection incidence rate of 3.09 events per 100 patient years.

### JAK Inhibitors: Prevention of Infectious Complications

Consideration of herpes zoster vaccination with either the live or a recently available recombinant vaccine (938) is suggested in patients with positive varicella zoster virus (VZV) serology or with a history of previous chickenpox at baseline, prior to the commencement of JAK inhibitors (939). Limited data suggest that use of the live herpes zoster vaccine may be safe if given 2 to 3 weeks prior to commencement of tofacitinib

in patients with documented previous VZV infection (940). The adjuvanted recombinant zoster vaccine appears to be immunogenic and safe in immunocompromised patients based on early trials (941). Screening for (and treatment of) latent tuberculosis and hepatitis B are also advised in all patients before commencement of JAK inhibitors (942, 943).

### JAK Inhibitors: Summary

JAK inhibitors are associated with a substantial risk of mild infections, such as upper respiratory tract infections (in up to 50% of patients in some trials), and a small but consistently observed risk of serious infections (of approximately 3 per 100 patient years). There is a strong signal for an increased risk of herpes zoster and, less so, of tuberculosis. There currently exist only limited postmarketing data for baricitinib, and further evidence of infectious complications may emerge with time. In addition, there are very limited data regarding the risk of JAK inhibitors in patients with chronic viral hepatitis and human immunodeficiency virus (HIV), although the increased risk of VZV reactivation suggests that reactivation of chronic viral infections is a theoretical concern. Hepatitis B virus reactivation has been reported on numerous occasions in association with ruxolitinib (944), but patients with chronic viral hepatitis were often excluded from RA JAK inhibitor trials involving tofacitinib and baricitinib, and hence, the risk of hepatitis B flares in these patients is unknown. In addition, the effect of JAK inhibitors on HIV control is unknown.

## BTK INHIBITORS

### BTK: Structure and Mechanism of Action

Bruton's tyrosine kinase (BTK) is a nonreceptor protein kinase expressed in B cells, myeloid cells, mast cells, and platelets (945). B cell receptor (BCR)-mediated signaling via BTK is essential for the activation, proliferation, and survival of B cells (945), and in B cell malignancies, BCR signaling via antigen stimulation or mutation promotes the survival, proliferation, and migration of malignant cells (946). BTK is an important component of the BCR signaling cascade and is critical for the transduction and amplification of signals from the BCR (946). BTK is also involved in chemokine-mediated homing and adhesion of chronic lymphocytic leukemia (CLL) cells to the microenvironment, contributing to their maintenance and proliferation (947). In mice and humans, loss of BTK function results in B cell dysfunction, with hypogammaglobulinemia and a predisposition to infections (947).

### BTK Inhibitors: Available Agents

There are two currently approved agents in this class (Table 14). Ibrutinib is a selective and irreversible inhibitor of the BTK protein. It is approved for the treatment of CLL, small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, marginal zone lymphoma (MZL), and chronic graft-versus-host disease (GVHD) (948–950).

Acalabrutinib is a small molecule irreversible BTK inhibitor granted accelerated approval in 2017 by the FDA for use in MCL on the basis of a phase II study (951). Phase III trials in MCL and CLL are under way. Compared to ibrutinib, acalabrutinib is thought to be more potent and more selective and, therefore, less likely to cause off-target effects mediated through other kinase signaling pathways, including epidermal growth factor receptor (EGFR) family kinases (945). It also has off-label uses in relapsed or refractory CLL.

### BTK Inhibitors: Infectious Complications

CLL is associated with inherent immune dysfunction that predisposes to infections, including defects in the complement system, cell-mediated immunity, and humoral immunity (952). Hence, it is difficult to dissect out the attributable risk of infection due to therapies used for CLL, including BTK inhibitors. Patients with CLL have hypogammaglobulinemia, downregulation of T cell function, and defects in antibody-dependent cellular toxicity (953). These defects lead to cases of VZV and HSV reactivation in

patients with CLL, related to impairments in cell-mediated immunity, and bacterial, particularly respiratory tract or sinobronchial infections, related to hypogammaglobulinemia (952).

**Ibrutinib.** Ibrutinib inhibits signal transduction from the BCR and blocks activation of B cells (954), and infections in patients treated with ibrutinib relate primarily to B cell dysfunction (952). In addition, however, invasive fungal disease (IFD) has frequently been reported in association with BTK inhibitors. It has been postulated that this may result from off-target effects of ibrutinib on other kinases, including IL-2-inducible T cell kinase (ITK) (952, 955). Inhibition of ITK weakens T-helper 2 cell immunity, thereby potentiating T-helper 1 cell immune responses, possibly resulting in the development of opportunistic infections (952). Nuclear factor of activated T cells (NFAT) is also BTK dependent and plays a key role in the macrophage inflammatory response to *Aspergillus fumigatus* (956), potentially contributing to an increased risk of invasive fungal disease.

Phase III studies examining the use of ibrutinib in previously treated CLL/SLL found evidence of frequent and significant infections: 70% of 195 patients with relapsed or refractory CLL/SLL treated with ibrutinib alone developed an infection of any grade in one key study (503). Neutropenia occurred in 22% of patients in this cohort, and upper respiratory tract infections, pneumonia (often severe), and urinary tract infections each occurred in 14 to 17% of patients. Patients with previously treated CLL/SLL in a phase III study receiving ibrutinib in combination with bendamustine and rituximab had similar rates of infection as those receiving bendamustine and rituximab alone (70% in both groups) (957). Frequent infectious complications included upper respiratory tract infections, pneumonia, and febrile neutropenia. The use of ibrutinib as first-line therapy for CLL/SLL has not been clearly associated with an increased incidence of infections in clinical trials, although pneumonia, often severe, did occur in a small number of patients (958). Phase II studies combining ibrutinib with rituximab in patients with high-risk CLL, both previously treated and treatment naive, reported clinically significant respiratory tract infections in 40% of patients over a median of 2 years of follow-up (959). The use of ibrutinib in patients with Waldenstrom's macroglobulinemia refractory to rituximab was associated with infections, most commonly involving the respiratory tract, in 68% of patients in a phase III study, and one case of aspergillosis (960).

Ibrutinib was granted accelerated approval by the FDA in 2017 for use in MZL based on a single phase II study. A multicenter phase II study involving 63 patients with previously treated, relapsed, or refractory MZL administered ibrutinib at 560 mg daily to all patients for up to 3 years (961). The median duration of ibrutinib exposure was 11.6 months, and 19% of patients experienced grade 3 or higher infections, most often pneumonia, which occurred in 8% of patients, and cellulitis, which occurred in 5% of patients.

In postmarketing surveillance, ibrutinib has been linked to a number of serious infections, including invasive fungal disease (IFD). Early reports of IFD complicating ibrutinib therapy were published in 2017, including a series of 18 patients with primary central nervous system (CNS) lymphoma treated with ibrutinib, 7 of whom (39%) developed invasive aspergillosis (962). Of the 18 patients, 2 developed fatal pulmonary and CNS aspergillosis while receiving ibrutinib alone (962). Multiple other cases of invasive aspergillosis in those receiving ibrutinib have been reported in the literature (963–965). The incidence of IFD with the use of ibrutinib has ranged from 0 to 44% in selected case series (966). A multicenter, retrospective French review published in 2018 reported 33 invasive fungal infections in patients treated with ibrutinib alone or in combination for largely relapsed or refractory CLL, MCL, or Waldenstrom's macroglobulinemia (967). Invasive aspergillosis accounted for 82% of cases of IFD, and 41% of these patients had CNS involvement. Other cases of IFD identified in this series included disseminated cryptococcosis, mucormycosis, or *Pneumocystis jirovecii* pneumonia (PJP). The median time between ibrutinib initiation and IFD diagnosis was 3 months (range, 1 to 30). A large number of patients had additional predisposing factors for IFD, including hypogammaglobulinemia, neutropenia, and corticosteroid or rituximab use.

A similar retrospective review of 566 patients receiving ibrutinib for CLL or other hematologic malignancies at a single American center between 2010 and 2016 reported opportunistic infections in 4.1% of patients overall, with a cumulative incidence of 2.3% at 6 months and 4.7% at 5 years of treatment (968). Most (74%) of the observed opportunistic infections were fungal, usually invasive aspergillosis, with additional cases of mucormycosis, cryptococcosis, blastomycosis, and histoplasmosis. Overall, 3% of patients developed IFD. Other reported opportunistic infections in this cohort included *Mycobacterium avium* complex pneumonia, PML, BK virus viruria, and *Toxoplasma* chorioretinitis. Risk factors for opportunistic infections in this patient group included $\geq$3 prior treatments, diabetes, and liver disease. Other reports have been published describing cases of disseminated cryptococcosis (964, 969, 970), fusariosis (971), HBV reactivation (972, 973), *Staphylococcus aureus* meningitis (974), miliary tuberculosis (975), cutaneous mucormycosis (976), amebic encephalitis (977), cutaneous *Mycobacterium chelonae* infection (978), additional cases of disseminated VZV infection (979), and severe pneumonia (980). Several cases of atypical PJP infection have been reported in patients taking single-agent ibrutinib, with an estimated incidence of 2.05 cases per 100 patient years (95% CI, 0.67 to 4.79) (981).

A systematic review of infectious events related to ibrutinib published in 2018 reported infectious complications of any grade in 56% of patients taking single-agent ibrutinib and 52% of patients taking combination therapy (956). Approximately 20% of patients developed pneumonia, and 2% of all patients died from pneumonia, including infections due to opportunistic pathogens such as *Pneumocystis*, *Histoplasma*, *Cryptococcus*, *Nocardia*, and *Aspergillus* species. The most common opportunistic infections were VZV and invasive aspergillosis, followed by PJP. In a series of 13 cases of ibrutinib-associated PJP reported to the FDA Adverse Event Reporting System, 54% of cases occurred in the first 6 months of ibrutinib therapy and seven patients were receiving concomitant immunosuppressive therapy (982). Similarly, a 2017 review of toxicity related to ibrutinib therapy reported an incidence of grade 3 or higher infections of 10 to 13% in treatment-naive patients and 24 to 52% in relapsed/refractory patients in the literature (983). Significantly higher risks for infection in patients with relapsed or refractory disease have also been reported in other reviews (953).

**Acalabrutinib.** Far fewer safety data are available for acalabrutinib than for ibrutinib. Data from phase I and II RCTs suggest that the infection risk profile of acalabrutinib is similar to that of ibrutinib (947, 984). A pooled analysis of safety data from 610 patients in seven clinical trials using acalabrutinib monotherapy in hematologic malignancies was presented at the American Society of Hematology Annual Meeting in 2017 (985). Infections of any grade were reported in 61% of patients, with grade 3 or higher infections occurring in 16.2% of patients, most frequently pneumonia. Grade 3 or higher pneumonia occurred in 5.7% of patients overall. Pneumonia was also the most frequent fatal adverse event, responsible for 27% of deaths in patients receiving acalabrutinib. One fatal case of hepatitis B virus reactivation and one fatal case of aspergillosis also occurred. Opportunistic fungal infections were reported in four patients: one case of grade 2 PJP, two cases of aspergillosis (grade 2 and grade 5), and one case of grade 2 cryptococcal pneumonia. Neutropenia of grade 3 or higher developed in 9.3% of all patients.

### BTK Inhibitors: Prevention of Infection

At present, prophylaxis recommendations for ibrutinib and acalabrutinib are not well defined. Further large-scale evaluation of the risk for PJP and fungal infections in patients receiving ibrutinib and acalabrutinib, with or without other agents, are required to better guide the need for prophylaxis in specific patient groups (953). Influenza and pneumococcal vaccination are recommended prior to the commencement of ibrutinib therapy (986), although the response to these vaccines is significantly impaired in patients with CLL receiving ibrutinib (987–989). The role of anti-infectious prophylaxis is unclear, and it is not routinely recommended; PJP prophylaxis can be considered in patients who have received prior chemoimmunotherapy or who have

other risk factors, including concomitant high-dose corticosteroid use (943, 986). Intravenous immunoglobulin G (IVIG) replacement should be considered in patients with recurrent infections and hypogammaglobulinemia (953). All patients should be screened for serological evidence of hepatitis B virus prior to commencement of ibrutinib, with prophylaxis recommended for patients who are HBsAg positive (953). Ibrutinib can be continued in patients who develop low-grade infections but should be withheld in patients with severe infection until resolved (986).

### BTK Inhibitors: Summary

BTK inhibitors have a substantial impact on B cell function, as well as off-target effects, which leads to a small but clear risk of invasive fungal infections. They are also associated with a high risk of nonserious bacterial infections, particularly respiratory tract infections. Since these drugs are used for hematological malignancies, the exact risk of BTK therapy independent of the underlying malignancy is unclear.

Phase III studies involving acalabrutinib are in progress, and these results may reveal heretofore unknown infectious complications associated with its use. The impact of ibrutinib on control of latent viral infections and hepatitis B virus remains unclear (953). Small numbers of cases of HBV reactivation have been reported in association with ibrutinib therapy, and screening and prophylaxis for HBV infection is recommended prior to treatment (952). The effect of BTK inhibitors in patients with chronic hepatitis C virus or HIV infection is uncertain.

## PI3K INHIBITORS

### PI3K: Structure and Mechanism of Action

Activation of the B cell receptor leads to downstream signaling pathways, including phosphatidylinositol 3-kinase (PI3K), protein kinase B (AKT), and mammalian target of rapamycin (mTOR) (990). The PI3K/AKT/mTOR pathways are key players in proliferation, cell survival, and angiogenesis and are constitutively activated in several B cell malignancies (991). PI3K is a lipid kinase with four different isoforms: alpha, beta, gamma, and delta. Activation of PI3K generates lipid second messengers at the cell membrane that recruit and activate multiple intracellular enzymes that are regulators of cell proliferation, survival, and motility (992). It transmits signals from various surface receptors, primarily the B cell receptor, thereby regulating cellular growth, survival, and migration (943). The gamma and delta isoforms of PI3K are highly restricted to hematopoietic cells, and the delta isoform (PI3K-$\delta$) plays a central role in normal B cell development and function (983, 993).

### PI3K Inhibitors: Available Agents

There are two currently available agents in this class (Table 14), and most of the data on both efficacy and safety apply to idelalisib. Idelalisib is a reversible inhibitor of PI3K-$\delta$ (983) and is approved for use in the treatment of CLL (in combination with rituximab), SLL, and follicular lymphoma (FL) (994–996). PI3K-$\delta$ kinase is hyperactive in B cell malignancies, and its inhibition by idelalisib results in induction of apoptosis, inhibition of proliferation, and inhibition of homing and retention in the lymphoid tissue and bone marrow of malignant B cells (953, 990). Inhibition of PI3K-$\delta$ has also been shown to impair T cell function, including cytokine production, migration, and proliferation in response to stimulation, potentially explaining the increased risk of CMV reactivation associated with PI3K-$\delta$ inhibitors (997). It has been proposed that the impact of idelalisib on $CD4^+$ regulatory T cell function is responsible for some of the immune-mediated toxicities observed in patients receiving idelalisib, including pneumonitis, colitis, and hepatitis (952, 991).

Copanlisib is an intravenous PI3K inhibitor with predominant activity against the PI3K-$\alpha$ and PI3K-$\delta$ isoforms (998). It was granted accelerated approval for use in previously treated, relapsed FL by the FDA in 2017 (999).

### PI3K Inhibitors: Infectious Complications

The risk of infection associated with PI3K-$\delta$ inhibition is complicated by the in-

creased risk of infection seen in patients with CLL even prior to treatment. Factors contributing to infection in patients with CLL include older age, hypogammaglobulinemia, downregulation of T cell function, defects in antibody-dependent cellular cytotoxicity, defective neutrophil and natural killer cell function, and decreased complement activity (953).

**Idelalisib.** An initial phase III study examining idelalisib in combination with rituximab for the treatment of CLL demonstrated that although infectious complications were common, they occurred at similar rates in those taking idelalisib as in patients taking rituximab and placebo (1000). Neutropenia occurred in 55%, fever in 29%, pneumonia in 6%, febrile neutropenia in 5%, sepsis in 4%, and PJP in 3%. In a second phase III study in patients with relapsed, indolent non-Hodgkin lymphoma treated with idelalisib alone, fever occurred in 28%, neutropenia in 27%, and pneumonia in 7% (993). Interim results from a phase III trial comparing the addition of idelalisib or placebo to bendamustine and rituximab in patients with relapsed or refractory CLL demonstrated neutropenia in 60% of patients and febrile neutropenia in 23% of patients in the idelalisib arm (1001). In this cohort, the incidence of all-grade infections was higher in patients receiving idelalisib than in the placebo group (69% versus 59%), and most infections were bacterial, including pneumonia in 14% of patients in the idelalisib group. Other observed infections included herpes zoster, CMV infection (in 6% of patients), PJP (in 2% of patients), and pulmonary mycoses (1001). The combination of idelalisib and ofatumumab, a monoclonal antibody directed against CD20, in previously treated patients with CLL was associated with grade 3 or higher neutropenia in 34% of patients and grade 3 or higher pneumonia in 14% of patients, compared to 16% and 8%, respectively, in patients receiving ofatumumab alone (1002). The most frequently reported serious adverse events in the combination group were pyrexia and pneumonia, which each occurred in 13% of patients. Serious infections occurring more frequently in the combination group than in the ofatumumab-only group included sepsis (11% versus 1%), PJP (5% versus 1%), urinary tract infections (4% versus 0%), and CMV infection (2% versus 0%).

Pneumonia is one of the most common infectious complications associated with idelalisib use, with a reported incidence of approximately 20%; the majority of cases are grade 3 or higher in severity (983). Atypical infections, including PJP and other invasive fungal infections, have also been observed, and noninfectious (autoimmune) pneumonitis is an important differential diagnosis for respiratory tract infections in the setting of idelalisib therapy, with a reported incidence of 3% (1003). A retrospective analysis of the incidence of PJP infection in 2,198 patients receiving idelalisib, with or without other treatments, was presented at the American Society of Hematology Annual Meeting in 2016 (1004). The overall incidence of PJP infection was 2.5% in patients receiving idelalisib, with or without rituximab and with or without bendamustine, compared to 0.2% in patients receiving only rituximab with or without bendamustine (1004). In this cohort, PJP prophylaxis reduced the incidence of infection in patients receiving idelalisib from 3.4% to 1.3%. In clinical trials, the majority of cases of PJP associated with idelalisib occurred in the absence of specific prophylaxis (943). Clinical experience has also revealed evidence of other, often opportunistic infections, including cases of PML (255) and disseminated herpes zoster infection in patients with CLL receiving idelalisib.

Fatal and/or serious infections have been reported in 21 to 48% of patients receiving idelalisib (994), and in March 2016, a warning was issued relating to an increased risk of death, mostly secondary to infections, in patients taking idelalisib in combination with other chemotherapeutic agents (1005). This advice was updated in April 2017 to reflect that these deaths frequently occurred within 180 days of starting treatment and were often due to infection, including sepsis and pneumonia (1006).

**Copanlisib.** Copanlisib is a second-generation intravenous PI3K inhibitor whose predominant activity is against the PI3K-$\alpha$ and PI3K-$\delta$ isoforms (998). It was granted accelerated approval for use in previously treated, relapsed follicular lymphoma (FL) by the FDA in 2017 (999).

A phase II study published in 2017 examined the use of copanlisib in 33 patients with indolent lymphoma or CLL and 51 patients with aggressive lymphoma (1007). Infections of any grade were reported in 64.3% of patients, with grade 3 or higher infections including pneumonia in 14.3%, febrile neutropenia in 3.6%, skin infection in 2.4%, and urinary tract infection in 2.4%. One case of PJP occurred and one patient died of *Cryptococcus neoformans* meningitis. Neutropenia occurred in 34.5% of patients, with grade 3 or higher neutropenia observed in 29.8% of patients.

A second single-arm phase II study published in 2017 administered copanlisib to 142 patients with previously treated relapsed or refractory indolent B cell lymphoma (1008). After a median duration of treatment of 22 weeks, pneumonia had occurred in 21% of patients overall, and 15% of patients experienced grade 3 or higher pneumonia. Upper respiratory tract infections, bronchial infections, flu-like symptoms, and skin infections were also common ($\geq$10% of patients, mainly grade 1 or 2). Three opportunistic infections occurred during the study; two patients developed PJP and one patient developed bronchopulmonary aspergillosis.

### PI3K Inhibitors: Prevention of Infections

The updated product information recommends a number of measures to prevent infections in patients receiving idelalisib, including PJP prophylaxis for all patients during treatment (953) and for 2 to 6 months following idelalisib cessation, in addition to close monitoring for serious infections (994–996). At least monthly clinical and laboratory monitoring is also recommended in patients who are CMV seropositive at the start of idelalisib treatment or have other evidence of CMV infection or disease. Patients with CMV viremia should be monitored for symptoms and for a rising viral load, with CMV treatment and at least temporary cessation of idelalisib considered if either of these occur. Monthly CMV PCR monitoring is also recommended by other authors (943, 952, 953). Patients should have absolute neutrophil counts monitored at least fortnightly for the first 6 months of treatment with idelalisib, and the agent should not be commenced in patients with an active infection (994–996). Patients should be monitored carefully for respiratory signs and symptoms, given the increased risk of both potentially fatal pneumonitis and respiratory tract infection. Pneumococcal and annual influenza vaccination is recommended (1009). Screening for and treatment of latent tuberculosis have been recommended by some authors, although tuberculosis thus far appears to be a rare complication of idelalisib therapy (1009). Insufficient data are currently available regarding the risk of HBV reactivation in patients taking idelalisib (1010). Based on its mechanism of action and effect on B cells, an increased risk of HBV reactivation would be anticipated. Screening and, if necessary, prophylaxis for hepatitis B virus is recommended prior to commencement of idelalisib (953). Until further data are available, the recommendations above should also be applied to copanlisib.

### PI3K Inhibitors: Summary

Although it is difficult to determine the exact risk attributable to PI3K inhibitors independent of underlying hematological malignancy, it appears clear that this drug class is causally associated with a substantially increased risk of pneumonia (in at least 20% of patients), serious and fatal infections (also in approximately 20%), and PJP (in 2 to 3%), with a possible increased risk of CMV and tuberculosis. As a result, the FDA has recommended that the agent is not indicated for first-line treatment of malignancy and is not indicated in combination with bendamustine and/or rituximab in patients with FL (994). Further clinical experience, investigation of whether particular patient subgroups are more likely to develop infectious complications, and optimization of drug combinations may lead to better definition of patients likely to derive more benefit than harm from idelalisib therapy (1011). At present, data from phase III trials and clinical experience regarding the use of copanlisib are awaited. There are currently insufficient data to determine whether the infectious risks associated with idelalisib, such as PJP and CMV reactivation, are seen at equivalent levels in patients receiving copanlisib. There is evidence suggesting that copanlisib is associated with fewer

autoimmune events than idelalisib, raising the possibility that its effect on the immune system and its predisposition to infectious complications may be different (990).

## BCR-ABL INHIBITORS

### BCR-ABL: Structure and Mechanism of Action

The breakpoint cluster region/Abelson leukemia virus (*BCR-ABL*) gene and the protein it produces are present in more than 90% of patients with chronic myeloid leukemia (CML) as a result of the reciprocal translocation of chromosomes 9 and 22 [t(9;22)], producing the "Philadelphia chromosome" (1012). The *BCR-ABL* fusion protein is a constitutively active tyrosine kinase that induces cell survival and proliferation (943). Cells possessing *BCR-ABL*, particularly in CML, demonstrate increased proliferation, resistance to apoptosis, and an alteration in their adhesion properties (1013). The presence of *BCR-ABL* alone is sufficient to cause CML, and the tyrosine kinase activity of the protein is required for its oncogenic activity (1014). In addition, up to 30% of adults and 5% of children with acute lymphoblastic leukemia (ALL) have the *BCR-ABL* fusion protein (1015).

### BCR-ABL Inhibitors: Available Agents

There are currently five agents available in this class, all of which are used to treat hematological malignancies caused as a result of the BCR-ABL fusion protein (Table 14). Imatinib was the first of the *BCR-ABL* inhibitors and is approved for use in the treatment of CML or ALL expressing the Philadelphia chromosome (Philadelphia chromosome positive [$Ph^+$]), previously treated myelodysplasia (MDS) or myeloproliferative disorder (MPD) associated with platelet-derived growth factor receptor (PDGFR) gene rearrangements, chronic eosinophilic leukemia or hypereosinophilic syndrome, aggressive systemic mastocytosis with eosinophilia, advanced dermatofibrosarcoma protuberans, and gastrointestinal stromal tumor (GIST) (1016–1018). Dasatinib is a second-generation inhibitor of *BCR-ABL* kinases approved for the treatment of $Ph^+$ CML or ALL (1019–1021). Nilotinib is also a second-generation *BCR-ABL* inhibitor approved for use in the treatment of $Ph^+$ CML (1022–1024). Ponatinib is a TKI active against both unmutated and mutated *BCR-ABL* and, hence, can be active against disease resistant to other *BCR-ABL* tyrosine kinase inhibitors (1025). It is approved for use in patients with CML or $Ph^+$ ALL resistant to or intolerant of other therapies or with the T315I mutation. Bosutinib is a small molecule, orally bioavailable, dual TKI, inhibiting both *SRC* (a kinase which is mutated and overexpressed is certain malignancies) and *BCR-ABL* with activity in imatinib-resistant CML cell lines (1026). It is approved for use in chronic-phase, accelerated-phase, or blast-phase $Ph^+$ CML (1027, 1028).

*BCR-ABL* inhibitors target the fusion protein *BCR-ABL*, but depending on the agent used, may also target other receptor tyrosine kinases and a wide range of nonreceptor kinases (1029). Imatinib functions through competitive inhibition at the ATP binding site of the *BCR-ABL* tyrosine kinase, leading to the inhibition of tyrosine phosphorylation of proteins involved in *BCR-ABL* signal transduction (1014). In addition to *BCR-ABL* inhibition, imatinib has specificity for other members of the ABL family, the receptor for platelet-derived growth factor (PDGFR), and c-KIT tyrosine kinases (1014). The emergence of imatinib resistance led to the development of second-generation *BCR-ABL* inhibitors with increased potency toward wild-type *BCR-ABL* and against the majority of CML clones carrying imatinib-resistant *BCR-ABL* mutants (1030). Nilotinib is a close analogue of imatinib with more potent *BCR-ABL* kinase inhibition, while dasatinib was developed as a dual SRC/ABL inhibitor but was subsequently shown to affect a wider array of kinases, including TEC family kinases like bone marrow kinase on chromosome X (BMX), TEC, and BTK (1030). Ponatinib is active against CML clones with the T315I mutation, a mutation that confers resistance to imatinib, dasatinib, and nilotinib by blocking the access of these drugs to the enzyme's ATP binding site (1025). It also has off-target activity against various other kinases, including PDGFR, vascular endothelial growth factor receptor (VEGFR), and c-KIT. Bosutinib is a dual inhibitor of SRC/ABL, with minimal inhibitory activity against c-KIT or PDGFR (1031).

**BCR-ABL Inhibitors: Infectious Complications**

Despite the fact they were designed to target only a pathological gene product, *BCR-ABL* inhibitors appear to affect the function of normal immune cells. Imatinib has been demonstrated to inhibit T cell receptor-mediated T cell proliferation and activation, with reductions in specific $CD8^+$ responses to CMV and EBV (1032, 1033). Data also suggest that imatinib may affect the development and function of dendritic cells (1034). Dasatinib and nilotinib have both been shown to inhibit $CD8^+$ T cell proliferation and function (1035, 1036). *BCR-ABL* inhibitors have also been found to inhibit both B cell immune responses to influenza and pneumococcal vaccination (1037) and the proliferation and function of regulatory T cells (1038, 1039). Reductions in immunoglobulin levels have also been observed in association with *BCR-ABL* inhibitors (1040). Dasatinib appears to have a greater effect on immune functions than other *BCR-ABL* inhibitors. It has been shown to inhibit T cell receptor-mediated signal transduction, cellular proliferation, cytokine production, and *in vivo* T cell response (1041, 1042). The broader range of kinases targeted by dasatinib may be responsible for its stronger predisposition toward infectious complications than other TKIs in its class (1030).

Postmarketing experience has demonstrated that *BCR-ABL* inhibitors are associated with a significant risk of HBV reactivation, with multiple cases reported in patients receiving imatinib, dasatinib, and nilotinib (1043–1049). A 2018 analysis of adverse events reported to the FDA also detected a statistically significant association between the use of imatinib and hepatitis B virus infection (1050). The American Gastroenterological Association categorizes TKI use, and specifically *BCR-ABL* inhibitors, as conferring moderate risk (1 to 10%) of HBV reactivation in patients with previous or active HBV infection (1051).

**Imatinib.** Initial phase III studies examining the use of imatinib in newly diagnosed patients with CML did not find evidence of significant infectious complications, although grade 3 or higher neutropenia occurred in 17% of patients, mainly within the first 2 years of therapy (1012, 1052, 1053). Patients receiving imatinib for advanced GIST did not have significant infections, although approximately 7% developed grade 3 or higher neutropenia (1054, 1055). No significant infectious complications were observed in a phase II study investigating the use of imatinib in other malignancies, including MDS and MPD, hypereosinophilic syndrome, and dermatofibrosarcoma protuberans (1056).

However, as is often the case, postmarketing surveillance tells a different story. Experience with imatinib has demonstrated multiple cases of reactivation of HBV, in addition to VZV infection or reactivation, which was observed in 2% of patients in a retrospective single-center study (1057). An Italian case series of patients with CML receiving imatinib described clinically and microbiologically documented infections in 13 to 16% of patients, most commonly herpes zoster and pneumonia (1058). Isolated cases of leishmaniasis (1059), Kaposi sarcoma (1060), and disseminated cryptococcal infection (1060) have been reported with the use of imatinib, and rare cases of *Listeria* meningitis associated with monocytopenia (1061) and tuberculosis have also been described (1062–1064).

**Dasatinib.** Initial phase III studies examining the use of dasatinib in patients with imatinib-refractory or imatinib-intolerant CML did not demonstrate significant infectious complications (1065, 1066), although over 7 years of follow-up, 66% of treated patients developed infections due to any cause, mostly of grade 1 or 2 severity (1067). Most of these were upper respiratory tract infections and pneumonia. Dasatinib, when compared to imatinib as first-line treatment of newly diagnosed CML, was not associated with an increased incidence of infections in short-term follow-up; both agents were associated with grade 3 or higher neutropenia in approximately 20% of patients (1068).

Dasatinib appears to be associated with a greater risk of infection than other *BCR-ABL* inhibitors. A comparative economic analysis of dasatinib and nilotinib demonstrated that infection-related inpatient hospital days constituted a higher proportion

of all-cause inpatient days in those receiving dasatinib than in those receiving nilotinib (1069). In clinical practice, multiple cases of CMV reactivation have also been reported (1029, 1070–1073). The risk of CMV reactivation in the setting of dasatinib therapy appears particularly pronounced following hematopoietic stem cell transplantation (HSCT); in one study involving 109 patients, the use of dasatinib significantly increased the incidence of CMV reactivation in the first year after transplantation (adjusted hazard ratio = 7.65; 95% CI, 1.84 to 31.7) (1071).

**Nilotinib.** Compared to imatinib in the treatment of newly diagnosed CML, nilotinib was not associated with infections and caused less neutropenia (1074). These findings were confirmed on 3-year follow-up of this patient cohort (1075) and in a subsequent phase III study (1076). Phase II studies examining the use of nilotinib in previously treated patients with chronic-phase CML also failed to demonstrate evidence of significant infections (1077, 1078), although neutropenia was more frequently seen than in newly diagnosed CML. A retrospective review of 169 patients with CML receiving nilotinib as first-line or salvage therapy described infection of any grade in 10% of treatment-naive patients and in 37% of patients receiving nilotinib as salvage treatment (1079). Most infections were bacterial, and no opportunistic infections occurred. Cases of HBV reactivation have been reported in association with nilotinib (1080).

**Ponatinib.** Phase II studies investigating the use of ponatinib in previously treated patients with $Ph^+$ CML or ALL did not demonstrate infectious complications, although grade 3 or higher neutropenia occurred in 12 to 26% of patients (1081). In a phase II study, first-line ponatinib in CML was associated with neutropenia in 14% of patients, without evidence of infection (1082). A phase III study comparing ponatinib to imatinib as first-line treatment of CML was halted early due to vascular events (1083). Postmarketing experience is limited.

**Bosutinib.** Phase I/II studies of bosutinib monotherapy in patients with imatinib-resistant or imatinib-intolerant chronic-phase CML found no evidence of infectious complications but reported grade 3 or higher neutropenia in 18% of patients on short-term follow-up and in 16% on long-term follow-up (1026, 1084). A phase III trial comparing bosutinib to imatinib in newly diagnosed chronic-phase CML noted grade 3 or higher neutropenia in 10% of patients at 24-month follow-up but, again, no significant infectious complications at either 12 or 24 months (1085–1087). Postmarketing experience is limited.

### BCR-ABL Inhibitors: Prevention of Infection

Given the moderately increased risk of HBV reactivation in those treated with these drugs, patients should be screened for HBV prior to starting treatment with *BCR-ABL* inhibitors (1029, 1088). Those with positive HBsAg should receive antiviral treatment or prophylaxis with entecavir or tenofovir, which should continue for 6 to 12 months after cessation of immunosuppressive treatment (1051, 1089). For HBsAg-negative/HBcAb-positive patients, close monitoring of liver enzymes and viral load is recommended (1090), although prophylaxis should be considered where there are no clear systems for regular monitoring and review of results (1089). Pneumococcal vaccination and annual influenza vaccination are recommended in patients receiving dasatinib, although there is some evidence that B cell responses may be impaired by the use of BCR-ABL inhibitors (1037).

### BCR-ABL Inhibitors: Summary

As a class, BCR-ABL inhibitors are associated with a small risk of infectious complications, primarily HBV, VZV, and CMV reactivation. These risks were not large enough to be detected in phase III trials, where neutropenia was observed but not an excess infection risk. These complications are likely due to off-target effects, rather than inhibition of BCR-ABL. Clinical data for bosutinib and ponatinib are at present limited and may be expected to emerge, given that most infectious complications were noted only in postmarketing experience for other agents in this class. Although cases of

hepatitis B have not yet been reported in association with ponatinib or bosutinib, it is prudent to assume that this predisposition is a class effect.

## Syk INHIBITORS

### Syk: Structure and Mechanism of Action

Spleen tyrosine kinase (Syk) is an intracellular cytoplasmic tyrosine kinase that mediates immunoreceptor signaling in macrophages, neutrophils, mast cells, and B cells (1091). It is widely expressed in hematopoietic system cells, particularly in B cells (1092). Syk plays a key role in the signaling of activating Fc receptors (FcRs) and the B cell receptor (1093). Syk family protein tyrosine kinases bind to the cytoplasmic region of immune receptors, including the T and B cell receptors, and play an important role in regulating T cell and B cell expansion and proliferation, as well as mediating immunoreceptor signaling in inflammatory cells (1092). When activated, Syk leads to the induction of proinflammatory cytokines and degranulation of effector cells (1092) and plays a central role in FcR-mediated signal transduction and propagation of the inflammatory response (1094).

### Syk: Available Agents

Fostamatinib is the only currently approved agent in this class. It was approved for use by the FDA in April 2018 for chronic immune thrombocytopenia (ITP) (1095) on the basis of two randomized controlled trials. It has also been used off-label for the treatment of RA, in which setting multiple trials have been conducted (1092).

### Syk Inhibitors: Infective Complications

Spleen tyrosine kinase inhibitors have been shown *in vitro* to reduce Syk-dependent FcR-mediated activation of monocytes, macrophages, and neutrophils and BCR-mediated activation of B cells (1093). Other *in vitro* studies have suggested that the inhibition of Syk leads to diminished proliferation of antigen-specific $CD4^+$ T cells and reduced production of inflammatory cytokines, such as IFN-$\gamma$ and IL-17 (1096). Given the pivotal role of Syk in the human immune response, one might expect its inhibition to have the potential to make the patient fully sick (or "fully Syk"?), but thus far, that does not appear to be the case.

Early phase II studies in patients with RA receiving fostamatinib reported reversible, dose-related neutropenia in 15% (1097) and 6 to 7% (1091) of patients. This represented a significant increase in comparison to patients receiving placebo in two trials (1091, 1097). A phase III study published in 2014 compared fostamatinib to placebo in patients with RA; neutropenia occurred in 5.3% and 9.7% of patients receiving fostamatinib at two different doses (1098). Neutropenia was not associated with any serious infectious events in this trial, and no patient had an absolute neutrophil count of $<0.5 \times 10^9$/liter. The overall event rates for any infection per 100 patient years of treatment ranged from 62.9 to 70.3 depending on the fostamatinib dose, and 25.5 to 28.3% of patients receiving fostamatinib developed an infection of any grade during treatment. Between 0.3% and 1.3% of patients receiving fostamatinib experienced a serious infection event, most commonly gastroenteritis. A second phase III study published in 2014 also compared two dosing schedules of fostamatinib to placebo in patients with RA taking background methotrexate and reported serious infections in 2.9% and 1.9% of patients in the fostamatinib groups, compared to 1.8% in the placebo group (1099). The overall incidences of infection of any grade over 24 months were 42.9% and 28.7% in the two fostamatinib groups and 24.8% in the placebo group. The most common infections in the fostamatinib groups were upper respiratory tract infections and bacterial infections. Dose-related decreases in leukocyte and neutrophil counts were seen in both fostamatinib groups.

A 2014 meta-analysis of the five phase II and III randomized controlled trials conducted to date examined the use of fostamatinib in 1,419 patients with RA (1092). Patients with active or latent tuberculosis infection, hepatitis B or C virus infection, or a history of cancer within the preceding 5 years were excluded. Over follow-up periods

of between 3 and 6 months, fostamatinib was associated with an increased risk of any infection compared to placebo (25% versus 14.7%; OR [95% CI] = 1.59 [1.2 to 2.11]; $P = 0.001$) and of neutropenia (6.8% versus 0.8%; OR [95% CI] = 5.68 [1.97 to 16.42]; $P = 0.001$) but no significant increase in the risk of serious infection. On the basis of efficacy results in these phase II and III trials, fostamatinib did not progress further in its development for use in RA.

A small phase II study published in 2009 enrolled 16 patients with chronic refractory ITP receiving various doses of fostamatinib and observed a small but statistically significant decrease in total white blood cell count, without increased rates of infection (1094). This was followed by two paired phase III studies comparing fostamatinib to placebo in patients with chronic ITP at a dose of 100 mg twice daily (b.i.d.) or 150 mg b.i.d. (1100). The frequency of any infection was slightly higher in the fostamatinib group (30% versus 21%), but rates of moderate or severe infections were similar (8% versus 6%). Neutropenia occurred in 7% of patients receiving fostamatinib. Respiratory tract infections, largely mild, occurred in 11% of patients on fostamatinib and 6% of patients receiving placebo.

### Syk Inhibitors: Prevention of Infection

Currently no specific recommendations can be made about the prevention of infectious complications in those treated with fostamatinib, but given the relative lack of data, vigilance is recommended. Monthly monitoring of the neutrophil count is also recommended during fostamatinib treatment, with dose reduction or temporary or permanent cessation of fostamatinib if the neutrophil count drops below $1.0 \times 10^9$/liter (1095).

### Syk Inhibitors: Summary

Fostamatinib appears associated with a moderate risk of neutropenia and a small risk of infectious complications, with no signal thus far of serious or opportunistic infections. However, fostamatinib has only recently entered clinical practice, and as a result, clinical experience is limited and further evidence of infectious complications may emerge with time. Although increased rates of nonsevere infections have been reported in numerous studies (1092, 1098, 1100, 1101), the types of infections experienced by these patients were not reported. In addition, patients with active or chronic viral infection were excluded from the fostamatinib trials, and hence, there are no data regarding the efficacy or safety of fostamatinib in this patient cohort. The role of fostamatinib in the immune response across the innate and adaptive immune systems suggests that further infectious complications are possible and that patients should be monitored closely.

## ALK INHIBITORS

### ALK: Structure and Mechanism of Action

The *ALK* gene codes for the ALK receptor tyrosine kinase, whose exact function is unknown but relates to cell proliferation, primarily of neurons. Activation of the *ALK* gene usually occurs via chromosomal rearrangement that results in the placement of one of several different fusion partners upstream from the kinase domain of *ALK* and has been described in several different malignancies (1102). The cellular consequences of activation of the *ALK* tyrosine kinase are subsequent signaling through the phospholipase gamma, PI3K, RAS/mitogen-activated protein kinase (MAPK), and JAK/STAT pathways (1103). *ALK* rearrangements are seen in 3 to 5% of non-small cell lung cancers (NSCLC), most commonly in adenocarcinomas (1104).

### ALK Inhibitors: Available Agents

There are four ALK inhibitors currently approved for use (Table 14). Crizotinib is an ALK inhibitor approved for treatment of advanced NSCLC possessing a documented ALK or ROS1 gene rearrangement (1105–1107). Ceritinib is a second-generation ALK inhibitor approved for use in locally advanced or metastatic NSCLC with an ALK gene rearrangement (1108–1110). Alectinib is an ALK inhibitor also active in the central

**TABLE 16** Key integrins important in leukocyte-endothelial cell interactions

| Integrin | Alternative name(s) | Usual endothelial cell ligands | Tissue specificity | Example(s) of inhibitor |
|---|---|---|---|---|
| $\alpha L\beta 2$ | LFA-1, CD11a | ICAM-1, ICAM-2 | Broad, including dermis and CNS | Efalizumab |
| $\alpha 4\beta 1$ | VLA-4 | VCAM-1, fibronectin | Broad, including CNS | Natalizumab |
| $\alpha 4\beta 7$ | LPAM-1 | VCAM-1 (weak), MAdCAM | Limited to gut | Vedolizumab, Etrolizumab |

nervous system (1111) and is approved for use in advanced or previously treated ALK-positive NSCLC (1112–1114).

### ALK Inhibitors: Infectious Complications

Although some ALK inhibitors, including crizotinib and brigatinib, have been associated with the development of upper respiratory tract infections, reported cases have been nonsevere (1115, 1116). The mechanism for this potential increased risk is unknown. Interstitial pneumonitis has been reported in association with all ALK inhibitors (1115, 1117–1120); this is an important differential diagnosis for respiratory tract infections in these patients.

Data from two randomized controlled trials performed in ALK-positive, treatment-naive and previously treated patients (1115, 1117) did not reveal evidence for an increased rate of infections associated with the use of crizotinib, although neutropenia occurred in 11 to 13% of patients. Febrile neutropenia was uncommon. Upper respiratory tract infections occurred at a higher rate in patients on crizotinib than in patients receiving chemotherapy but were not associated with significant morbidity or mortality (1115). In addition, crizotinib is associated with the development of complex renal cysts, and secondary infection of these cysts has been reported (1121). No new infectious toxicities were identified in a phase I study using crizotinib in patients with ROS1-rearranged NSCLC (1122). Infective complications have not been reported in clinical trials of ceritinib, alectinib, or brigatinib (1111, 1123, 1124), although 20% of patients on both crizotinib and alectinib developed nasopharyngitis in a Japanese study (1125).

### ALK Inhibitors: Prevention of Infection

No specific recommendations can be made for prevention of infectious complications of ALK inhibitors, since there is no clear evidence that these agents increase the risk of infection.

### ALK Inhibitors: Summary

Although the impact of infectious complications in patients receiving ALK inhibitors appears minimal, clinical experience with many of these agents is limited and further infectious toxicities may emerge with time. In addition, recent studies have begun to combine ALK inhibitors with other agents, including immune checkpoint inhibitors (1126), and the infectious complications resulting from this are at present undefined.

## INTEGRIN INHIBITORS

### Integrins: Structure and Mechanism of Action

Integrins are transmembrane receptors present in many mammalian cell types; they play roles in signal transduction in a range of biological processes (1127–1129), but in the current context, they are primarily important in the adhesion, crawling, and migration of lymphocytes. Leukocytes in general express integrins on their cell surface, but these are usually in a low-avidity state until the leukocyte is activated by chemokine stimulation (1130). Integrins on leukocytes bind to specific endothelial cell surface ligands (Table 16) (1131), and it is the distribution of these ligands that gives particular integrins their tissue specificity. Once lymphocytes are bound to endothelial cells through integrin-ligand interactions, slow rolling of the lymphocytes along the apical endothelial cell surface is enabled, followed by arrest and transmigration out of blood vessels and into tissues, where they can act as immune effector or recruitment cells.

Integrins consist of noncovalently bound dimers of $\alpha$ and $\beta$ transmembrane domains. There are currently 24 known $\alpha$ and 9 known $\beta$ subunits, which can combine in

various combinations to form integrin dimers (1130). The $\beta$1, $\beta$2, and $\beta$7 integrin families are important in lymphocyte-endothelial cell interaction. In this article, we will not be discussing other integrins, such as $\alpha$2b$\beta$3 (important in platelets and coagulation) or $\alpha$v$\beta$5 (osteoclasts and tumor angiogenesis). From here onward, when we refer to integrin inhibitors, we mean only those important in leukocyte-endothelial cell interactions (i.e., those which are immunomodulatory).

Integrin binding can be pharmacologically inhibited by monoclonal antibodies or small molecules, such as peptidomimetics; all integrin inhibitors discussed in this article are antibodies targeting the extracellular domains. Integrin inhibitors affect a broad range of immune effector cells. For example, natalizumab ($\alpha$4$\beta$1 inhibitor) prevents activated monocytes and several types of memory T cells from entering the central nervous system. Vedolizumab is more specific for gut endothelium, because of the distribution of $\alpha$4$\beta$7 integrin ligands. VCAM-1 is widely distributed but is a relatively weak ligand of $\alpha$4$\beta$7 integrins; the main ligand for leukocytes expressing $\alpha$4$\beta$7 integrins is mucosal addressin cellular adhesion molecule-1 (MAdCAM-1), which is preferentially expressed on endothelial venules of gut mucosal lymphoid tissue. Hence, blocking $\alpha$4$\beta$7 integrins prevents the adhesion of immunocompetent leukocytes to the gut mucosal endothelium and the subsequent migration into gut tissues.

### Integrin Inhibitors: Available Agents

In general, integrin inhibitors are used to deny entry of leukocytes to target tissues and, thus, to prevent or attenuate immune responses at these sites. Hence, they are used in well characterized autoimmune conditions, such as multiple sclerosis (MS) and inflammatory bowel disease (IBD).

Natalizumab was the first widely used integrin inhibitor and is licensed for use in both MS and Crohn's disease. Intermittent intravenous infusions of natalizumab have been shown to reduce the relapse rate in relapsing-remitting MS (1132), but because of the risk of the potentially fatal infectious complication progressive multifocal leukoencephalopathy (PML), it is generally reserved for those with more aggressive MS or where other therapies have failed (1133). Although natalizumab is effective for inducing remission in Crohn's disease (60), it is rarely used for this indication because of the risk of PML and the availability of safer alternatives, such as vedolizumab.

Vedolizumab is used for both the induction and maintenance of remission in adults with Crohn's disease or ulcerative colitis. It is indicated for these conditions where first-line therapies, such as TNF inhibitors, have failed due to loss or lack of responsiveness or intolerance (1134, 1135). Small case series have reported efficacy of vedolizumab for the off-label indication of steroid-refractory gastrointestinal graft-versus-host disease following bone marrow transplantation (1136, 1137).

Etrolizumab specifically targets $\beta$7 integrins and is currently in phase III trials for IBD (1138). Efalizumab targets $\alpha$L$\beta$2 integrin, which binds to ICAM-1, found on endothelial cells and antigen-presenting cells, and is used in plaque psoriasis (1139, 1140). It was withdrawn from market in 2009 following several case reports of PML (1141, 1142).

### Integrin Inhibitors: Infectious Complications

By far the most well characterized infectious complication of integrin inhibitors is progressive multifocal leukoencephalopathy (PML), caused by reactivation of latent infection with JC polyomavirus. This was previously a well-known complication of profound immunosuppression from HIV infection (1143) but was first reported as a complication of integrin inhibition in 2005, in three patients treated with natalizumab (two with MS and one with Crohn's disease) (1144–1146).

The risk of PML in those treated for MS with natalizumab correlates strongly with three key variables: (i) JC virus serology, (ii) duration of natalizumab use, and (iii) previous use of other immunosuppression (1147). Ho et al. estimated this risk in a pooled cohort of 21,696 patients being treated with integrin inhibitors (1147). Those who are seronegative for JC virus have a very low risk of PML (0.07 per 1,000 treated patients). Those who are seropositive have a higher risk: for example, a patient with

strongly positive JC virus serology but no prior immunosuppression has a risk of 0.9/1,000 patients after 2 years of treatment and 7.9/1,000 after 5 years of treatment. Schwab et al. summarized the risk of PML in MS patients treated with natalizumab as 4.2 cases per 1,000 treated patients, collating over 650 cases (1148).

Latent JC virus infection is highly prevalent worldwide, with 57% of 7,724 adults from 10 countries seropositive (1149). It can be found in peripheral blood mononuclear cells, kidneys, and oligodendrocytes in the central nervous system. Integrin inhibition with natalizumab and/or efalizumab allows reactivation of latent JC virus infection both peripherally and in the CNS, because of a decrease in cell-mediated immunity directed against it by memory T cells. The lack of immune surveillance also leads to genetic rearrangement of part of the JC virus genome, which allows it to become neurotropic (1150). This then allows viral replication in oligodendrocytes and astrocytes, leading to demyelination, particularly in subcortical and cerebellar white matter (1151). PML is a devastating diagnosis with high mortality, and the only effective management is a decrease in immunosuppressive medications. A recent case series provides some hope for those suffering from PML: eight adults with PML due to various immunosuppressive conditions (mostly CLL or HIV) were treated with the programmed cell death protein 1 (PD-1) checkpoint inhibitor pembrolizumab in an effort to reinvigorate T cell responsiveness to JC virus-infected cells, resulting in clinical and virological improvement in five of the eight (430). It should be noted, however, that none of these eight patients were being treated for MS, and so it is unclear if it would apply to such patients. Moreover, augmenting immune responses to the JC virus could have the unintended consequence of causing an immune reconstitution inflammatory syndrome, thereby worsening the disease (1152–1154). Hence, further research is needed on the risks and benefits of pembrolizumab and other immune checkpoint inhibitors in the treatment of PML before they can be recommended in routine clinical practice.

Given the mechanism of action of integrin inhibitors (prevention of a range of important immune effector cells from adhering to endothelium and migrating out of the bloodstream), one might expect to see a spectrum of other infectious complications, particularly where cell-mediated immunity is important, such as viral and fungal infections. However, despite searching hard in large cohorts of patients, there is little evidence of other major infectious risk from integrin inhibitor use, with some minor exceptions.

The risk of herpesvirus infections (HSV and VZV) appears to be slightly increased in those treated with integrin inhibitors. Although registrational trials did not find any risk of herpesvirus reactivation, postmarketing surveillance has detected more than 30 case reports of HSV or VZV infections of the central nervous system in those treated with natalizumab (1155). However, it is unclear whether this incidence is higher than that of the background population not treated with integrin inhibitors.

The risk of other common infections appears to be either slightly increased or not increased at all in those treated with integrin inhibitors. In the GEMINI 2 trial of maintenance vedolizumab for 52 weeks in 461 patients with Crohn's disease, serious infections occurred in 5.5% of the vedolizumab group, compared with 3.0% of the placebo group (1135). The risk of respiratory tract infections does not appear to be increased in those treated with vedolizumab. For example, in a meta-analysis of three RCTs, including 1,731 patients treated with vedolizumab, the hazard ratio was 1.12 ($P = 0.46$) for upper respiratory tract infection and 0.85 ($P = 0.59$) for lower respiratory tract infection for vedolizumab versus placebo (1155). In a meta-analysis that included data from 12 RCTs of integrin inhibitors, there was a nonstatistically small numerical excess of opportunistic infections in those treated with non-gut-specific integrin inhibitors (7/643 patients versus 1/554 in the placebo group) and an even smaller numerical difference with gut-specific integrin inhibitors (2 of 1,146 patients versus 0 of 664) (1156).

### Integrins: Prevention of Infection

Given that PML has a poor prognosis and no consistently effective treatment, a PML

risk assessment is the essential consideration prior to commencing treatment for MS with natalizumab. This involves JC virus serology and assessment of prior and concurrent immunosuppression, along with the type, severity, and time course of the MS. Experts recommend repeating JC virus serology after 12 months of treatment and at 6-month intervals thereafter and repeating MRI brain scans regularly to detect early PML changes (with the frequency depending on the anti-JCV antibody index) (537). Other preventative strategies (e.g., immunizations and testing for HBV infection and latent tuberculosis infection) are not specifically required prior to initiating integrase inhibitors but are generally recommended in this scenario because of the prior or concurrent use of other immunosuppressive therapies, such as corticosteroids, methotrexate, or TNF inhibitors.

### Integrin Inhibitors: Summary

Natalizumab is associated with a small risk of the devastating infectious complication PML, on the order of 4.2 per 1,000 treated patients. Aside from this, there is either a small risk or no risk of other infections, including herpes zoster and upper respiratory tract infections. Gut-specific integrin inhibitors, such as vedolizumab, are not associated with PML, and there are no convincing data for excess risk of infection in patients treated with this agent, although vigilance and further postmarketing surveillance should continue.

## IMMUNE CHECKPOINT INHIBITORS

### Structure and Function of the Immune Checkpoint System

The immune systems of higher organisms have naturally evolved over time in response to an evolutionary arms race against bacterial, fungal, protozoal, and viral infection (1157). But more importantly, higher organisms have evolved to live symbiotically with microbiota, and indeed, a healthy microbiome is essential to good health (1158). Therefore, a key component of the immune system is regulatory in nature, maintaining a beneficial microbiota but preventing infection and damage from pathogenic microorganisms. All levels of the immune system are regulated by multiple influences, in the innate and adaptive systems, with various subsets of $CD4^+$, $CD8^+$, and NK cells providing and maintaining homeostasis. One key component of these interactions involves a diverse family of signaling molecules called immune checkpoints. The key molecules involved in immune checkpoint signaling are programmed cell death protein 1 (PD-1, also known as CD279), ligand of PD-1 (PD-L1), and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). The canonical cognate pairs of PD-1/PD-L1 and CTLA-4/CD80/CD86 are well known, but dozens of signaling partners are now described (1159).

The role of immune checkpoints in cancer and infection has been exhaustively discussed elsewhere (1160), but in brief, immune checkpoint signaling molecules are displayed on the surface of various populations of immune cells and on the surface of every normal cell in the body. As part of normal immune surveillance, immune cells (predominantly $CD8^+$ cytotoxic lymphocytes) circulate and patrol the body, interrogating cells for their immune identity and status. Cells infected with viruses are likely to generate viral proteins that are processed and degraded in the proteasome, with these peptides presented on the cell surface on MHC class I and class II molecules. Lymphocytes expressing T or B cell receptors may then interact with these infected cells. When the antigen being displayed by the infected cell is recognized, an immune synapse between the target cell and immune cell is created. At this point, the immune checkpoint signaling partners align within the immune synapse and a quorum is reached depending on the balance of positive and negative regulatory signals. The canonical signaling pair PD-1/PD-L1 illustrates this balance well; if there is sufficiently strong negative costimulatory signaling from PD-L1 expression, then T cells become anergic and unresponsive; otherwise, the T cell becomes activated and initiates cell-mediated immune destruction of the target cell.

**TABLE 17** Available immune checkpoint inhibitors

| Target | Drug | Isotype[a] | On-label indication(s)[b] |
|---|---|---|---|
| Anti-CTLA-4 Ab | Ipilimumab | Human IgG1 | Melanoma, renal carcinoma |
| | Tremelimumab | Human IgG2 | None yet |
| Anti-PD-1 Ab | Pembrolizumab | Humanized IgG4($\kappa$) | Melanoma, lung cancer, head and neck cancer, bladder cancer, renal carcinoma, Hodgkin's disease, MSI-high cancers |
| | Nivolumab | Human IgG4 | Melanoma, lung cancer, head and neck cancer, bladder cancer, renal carcinoma, Hodgkin's disease |
| | Cemiplimab | Human IgG4 | Squamous carcinoma of skin |
| Anti-PD-L1 Ab | Atezolizumab | Humanized IgG1 with modified Fc to limit ADCC | Bladder cancer, breast cancer, lung cancer |
| | Avelumab | Human IgG1, ADCC enabled | Merkel cell carcinoma, bladder cancer |
| | Durvalumab | Human IgG1($\kappa$) | Bladder cancer, lung cancer |

[a]ADCC, antibody-dependent cellular cytotoxicity.
[b]MSI, microsatellite instability.

Originally evolved to manage viral infections, this immunosurveillance process is also critical for identification and destruction of transformed cancerous cells. There is considerable overlap between these two processes, as one of the key oncogenic processes leading to cancer is viral infection, e.g., human papillomavirus (HPV)-related squamous carcinomas or hepatitis B virus-related hepatocellular carcinoma. Immune checkpoint inhibitors (ICIs) are a rapidly evolving class of drugs whose members currently target three molecules: PD-1, PD-L1, and CTLA-4. Originally conceived for the treatment of resistant viral infection, it was rapidly appreciated that cancer treatment would be a major use of this drug class. In and of themselves, ICIs cause negligible side effects, barring the rare cases of infusion reaction ($<$0.5%). However, the mechanism of action and, thus, side effects are almost entirely related to their pharmacodynamic effects, i.e., whether they induce immune activation or not, so we will consider their influence on infectious complications as a group but account for variations in terms of the degree of immune activation.

### Immune Checkpoint Inhibitors: Available Agents

The structures of ICIs are very similar across the class (Table 17), all comprising human or fully humanized immunoglobulins with some minor differences that are speculated to have an influence on mode of action that is not necessarily proven in clinical practice. For example, avelumab is said to enable antibody-dependent cellular cytotoxicity (ADCC), though whether this has any relevance *in vivo* is unclear (1161). Likewise, ipilimumab, a human IgG1 anti-CTLA-4, has been shown to mediate Fc$\gamma$R-mediated cytotoxicity of human regulatory T cells *ex vivo* and to be associated with intratumoral regulatory T cell depletion (1162). However, the binding and therapeutic activity of different anti-CTLA-4 antibodies appear to be very similar (1163). The on-label indications for ICI are changing rapidly and continuously, but approved indications at the time of writing are shown in Table 17.

### Immune Checkpoint Inhibitors: Infectious Complications

The epidemiology of infectious complications with ICI is hard to define, as this is a comparatively recent drug class. The overall incidence of infections in those taking ICIs is modest, and it is difficult to discern if there is any additive risk of infection on top of an already elevated background risk of infection in patients immunocompromised by being burdened with metastatic cancers.

A number of authors have examined the incidence of infections in people with various cancers taking ICIs. In one report (1164), 84 non-small cell lung cancer (NSCLC) patients taking nivolumab were observed. One-quarter of patients developed an infection, including pneumonia, lung abscess, and septicemia. Of the patients who developed infection, 50% were taking corticosteroids. In a retrospective case series, 740 patients taking ICIs for metastatic melanoma were reviewed, and serious infection

occurred in 54 patients (7.3%) (1165). Again, the main risk factors were the need for corticosteroids and/or infliximab.

A systematic review and meta-analysis examining the risk of pneumonitis and pneumonia associated with ICI therapy identified 23 randomized controlled trials in patients with solid cancers (1166). Compared with taking chemotherapy or other agents, patients taking various classes of ICIs had higher levels of pneumonitis (immune-mediated noninfectious lung inflammation) but did not have any apparent increase in the risk of infectious pneumonia. The absolute risk of pneumonitis remains relatively low (1 to 5%) (1167), making pneumonia an important diagnosis to exclude in patients presenting with respiratory syndromes. A retrospective review of patients with melanoma, renal cell carcinoma, or NSCLC taking ICIs identified 39 infectious episodes (35 bacterial and 4 viral) among 111 patients, of which 12.6% were defined as serious (requiring intravenous therapy and/or hospitalization). While there was no association with the specific ICI or the type of cancer, corticosteroid use was again associated with serious infections (85.7% versus 28.4%; $P = 0.0003$) (1168).

Systemic immunosuppression is a key risk and cause of treatment-related mortality in people taking cytotoxic chemotherapy, with neutropenia or neutropenic sepsis occurring in some degree in up to one-sixth of patients taking chemotherapy (1169). Conversely, though rarely reported (1170), the incidence of cytopenia after treatment with ICIs remains extremely low, $<$1% (1169). No cases of neutropenic sepsis appear to have been reported, however, indicating that this is one risk factor for infection that is of very low frequency.

These early retrospective reports suggest that there is no specific increased risk of infection in patients taking ICIs, but by placing patients at risk of requiring immunosuppression (e.g., corticosteroids used to treat ICI-induced pneumonitis), this in turn does appear to increase the risk of serious and opportunistic infections.

Whereas immune checkpoint blockade may unleash potentially beneficial tumor-specific T cell responses, the influence of ICIs on pathogen-specific T cell function through PD-1 blockade is unclear. In humans, immune checkpoint expression levels on circulating lymphocytes, in particular on *Mycobacterium tuberculosis*-specific CD4 T cells, are increased during active infection, while levels of PD-1 expression decrease after successful tuberculosis treatment (1171, 1172). PD-1 checkpoint inhibition has therefore been suggested as an adjunctive treatment for tuberculosis, but it remains unclear whether PD-1 inhibitors would be beneficial or harmful in human tuberculosis infection. There have been several case reports of tuberculosis reactivation in patients being treated with ICIs (1173–1178), but most of these were in the context of previous or concomitant cytotoxic chemotherapy, so the relative contribution (if any) of ICIs to the reactivation is unknown. These sparse case reports should be viewed in the context of the known risk of tuberculosis reactivation in people with metastatic malignancies in general. A systematic review and meta-analysis that included over 900,000 patients with cancer confirmed a substantially increased risk of tuberculosis, in particular in adults with metastatic lung cancer or hematological malignancies and in children with all malignancies (1179). The standardized incidence rate varied with tumor group and time since diagnosis but ranged from ~2 to 12 per 100,000 per annum. In a second systematic review and meta-analysis, including over 300,000 patients with cancer treated between 1950 and 2011, almost 600 cases of tuberculosis were reported, again giving an incidence of around 2 per 100,000 (1180). Compared to that in the general population, the incidence rate ratio was over 9 times higher, and again, the risk was highest in patients with lung cancer and hematological cancers. Contextualizing this background risk, it is difficult to know if our early experience with ICIs in cancer is associated with a further increase in the risk of tuberculosis reactivation.

### Potential Use of Immune Checkpoint Inhibitors for the Treatment of Infections

Not only does it appear that ICIs are not associated with an increased risk of infections; they may actually be a useful adjunctive therapeutic against infections. ICIs have shown potential to restore HIV-specific antiviral cellular immune responses in

early-stage clinical trials (1181). However, due to the multiple mechanisms influencing HIV persistence, clinical benefit from monotherapy is unlikely and combination therapies are the most likely path forward for the chance of HIV cure. People with HIV are routinely excluded from clinical trials in cancer therapy, presumably for fear of complications or competing medical problems that will interfere with interpretation of the trial results. In a literature review and case report, 63 patients were identified as having been treated with ICIs in the context of having established HIV infection. There were no apparent differences in the safety or efficacy of ICIs in this cohort compared to their safety or efficacy in other patient populations (1182). Apart from the HIV examples mentioned above, there are several other situations under active study. Alveolar echinococcosis is a rare zoonotic parasitic disease of the liver characterized by pseudotumor formation and distinct from hydatid disease (cystic echinococcosis). In preclinical studies, PD-1/PD-L1 immune checkpoint blockade improves outcomes in mice suffering alveolar echinococcosis (1183). The PD-1/PD-L1 pathway is overexpressed in the liver during the chronic stage of alveolar echinococcosis, and in a mouse model, PD-L1 inhibitor therapy was associated with reduced parasite load, increased Th1 responses, decreased Treg responses, and reduced liver lesions.

In a mouse model, anti-PD-1 antibody therapy was found to promote clearance of persistent cryptococcal lung infection in mice (1184). Immunosuppressive immune checkpoints like PD-1 were found to be upregulated in the lungs of infected mice, while PD-1 treatment reduced IL-5 and IL-10 expression and upregulated OX40 by Th1 and Th17 cells but did not alter immune effector cell numbers or myeloid cell activation.

Targeting immune checkpoints during sepsis is another strategy being explored. Preclinical and clinical studies show that inhibitory molecules like PD-1, PD-L1, CTLA-4, TIM3, and LAG3 are upregulated in patients with sepsis. In preclinical models, immune checkpoint inhibitors improve innate and adaptive immune cell function, increase host resistance to infection, and significantly improve survival (1185). In a phase I clinical trial, people suffering sepsis with low absolute lymphocyte counts were given two doses of an anti-PD-L1 antibody, BMS-936559, in a dose-escalation study (1186). The drug was well tolerated with only low-grade toxicity, and the levels of HLA-DR on peripheral monocytes were increased following treatment. $CD14^+$ $HLA\text{-}DR^{low}$ peripheral blood monocytes are commonly referred to as monocytic myeloid-derived suppressor cells and were first characterized in patients with sepsis, where they regulate a transition from a proinflammatory state to an immunosuppressive state, both in the face of infection and cancer (1187, 1188).

Finally, immune checkpoints and ICIs have recently been implicated in the pathogenesis and perhaps treatment of JC polyomavirus-associated progressive multifocal leukoencephalopathy (PML). Recent case reports suggest that ICI therapy with pembrolizumab may improve the outcome from this devastating infection, by restoring immune responses to the JC virus (430).

Finally, there appears to be an interaction of the human gut microbiota and response to ICI therapy (1189). For example, one group used metagenomics of patient stool samples prior to ICI therapy to show correlations between clinical response and the relative abundance of *Akkermansia muciniphila*. Oral supplementation of this same organism into mice bearing tumors improved the efficacy of anti-PD-1 therapy by driving recruitment of $CCR9^+$ $CXCR3^+$ $CD4^+$ T lymphocytes into tumors (1190). Likewise, there is an abundance of data showing that taking antibiotics concurrently or immediately prior to taking an ICI for cancer immunotherapy is associated with decreased efficacy of ICI therapy, for example, in kidney cancer (1191), non-small cell lung cancer (1192, 1193), and metastatic melanoma (1194), and in cancers more broadly (1195). Whether the type of antibiotic, timing of therapy, or underlying medical comorbidity that necessitated the antibiotic prescription is relevant is unclear.

### Immune Checkpoint Inhibitors: Prevention of Infection

Given that the side effects of ICIs are directly related to excessive immune dysregulation, one of the key management steps in abrogating and reversing these toxicities

involves the judicious use of immunosuppressants, such as corticosteroids. While in most cases, severe immune-related adverse effects resolve quickly with cessation of the ICI and administration of corticosteroids, in some patients, prolonged courses (over 6 weeks) of corticosteroids or more complex immunosuppressants, such as mycophenolate mofetil, infliximab, or other biologics, are needed.

Given that the noninvasive diagnosis of tuberculosis remains challenging, a heightened awareness of the possibility of tuberculosis reactivation and a low threshold to consider investigations should be a minimum for preventative measures. Of note, initial and ongoing clinical trials for ICIs in cancer typically have shown no evidence of HIV infection or active hepatitis B or C virus infection.

### Immune Checkpoint Inhibitors: Summary

Immune checkpoint inhibitors do not appear to be associated with an increased risk of infection, independent of background diagnoses and the concomitant use of immunosuppressive agents. In fact, they may even be beneficial as adjunctive therapy in certain infections. However, this drug class has only been used in clinical practice for less than a decade, and it is possible that rare infectious complications will emerge as further data accumulate.

## COMPLEMENT PATHWAY INHIBITORS

### Role of the Complement Pathway

The complement pathway is a pivotal component of both the innate and adaptive immune systems (1196, 1197). Complements are a series of proteins that work together with antibodies to help destroy and clear pathogens by opsonization and lysis. There are several recognized complement pathways (classical, alternative, and lectin), with different triggers. The final common pathway for all of these is the activation of complement component 5 (C5) and the consequent formation of the membrane attack complex (MAC), which destroys foreign cells. The "late" components of the complement cascade (C5 to C9) are important in the immune response to encapsulated organisms, particularly *Neisseria* species. Those with genetic mutations causing deficiencies of the late complement pathway are predisposed to *Neisseria gonorrhoeae* and *Neisseria meningitidis* infections, which have been reported in up to 50% of such patients, but have minimal or no increase in risk of other infections (1198–1201).

### Complement Pathway Inhibitors: Available Agents

The only currently approved complement inhibitor is eculizumab, a humanized IgG monoclonal antibody directed against C5 complement (1202). This inhibits the terminal part of the complement pathway, thus preventing the destruction of red blood cells in those with paroxysmal nocturnal hemoglobinuria (PNH) while preserving the function of earlier parts of the complement pathway, allowing C3b and C4b opsonins to clear pathogens and immune complexes. Eculizumab is also indicated for use in atypical hemolytic uremic syndrome (aHUS) (1203), which is caused by mutations in regulatory genes that lead to hyperactivation of the alternative complement pathway, as well as in myasthenia gravis and neuromyelitis optica spectrum disorder. It has been used off-label to prevent or treat antibody-mediated rejection (1204–1208), thrombotic microangiopathy (1209), and ischemia-reperfusion injury (1210) following kidney transplant. Eculizumab prevents both hemolysis and thrombosis in PNH and leads to decreased transfusion requirements (1202). It is said to be one of the most expensive medicines in the world currently, at over $500,000 per patient per year. Because PNH is a genetic disorder, eculizumab needs to be used long-term, with fortnightly intravenous maintenance infusions. Ravulizumab is a selective C5 inhibitor currently undergoing phase III trials; it appears to have similar efficacy to eculizumab but more convenient dosing, needing 8-weekly rather than 2-weekly infusions (1211, 1212). Selective inhibitors of other parts of the complement pathway are under development, including inhibitors of the alternative pathway currently being developed for macular degeneration (1213, 1214).

### Complement Pathway Inhibitors: Infectious Complications

In line with the data from those with inborn complement deficiencies, treatment with eculizumab is associated with a clear increased risk of *Neisseria* infections but little other infectious risk. Although too rare to have been detected in registrational trials, shortly after this agent entered clinical use, case reports emerged of meningococcal and gonococcal infections (1215–1217). Infections with species of *Neisseria*, which are usually regarded as harmless commensals, have also been reported (1218, 1219) in those taking eculizumab. Disseminated gonococcal infection has recently emerged as a risk in those on treatment (1220).

Ten years of safety data on eculizumab have recently been compiled (1221). In 28,518 cumulative patient years of exposure, there were 76 reported cases of meningococcal infection (0.25 per 100 patient years), 8 of which were fatal. Nonmeningococcal serious infections were also common, including pneumonia (11.8% of patients), sepsis (11.1%), and urinary tract infections (4.1%). Although the absolute risk of invasive meningococcal infection is low, it is at least 1,000-fold higher than that in the background population (1222). Unfortunately, many of these infections occurred in patients who had been vaccinated against meningococcus (1217, 1223–1225). This is likely due to a combination of poor serological response to the vaccine (1226), nonvaccine strains (1222), or an initial good vaccine response which then became ineffective in the absence of an adequate C5 response because of eculizumab.

### Complement Pathway Inhibitors: Prevention of Infection

Given the risk of meningococcal infection, ideally patients should be immunized with conjugate tetravalent meningococcal vaccine (Men ACWY) at least 4 weeks before treatment commences. Two doses should be given, 8 to 12 weeks apart. In addition, meningococcus group B vaccine should be given (two or three doses depending on which product is used). Antibiotic prophylaxis (e.g., with oral phenoxymethyl penicillin at 500 mg twice daily) should be given until 4 to 8 weeks following the completion of both vaccine courses and should be continued in those receiving other immunosuppressive therapy as long as the patient is on eculizumab. Although there is no clear evidence of increased risk of pneumococcal or *Haemophilus* infection, it is prudent to also vaccinate against these pathogens prior to commencing treatment with eculizumab. Patients should be educated about the risk of gonococcal infection and how to avoid it. Those who are sexually active, especially with more than one partner over time, should be offered regular screening for urogenital and/or pharyngeal gonorrhoea.

### Complement Pathway Inhibitors: Summary

Eculizumab, a monoclonal antibody directed against C5, is the only currently available complement pathway inhibitor. It is unusual among biological immunosuppressive agents in that it is often used without any concomitant immunosuppression and in that the predicted infection risk (based on basic science, animal models, and complement-deficient humans) appears to be exactly correct. The risk of *Neisseria* infections (especially meningococcus) is markedly increased in patients treated with eculizumab, but it is unclear if there is increased risk of other infections.

## SUMMARY AND CONCLUSIONS

At the end of this long journey through the literature, there are several key lessons which emerge. (i) Most biological immunomodulatory agents are used in the context of concomitant conventional immunosuppressive therapy (such as corticosteroids), and hence, it is often difficult to tease out the attributable risk of infectious complications and to prove associations between particular infections and specific agents. (ii) We do not know as much about the human immune system as we think we do. It is vastly complex, with substantial redundancy. Many observed infectious complications were not anticipated (e.g., PML in those treated with integrin inhibitors or HBV reactivation due to B cell inhibition with rituximab), and conversely, many that were predicted did

**TABLE 18** Biological immunomodulatory agents with no or minimal increased risk of infection

| Agent(s) | Mechanism of action | Notes |
|---|---|---|
| Anakinra | IL-1 receptor antagonist | Nonsignificant increase in upper respiratory tract infections; canakinumab (another IL-1 receptor antagonist) appears to have a higher infection risk than anakinra |
| Ustekinumab, risankizumab, tildrakizumab, guselkumab | IL-12 and/or IL-23 | Possible small increase in risk of nonserious upper respiratory tract infections |
| Mepolizumab, reslizumab, benralizumab | IL-5 | Possible small increase in risk of geohelminth infection, but no definite such risk detected thus far despite specifically looking for it |
| Omalizumab | IgE | Possible small increase in risk of geohelminth infection, but no definite such risk detected thus far despite specifically looking for it |
| Dupilumab | IL-4 | Lower risk of skin infection than placebo in those treated for atopic eczema |
| Ipilimumab | CTLA-4 | Observed infection risk relates to use of corticosteroids to treat complications |
| Nivolumab | PD-1 | Also applies to pembrolizumab, atezolizumab, and avelumab; observed infection risk relates primarily to use of corticosteroids to treat complications |

not turn out to be a problem (e.g., parasitic infection in those treated with IL-5 or eosinophil inhibition or overwhelming sepsis in those treated with IL-6 inhibition). (iii) Corticosteroids are worse than you think. We often tend to underestimate the risk of the familiar and assume that the infection risk from new and expensive biologicals must be much higher than that of corticosteroids, which most clinicians prescribe quite often. However, the reverse seems to be true: the risk of any serious infection appears to be higher with prolonged corticosteroids than with most biologics, and combining steroids with biologics greatly augments the infection-related risk. (iv) Biologic and small molecule immunosuppressive agents should not all be painted with the same brush—there is a wide spectrum of risk between the various agents, ranging from almost none to very high (Tables 18 and 19). (v) Preventive strategies are usually effective but often are neglected or are impractical. Clinicians treating a patient with one of these agents are usually primarily concerned with the target syndrome, which may be rapidly progressive and life-threatening. Hence, opportunities for prevention may be overlooked or be impossible in the time frame (e.g., vaccinations prior to treatment or treatment of LTBI with isoniazid or rifampin). Simpler and more effective prevention strategies are needed and should be an active area of research. This includes vaccines that are safe to give after the onset of immunosuppression (e.g., the new recombinant varicella vaccine), shorter courses of treatment for latent tuberculosis infection, and better risk prediction models to select out those who should be offered prophylactic anti-infectious treatments. Finally, (vi) practicing clinicians need to learn about and keep abreast of new developments in biologic therapies. While these started out being developed for relatively niche indications in rheumatoid arthritis and selected malignancies, biologics and small molecule immunosuppressive agents are now mainstream treatments in dermatology, ophthalmology, respiratory medicine, gastroenterology, oncology, hematology, neurology, rheumatology, immunology, and transplant medicine, and this list will almost certainly grow over time. In addition, the practice of infectious diseases and general internal medicine is highly relevant to all of these agents, because of their consequences.

Despite the caveats listed above, there are some infectious complications with well-established evidence for a specific association, independent of background immunosuppression. Such associations are presented in Table 20.

Prevention of infection should be considered in every patient prior to the initiation of biologic or small molecule immunomodulatory therapy, with the possible exception of the agents listed in Table 18. The recommendations for specific actions are contextual, depending on the agent, the concomitant therapy, the underlying disease process, and the geographical and behavioral circumstances of the patient. Hence, it is difficult to summarize the recommendations across all agents. The discussion of prevention at the end of each section of this article is the best place to look for these recommendations, although even there, the recommendations are often uncertain or limited due to a lack of evidence or large interindividual variation in risk. Having said that, there are several measures that can be recommended in all patients prior to the use of any agent

**TABLE 19** Infection risk gradient for biological immunomodulatory agents

| Risk category, drug(s) | Key details[a] |
|---|---|
| High risk | |
| Anti-CD52 MAb (alemtuzumab) | Herpes zoster in ~3%<br>CMV reactivation at 20–50% in lymphoma patients and <1% in MS patients<br>PML in 0.5%<br>Serious infections in 4.2%<br>*Pneumocystis* pneumonia and tuberculosis reactivation also described, but risk estimates vary widely<br>Also applies to blinatumomab, daratumumab and elotuzumab, but fewer data are available for these agents |
| Moderate risk—high consequences | |
| Natalizumab | PML due to JC virus reactivation in 4.2/1,000 patients after 5 years of treatment; individual risk depends on JC virus serology, previous or concomitant immunosuppression, and duration of therapy |
| Bruton's tyrosine kinase inhibitors (ibrutinib, acalabrutinib) | Invasive fungal infections; reported incidence varies widely, from 0–44%<br>Serious respiratory tract infections in 20–68% |
| Moderate risk—low to moderate consequences | |
| TNF inhibitors (infliximab, etanercept, adalimumab, certolizumab, golimumab) | HBV reactivation in 12–39%<br>Tuberculosis reactivation at 117/100,000 PY<br>Serious infections at 4.5–14.0/100 PY |
| Anti-CD20 MAbs (rituximab, ocrelizumab, ofatumumab, obinutuzumab) | Serious infections at 31.8/100 PY with underlying lymphoma and 5/100 PY with underlying RA<br>HBV reactivation in up to 42% |
| IL-6 pathway inhibitors (tocilizumab, sarilumab, siltuximab) | Serious infections in 2.7% or at 4.0–4.5/100 PY |
| IL-17 pathway inhibitors (secukinumab, ixekizumab, brodalumab) | Mucocutaneous candidiasis in 3–4% |
| JAK inhibitors (tofacitinib, baricitinib, ruxolitinib) | Serious infections at 2.6–3.1/100 PY for tofacitinib<br>Herpes zoster at 2.5–5.3/100 PY |
| BCR-ABL inhibitors (most data relate to imatinib) | HBV in 1–10% if $HBsAg^+$<br>Herpes zoster and CMV present low risk, not clearly quantified, but higher than for placebo |

[a]Percentages refer to proportion of patients experiencing each infection during the reported trial or cohort study, over various periods of follow up. HBV, hepatitis B virus; PML, progressive multifocal leukoencephalopathy; RA, rheumatoid arthritis; CMV; cytomegalovirus.

discussed in this article, including those listed in Table 18. These include the following: (i) optimization of skin health, through identification and treatment of xerodermatitis, pyoderma, ulcerating skin cancers, scabies infection, and other potential portals of infection; (ii) optimization of respiratory health, through smoking cessation, use of regular inhaled long-acting bronchodilators and/or corticosteroids where indicated, and treatment of chronic or recurrent sinusitis with antibiotics and/or local measures like lavage or functional endoscopic sinus surgery; (iii) provision of pneumococcal vaccination (13-valent conjugate vaccine followed 8 weeks later by 23-valent polysaccharide vaccine, with a repeat 23-valent polysaccharide vaccine every 5 years) and influenza vaccination (yearly); and (iv) behavior modification to minimize infection risk, including the use of personal protective equipment (gloves, respirator, boots, and long

**TABLE 20** Key well-established associations between biological agents and particular infections

| Target | Exemplar | Key infectious association | Notes |
|---|---|---|---|
| TNF | Infliximab | Reactivation of latent tuberculosis | Gradient of risk: etanercept/certolizumab→infliximab |
| CD20 | Rituximab | Reactivation of HBV infection | Also described with ocrelizumab |
| CD52 | Alemtuzumab | AIDS-like syndrome (profound CD4 depletion) | Pneumocystis pneumonia, reactivation of CMV, VZV, HSV, and tuberculosis |
| IL-17 | Secukinumab | Mucocutaneous candidiasis | Also seen with brodalumab and ixekizumab; minimal other infectious risk |
| Integrins | Natalizumab | PML due to JC virus reactivation | Not seen with gut selective agents (vedolizumab) |
| Bruton's tyrosine kinase | Ibrutinib | Invasive fungal infections | Aggressive/atypical presentations |
| Complement pathway inhibitors | Eculizumab | Infections with *Neisseria* spp. | About 1,000 times the rate in the background population |

pants) when gardening or renovating houses, avoidance of unprotected sexual intercourse with casual partners, avoidance of major building excavation, avoidance of foods with a potential for contamination by *Listeria* spp., including soft cheeses, raw seafood, and salad bars, and seeking expert advice prior to travelling to low- or middle-income countries.

In conclusion, biologic and small molecule targeted immunosuppressive therapies have revolutionized the treatment of many conditions over the past 2 decades and are likely to become more commonly used for a wider range of indications in the near future. Awareness of, vigilance for, and tailored preventative strategies against their infectious complications are needed to ensure that the risk-benefit ratio of these agents remains firmly on the benefit side of the ledger.

## ACKNOWLEDGMENTS

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. J.S.D. received salary support from Australia's National Health and Medical Research Council (Career Development Fellowship number 1160331).

## REFERENCES

1. Ecker DM, Jones SD, Levine HL. 2015. The therapeutic monoclonal antibody market. MAbs 7:9–14. https://doi.org/10.4161/19420862.2015.989042.
2. Singh S, Kumar N, Dwiwedi P, Charan J, Kaur R, Sidhu P, Chugh VK. 2018. Monoclonal antibodies: a review. Curr Clin Pharmacol 13:85–99. https://doi.org/10.2174/1574884712666170809124728.
3. PhRMA. 2013. Medicines in development for biologics 2013 report. Pharmaceutical Research and Manufacturers of America, Washington, DC.
4. Keyser FD. 2011. Choice of biologic therapy for patients with rheumatoid arthritis: the infection perspective. Curr Rheumatol Rev 7:77–87.618. https://doi.org/10.2174/157339711794474620.
5. D'Haens G. 2007. Risks and benefits of biologic therapy for inflammatory bowel diseases. Gut 56:725–732. https://doi.org/10.1136/gut.2006.103564.
6. Salvana EMT, Salata RA. 2009. Infectious complications associated with monoclonal antibodies and related small molecules. Clin Microbiol Rev 22:274–290. https://doi.org/10.1128/CMR.00040-08.
7. Burton DR. 1987. Structure and function of antibodies, p 1–50. *In* Calabi F, Neuberger MS (ed), Molecular genetics of immunoglobulin. New comprehensive biochemistry, vol 17. Elsevier Science, New York, NY.
8. Sela-Culang I, Kunik V, Ofran Y. 2013. The structural basis of antibody-antigen recognition. Front Immunol 4:302. https://doi.org/10.3389/fimmu.2013.00302.
9. Scheen AJ. 2009. International classification of various types of monoclonal antibodies. Rev Med Liege 64:244–247.
10. Harding FA, Stickler MM, Razo J, DuBridge RB. 2010. The immunogenicity of humanized and fully human antibodies: residual immunogenicity resides in the CDR regions. MAbs 2:256–265. https://doi.org/10.4161/mabs.2.3.11641.
11. Weiner LM. 2006. Fully human therapeutic monoclonal antibodies. J Immunother 29:1–9. https://doi.org/10.1097/01.cji.0000192105.24583.83.
12. Baldo BA. 2015. Chimeric fusion proteins used for therapy: indications, mechanisms, and safety. Drug Saf 38:455–479. https://doi.org/10.1007/s40264-015-0285-9.
13. Bolton AE. 2005. Biologic effects and basic science of a novel immune-modulation therapy. Am J Cardiol 95:24–29. https://doi.org/10.1016/j.amjcard.2005.03.009.
14. Bolon B. 2012. Cellular and molecular mechanisms of autoimmune disease. Toxicol Pathol 40:216–229. https://doi.org/10.1177/0192623311428481.
15. Prakash O, Gill J, Farr G. 2002. Immune disorders and susceptibility to neoplasms. Ochsner J 4:107–111.
16. Lucey DR, Clerici M, Shearer GM. 1996. Type 1 and type 2 cytokine dysregulation in human infectious, neoplastic, and inflammatory diseases. Clin Microbiol Rev 9:532–562. https://doi.org/10.1128/CMR.9.4.532.
17. Arend WP. 1991. Interleukin 1 receptor antagonist. A new member of the interleukin 1 family. J Clin Invest 88:1445–1451. https://doi.org/10.1172/JCI115453.
18. Bendtzen K, Hansen MB, Ross C, Poulsen LK, Svenson M. 1995. Cytokines and autoantibodies to cytokines. Stem Cells 13:206–222. https://doi.org/10.1002/stem.5530130303.
19. van der Velden VH. 1998. Glucocorticoids: mechanisms of action and anti-inflammatory potential in asthma. Mediators Inflamma 7:229–237. https://doi.org/10.1080/09629359890910.
20. Magy N, Cribier B, Schmitt C, Ellero B, Jaeck D, Boudjema K, Wolf P, Labouret N, Doffoel M, Kirn A, Stoll-Keller F. 1999. Effects of corticosteroids on HCV infection. Int J Immunopharmacol 21:253–261. https://doi.org/10.1016/S0192-0561(99)00005-3.
21. Smitten AL, Choi HK, Hochberg MC, Suissa S, Simon TA, Testa MA, Chan KA. 2008. The risk of hospitalized infection in patients with rheumatoid arthritis. J Rheumatol 35:387–393.
22. Bryant PA, Baddley JW. 2017. Opportunistic infections in biological therapy, risk and prevention. Rheum Dis Clin North Am 43:27–41. https://doi.org/10.1016/j.rdc.2016.09.005.
23. Uettwiller F, Rigal E, Hoarau C. 2011. Infections associated with monoclonal antibody and fusion protein therapy in humans. MAbs 3:461–466. https://doi.org/10.4161/mabs.3.5.16553.
24. Ali T, Kaitha S, Mahmood S, Ftesi A, Stone J, Bronze MS. 2013. Clinical use of anti-TNF therapy and increased risk of infections. Drug Healthc Patient Saf 5:79–99. https://doi.org/10.2147/DHPS.S28801.
25. Kelesidis T, Daikos G, Boumpas D, Tsiodras S. 2011. Does rituximab increase the incidence of infectious complications? A narrative review. Int J Infect Dis 15:e2–e16. https://doi.org/10.1016/j.ijid.2010.03.025.
26. Dorner T, Radbruch A. 2007. Antibodies and B cell memory in viral immunity. Immunity 27:384–392. https://doi.org/10.1016/j.immuni.2007.09.002.
27. Parkin J, Cohen B. 2001. An overview of the immune system. Lancet 357:1777–1789. https://doi.org/10.1016/S0140-6736(00)04904-7.
28. Kang I, Park SH. 2003. Infectious complications in SLE after immunosuppressive therapies. Curr Opin Rheumatol 15:528–534. https://doi.org/10.1097/00002281-200309000-00002.
29. Glück T, Kiefmann B, Grohmann M, Falk W, Straub RH, Schölmerich J. 2005. Immune status and risk for infection in patients receiving chronic immunosuppressive therapy. J Rheumatol 32:1473–1480.
30. Toruner M, Loftus EV, Jr, Harmsen WS, Zinsmeister AR, Orenstein R, Sandborn WJ, Colombel JF, Egan LJ. 2008. Risk factors for opportunistic infections in patients with inflammatory bowel disease. Gastroenterology 134:929–936. https://doi.org/10.1053/j.gastro.2008.01.012.
31. McConachie SM, Wilhelm SM, Bhargava A, Kale-Pradhan PB. 2018. Biologic-induced infections in inflammatory bowel disease: the TNF-

alpha antagonists. Ann Pharmacother 52:571–579. https://doi.org/10.1177/1060028018754896.
32. Maini RN, Brennan FM, Williams R, Chu CQ, Cope AP, Gibbons D, Elliott M, Feldmann M. 1993. TNF-alpha in rheumatoid arthritis and prospects of anti-TNF therapy. Clin Exp Rheumatol 11(Suppl 8):S173–S175.
33. Feldmann M, Maini RN. 2001. Anti-TNF alpha therapy of rheumatoid arthritis: what have we learned? Annu Rev Immunol 19:163–196. https://doi.org/10.1146/annurev.immunol.19.1.163.
34. Plevy SE, Landers CJ, Prehn J, Carramanzana NM, Deem RL, Shealy D, Targan SR. 1997. A role for TNF-alpha and mucosal T helper-1 cytokines in the pathogenesis of Crohn's disease. J Immunol 159:6276.
35. Bradley JR. 2008. TNF-mediated inflammatory disease. J Pathol 214:149–160. https://doi.org/10.1002/path.2287.
36. Parameswaran N, Patial S. 2010. Tumor necrosis factor-$\alpha$ signaling in macrophages. Crit Rev Eukaryot Gene Expr 20:87–103. https://doi.org/10.1615/CritRevEukarGeneExpr.v20.i2.10.
37. Roach DR, Bean AG, Demangel C, France MP, Briscoe H, Britton WJ. 2002. TNF regulates chemokine induction essential for cell recruitment, granuloma formation, and clearance of mycobacterial infection. J Immunol 168:4620–4627. https://doi.org/10.4049/jimmunol.168.9.4620.
38. Tzeng H-T, Tsai H-F, Chyuan IT, Liao H-J, Chen C-J, Chen P-J, Hsu P-N. 2014. Tumor necrosis factor-alpha induced by hepatitis B virus core mediating the immune response for hepatitis B viral clearance in mice model. PLoS One 9:e103008. https://doi.org/10.1371/journal.pone.0103008.
39. Chyuan IT, Tsai H-F, Tzeng H-T, Sung C-C, Wu C-S, Chen P-J, Hsu P-N. 2015. Tumor necrosis factor-alpha blockage therapy impairs hepatitis B viral clearance and enhances T-cell exhaustion in a mouse model. Cell Mol Immunol 12:317–325. https://doi.org/10.1038/cmi.2015.01.
40. Carroll MB, Forgione MA. 2010. Use of tumor necrosis factor alpha inhibitors in hepatitis B surface antigen-positive patients: a literature review and potential mechanisms of action. Clin Rheumatol 29:1021–1029. https://doi.org/10.1007/s10067-010-1523-2.
41. Hayasaka D, Shirai K, Aoki K, Nagata N, Simantini DS, Kitaura K, Takamatsu Y, Gould E, Suzuki R, Morita K. 2013. TNF-$\alpha$ acts as an immunoregulator in the mouse brain by reducing the incidence of severe disease following Japanese encephalitis virus infection. PLoS One 8:e71643. https://doi.org/10.1371/journal.pone.0071643.
42. Ismail N, Stevenson HL, Walker DH. 2006. Role of tumor necrosis factor alpha (TNF-$\alpha$) and interleukin-10 in the pathogenesis of severe murine monocytotropic ehrlichiosis: increased resistance of TNF receptor p55- and p75-deficient mice to fatal ehrlichial infection. Infect Immun 74:1846–1856. https://doi.org/10.1128/IAI.74.3.1846-1856.2006.
43. Delfino D, D'Adamio F, Migliorati G, Riccardi C. 1991. Growth of murine natural killer cells from bone marrow in vitro: role of TNF alpha and IFN gamma. Int J Immunopharmacol 13:943–954. https://doi.org/10.1016/0192-0561(91)90047-B.
44. Currier NL, Miller SC. 2001. TNF-alpha further augments natural killer cells when co-administered with an interferon inducer to irradiated, leukemic, bone-marrow-transplanted mice. Cancer Chemother Pharmacol 47:185–186. https://doi.org/10.1007/s002800000222.
45. Pfeffer K, Matsuyama T, Kundig TM, Wakeham A, Kishihara K, Shahinian A, Wiegmann K, Ohashi PS, Kronke M, Mak TW. 1993. Mice deficient for the 55 kD tumor necrosis factor receptor are resistant to endotoxic shock, yet succumb to L. monocytogenes infection. Cell 73:457–467. https://doi.org/10.1016/0092-8674(93)90134-C.
46. Flynn JL, Goldstein MM, Chan J, Triebold KJ, Pfeffer K, Lowenstein CJ, Schrelber R, Mak TW, Bloom BR. 1995. Tumor necrosis factor-alpha is required in the protective immune response against Mycobacterium tuberculosis in mice. Immunity 2:561–572. https://doi.org/10.1016/1074-7613(95)90001-2.
47. Jeong D-G, Seo J-H, Heo S-H, Choi Y-K, Jeong E-S. 2015. Tumor necrosis factor-alpha deficiency impairs host defense against Streptococcus pneumoniae. Lab Anim Res 31:78–85. https://doi.org/10.5625/lar.2015.31.2.78.
48. Benton KA, VanCott JL, Briles DE. 1998. Role of tumor necrosis factor alpha in the host response of mice to bacteremia caused by pneumolysin-deficient Streptococcus pneumoniae. Infect Immun 66:839–842. https://doi.org/10.1128/IAI.66.2.839-842.1998.
49. Stoycheva M, Murdjeva M. 2005. Serum levels of interferon-gamma, interleukin-12, tumour necrosis factor-alpha, and interleukin-10, and bacterial clearance in patients with gastroenteric Salmonella infection. Scand J Infect Dis 37:11–14. https://doi.org/10.1080/00365540410026068.
50. Tripp CS, Wolf SF, Unanue ER. 1993. Interleukin 12 and tumor necrosis factor alpha are costimulators of interferon gamma production by natural killer cells in severe combined immunodeficiency mice with listeriosis, and interleukin 10 is a physiologic antagonist. Proc Natl Acad Sci U S A 90:3725–3729. https://doi.org/10.1073/pnas.90.8.3725.
51. Ferrante A. 1989. Tumor necrosis factor alpha potentiates neutrophil antimicrobial activity: increased fungicidal activity against Torulopsis glabrata and Candida albicans and associated increases in oxygen radical production and lysosomal enzyme release. Infect Immun 57:2115–2122. https://doi.org/10.1128/IAI.57.7.2115-2122.1989.
52. Roilides E, Dimitriadou-Georgiadou A, Sein T, Kadiltsoglou I, Walsh TJ. 1998. Tumor necrosis factor alpha enhances antifungal activities of polymorphonuclear and mononuclear phagocytes against Aspergillus fumigatus. Infect Immun 66:5999–6003. https://doi.org/10.1128/IAI.66.12.5999-6003.1998.
53. Huffnagle GB, Toews GB, Burdick MD, Boyd MB, McAllister KS, McDonald RA, Kunkel SL, Strieter RM. 1996. Afferent phase production of TNF-alpha is required for the development of protective T cell immunity to Cryptococcus neoformans. J Immunol 157:4529–4536.
54. Allendoerfer R, Deepe GS, Jr. 1998. Blockade of endogenous TNF-alpha exacerbates primary and secondary pulmonary histoplasmosis by differential mechanisms. J Immunol 160:6072–6082.
55. Aaltonen KJ, Virkki LM, Malmivaara A, Konttinen YT, Nordstrom DC, Blom M. 2012. Systematic review and meta-analysis of the efficacy and safety of existing TNF blocking agents in treatment of rheumatoid arthritis. PLoS One 7:e30275. https://doi.org/10.1371/journal.pone.0030275.
56. Lemos LL, de Oliveira Costa J, Almeida AM, Junior HO, Barbosa MM, Kakehasi AM, Acurcio FA. 2014. Treatment of psoriatic arthritis with anti-TNF agents: a systematic review and meta-analysis of efficacy, effectiveness and safety. Rheumatol Int 34:1345–1360. https://doi.org/10.1007/s00296-014-3006-2.
57. Moots RJ, Curiale C, Petersel D, Rolland C, Jones H, Mysler E. 2018. Efficacy and safety outcomes for originator TNF inhibitors and biosimilars in rheumatoid arthritis and psoriasis trials: a systematic literature Review. BioDrugs 32:193–199. https://doi.org/10.1007/s40259-018-0283-4.
58. Arnott ID, Watts D, Satsangi J. 2003. Azathioprine and anti-TNF alpha therapies in Crohn's disease: a review of pharmacology, clinical efficacy and safety. Pharmacol Res 47:1–10. https://doi.org/10.1016/S1043-6618(02)00264-5.
59. Oussalah A, Danese S, Peyrin-Biroulet L. 2010. Efficacy of TNF antagonists beyond one year in adult and pediatric inflammatory bowel diseases: a systematic review. Curr Drug Targets 11:156–175. https://doi.org/10.2174/138945010790309939.
60. Ford AC, Sandborn WJ, Khan KJ, Hanauer SB, Talley NJ, Moayyedi P. 2011. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol 106:644–659. https://doi.org/10.1038/ajg.2011.73.
61. Havmose M, Thomsen SF. 2017. Development of paradoxical inflammatory disorders during treatment of psoriasis with TNF inhibitors: a review of published cases. Int J Dermatol 56:1087–1102. https://doi.org/10.1111/ijd.13691.
62. Matucci A, Cammelli D, Cantini F, Goletti D, Marino V, Milano GM, Scarpa R, Tocci G, Maggi E, Vultaggio A. 2016. Influence of anti-TNF immunogenicity on safety in rheumatic disease: a narrative review. Expert Opin Drug Saf 15:3–10. https://doi.org/10.1080/14740338.2016.1221398.
63. Anonymous. 2012. Enbrel (etanercept). Full prescribing information. Reference ID 3225283. Food and Drug Administration, Silver Spring, MD.
64. Murdaca G, Negrini S, Magnani O, Penza E, Pellecchio M, Gulli R, Mandich P, Puppo F. 2018. Update upon efficacy and safety of etanercept for the treatment of spondyloarthritis and juvenile idiopathic arthritis. Mod Rheumatol 28:417–431. https://doi.org/10.1080/14397595.2017.1366006.
65. Horneff G. 2015. Biologic-associated infections in pediatric rheumatology. Curr Rheumatol Rep 17:66. https://doi.org/10.1007/s11926-015-0542-z.
66. Paller AS, Siegfried EC, Pariser DM, Rice KC, Trivedi M, Iles J, Collier DH, Kricorian G, Langley RG. 2016. Long-term safety and efficacy of etanercept in children and adolescents with plaque psoriasis. J Am

Acad Dermatol 74:280–287.e1-e3. https://doi.org/10.1016/j.jaad.2015.09.056.
67. Becker I, Horneff G. 2017. Risk of serious infection in juvenile idiopathic arthritis patients associated with tumor necrosis factor inhibitors and disease activity in the German Biologics in Pediatric Rheumatology Registry. Arthritis Care Res (Hoboken) 69:552–560. https://doi.org/10.1002/acr.22961.
68. Puig L, Camacho Martínez FM, Gimeno Carpio E, López-Ávila A, García-Calvo C. 2012. Efficacy and safety of clinical use of etanercept for the treatment of moderate-to-severe psoriasis in Spain: results of a multicentric prospective study at 12 months follow-up. Dermatology 225:220–230. https://doi.org/10.1159/000343605.
69. van der Heijde D, Zack D, Wajdula J, Sridharan S, Koenig AS. 2014. Rates of serious infections, opportunistic infections, inflammatory bowel disease, and malignancies in subjects receiving etanercept vs. controls from clinical trials in ankylosing spondylitis: a pooled analysis. Scand J Rheumatol 43:49–53. https://doi.org/10.3109/03009742.2013.834961.
70. Anonymous. 2017. Cimzia (certolizumab pegol). Full prescribing information. Reference ID 4036048. Food and Drug Administration, Silver Spring, MD. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125160s270lbl.pdf.
71. Maiz Alonso O, Blanco Esteban AC, Egües Dubuc CA, Martinez Zabalegui D. 2015. Effectiveness of certolizumab pegol in chronic anterior uveitis associated to Crohn's disease and ankylosing spondylitis. Reumatol Clin 11:189–190. https://doi.org/10.1016/j.reumae.2015.01.005.
72. Lopalco G, Emmi G, Gentileschi S, Guerriero S, Vitale A, Silvestri E, Becatti M, Cavallo I, Fabiani C, Frediani B, Iannone F, Cantarini L. 2017. Certolizumab pegol treatment in Behcet's disease with different organ involvement: a multicenter retrospective observational study. Mod Rheumatol 27:1031–1035. https://doi.org/10.1080/14397595.2017.1285857.
73. Murdaca G, Gulli R, Spano F, Lantieri F, Burlando M, Parodi A, Mandich P, Puppo F. 2014. TNF-alpha gene polymorphisms: association with disease susceptibility and response to anti-TNF-alpha treatment in psoriatic arthritis. J Invest Dermatol 134:2503–2509. https://doi.org/10.1038/jid.2014.123.
74. Murdaca G, Spano F, Contatore M, Guastalla A, Magnani O, Puppo F. 2014. Pharmacogenetics of etanercept: role of TNF-alpha gene polymorphisms in improving its efficacy. Expert Opin Drug Metab Toxicol 10:1703–1710. https://doi.org/10.1517/17425255.2014.970165.
75. Mascheretti S, Schreiber S. 2004. The role of pharmacogenomics in the prediction of efficacy of anti-TNF therapy in patients with Crohn's disease. Pharmacogenomics 5:479–486. https://doi.org/10.1517/14622416.5.5.479.
76. Bek S, Bojesen AB, Nielsen JV, Sode J, Bank S, Vogel U, Andersen V. 2017. Systematic review and meta-analysis: pharmacogenetics of anti-TNF treatment response in rheumatoid arthritis. Pharmacogenomics J 17:403–411. https://doi.org/10.1038/tpj.2017.26.
77. Komano Y, Tanaka M, Nanki T, Koike R, Sakai R, Kameda H, Nakajima A, Saito K, Takeno M, Atsumi T, Tohma S, Ito S, Tamura N, Fujii T, Sawada T, Ida H, Hashiramoto A, Koike T, Ishigatsubo Y, Eguchi K, Tanaka Y, Takeuchi T, Miyasaka N, Harigai M. 2011. Incidence and risk factors for serious infection in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors: a report from the Registry of Japanese Rheumatoid Arthritis Patients for Longterm Safety. J Rheumatol 38:1258–1264. https://doi.org/10.3899/jrheum.101009.
78. Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell LJ, MacDonald JK, Filippini G, Skoetz N, Francis DK, Lopes LC, Guyatt GH, Schmitt J, Mantia L, Weberschock T, Roos JF, Siebert H, Hershan S, Cameron C, Lunn MPT, Tugwell P, Buchbinder R. 2011. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev 16:CD008794. https://doi.org/10.1002/14651858.CD008794.pub2.
79. Murdaca G, Spano F, Contatore M, Guastalla A, Penza E, Magnani O, Puppo F. 2015. Infection risk associated with anti-TNF-alpha agents: a review. Expert Opin Drug Saf 14:571–582. https://doi.org/10.1517/14740338.2015.1009036.
80. van Dartel SAA, Fransen J, Kievit W, Flendrie M, den Broeder AA, Visser H, Hartkamp A, van de Laar M, van Riel P. 2013. Difference in the risk of serious infections in patients with rheumatoid arthritis treated with adalimumab, infliximab and etanercept: results from the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry. Ann Rheum Dis 72:895–900. https://doi.org/10.1136/annrheumdis-2012-201338.
81. Yoo IK, Choung RS, Hyun JJ, Kim SY, Jung SW, Koo JS, Lee SW, Choi JH, Kim H, Lee HS, Keum B, Kim ES, Jeen YT. 2014. Incidences of serious infections and tuberculosis among patients receiving anti-tumor necrosis factor-alpha therapy. Yonsei Med J 55:442–448. https://doi.org/10.3349/ymj.2014.55.2.442.
82. Salmon-Ceron D, Tubach F, Lortholary O, Chosidow O, Bretagne S, Nicolas N, Cuillerier E, Fautrel B, Michelet C, Morel J, Puéchal X, Wendling D, Lemann M, Ravaud P, Mariette X, RATIO Group. 2011. Drug-specific risk of non-tuberculosis opportunistic infections in patients receiving anti-TNF therapy reported to the 3-year prospective French RATIO registry. Ann Rheum Dis 70:616–623. https://doi.org/10.1136/ard.2010.137422.
83. Zingarelli S, Frassi M, Bazzani C, Scarsi M, Puoti M, Airo P. 2009. Use of tumor necrosis factor-alpha-blocking agents in hepatitis B virus-positive patients: reports of 3 cases and review of the literature. J Rheumatol 36:1188–1194. https://doi.org/10.3899/jrheum.081246.
84. Lee YH, Bae SC, Song GG. 2013. Hepatitis B virus reactivation in HBsAg-positive patients with rheumatic diseases undergoing anti-tumor necrosis factor therapy or DMARDs. Int J Rheum Dis 16:527–531. https://doi.org/10.1111/1756-185X.12154.
85. Cho YT, Chen CH, Chiu HY, Tsai TF. 2012. Use of anti-tumor necrosis factor-alpha therapy in hepatitis B virus carriers with psoriasis or psoriatic arthritis: a case series in Taiwan. J Dermatol 39:269–273. https://doi.org/10.1111/j.1346-8138.2011.01434.x.
86. Pérez-Alvarez R, Díaz-Lagares C, García-Hernández F, Lopez-Roses L, Brito-Zerón P, Pérez-de-Lis M, Retamozo S, Bové A, Bosch X, Sanchez-Tapias J-M, Forns X, Ramos-Casals M. 2011. Hepatitis B virus (HBV) reactivation in patients receiving tumor necrosis factor (TNF)-targeted therapy: analysis of 257 cases. Medicine (Baltimore) 90:359–371. https://doi.org/10.1097/MD.0b013e3182380a76.
87. Shale MJ. 2009. The implications of anti-tumour necrosis factor therapy for viral infection in patients with inflammatory bowel disease. Br Med Bull 92:61–77. https://doi.org/10.1093/bmb/ldp036.
88. Caso F, Cantarini L, Morisco F, Del Puente A, Ramonda R, Fiocco U, Lubrano E, Peluso R, Caso P, Galeazzi M, Punzi L, Scarpa R, Costa L. 2015. Current evidence in the field of the management with TNF-alpha inhibitors in psoriatic arthritis and concomitant hepatitis C virus infection. Expert Opin Biol Ther 15:641–650. https://doi.org/10.1517/14712598.2015.1011616.
89. Pompili M, Biolato M, Miele L, Grieco A. 2013. Tumor necrosis factor-$\alpha$ inhibitors and chronic hepatitis C: a comprehensive literature review. World J Gastroenterol 19:7867–7873. https://doi.org/10.3748/wjg.v19.i44.7867.
90. Brunasso AMG, Puntoni M, Gulia A, Massone C. 2011. Safety of anti-tumour necrosis factor agents in patients with chronic hepatitis C infection: a systematic review. Rheumatology 50:1700–1711. https://doi.org/10.1093/rheumatology/ker190.
91. Zein NN, Etanercept Study Group. 2005. Etanercept as an adjuvant to interferon and ribavirin in treatment-naive patients with chronic hepatitis C virus infection: a phase 2 randomized, double-blind, placebo-controlled study. J Hepatol 42:315–322. https://doi.org/10.1016/j.jhep.2004.11.025.
92. Cepeda EJ, Williams FM, Ishimori ML, Weisman MH, Reveille JD. 2007. The use of anti-tumour necrosis factor therapy in HIV-positive individuals with rheumatic disease. Ann Rheum Dis 67:710–712. https://doi.org/10.1136/ard.2007.081513.
93. Gallitano SM, McDermott L, Brar K, Lowenstein E. 2016. Use of tumor necrosis factor (TNF) inhibitors in patients with HIV/AIDS. J Am Acad Dermatol 74:974–980. https://doi.org/10.1016/j.jaad.2015.11.043.
94. Beltrán B, Nos P, Bastida G, Iborra M, Hoyos M, Ponce J. 2006. Safe and effective application of anti-TNF-$\alpha$ in a patient infected with HIV and concomitant Crohn's disease. Gut 55:1670–1671. https://doi.org/10.1136/gut.2006.101386.
95. Checchin D, Buda A, Sgarabotto D, Sturniolo GC, D'Incà R. 2009. Successful prophylaxis with valaciclovir for relapsing HSV-1 in a girl treated with infliximab for moderate Crohn's disease. Eur J Gastroenterol Hepatol 21:1095–1096. https://doi.org/10.1097/MEG.0b013e32831de271.
96. Bradford RD, Pettit AC, Wright PW, Mulligan MJ, Moreland LW, McLain DA, Gnann JW, Bloch KC. 2009. Herpes simplex encephalitis during treatment with tumor necrosis factor-$\alpha$ inhibitors. Clin Infect Dis 49:924–927. https://doi.org/10.1086/605498.

97. Strangfeld A, Listing J, Herzer P, Liebhaber A, Rockwitz K, Richter C, Zink A. 2009. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. JAMA 301:737–744. https://doi.org/10.1001/jama.2009.146.
98. Smitten AL, Choi HK, Hochberg MC, Suissa S, Simon TA, Testa MA, Chan KA. 2007. The risk of herpes zoster in patients with rheumatoid arthritis in the United States and the United Kingdom. Arthritis Rheum 57:1431–1438. https://doi.org/10.1002/art.23112.
99. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, Fischkoff SA, Chartash EK. 2004. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum 50:1400–1411. https://doi.org/10.1002/art.20217.
100. McKeown E, Pope JE, Leaf S. 2009. Epstein-Barr virus (EBV) prevalence and the risk of reactivation in patients with inflammatory arthritis using anti-TNF agents and in those who are biologic naive. Open Rheumatol J 3:30–34. https://doi.org/10.2174/1874312900903010030.
101. Couderc M, Payet S, Henquell C, Dubost JJ, Soubrier M. 2010. TNFalpha antagonist therapy does not increase the Epstein-Barr virus burden in patients with rheumatoid arthritis or ankylosing spondylitis. Joint Bone Spine 77:414–417. https://doi.org/10.1016/j.jbspin.2010.04.014.
102. Kim SY, Solomon DH. 2010. Tumor necrosis factor blockade and the risk of viral infection. Nat Rev Rheumatol 6:165–174. https://doi.org/10.1038/nrrheum.2009.279.
103. Mootoo A, Stylianou E, Arias MA, Reljic R. 2009. TNF-alpha in tuberculosis: a cytokine with a split personality. Inflamm Allergy Drug Targets 8:53–62. https://doi.org/10.2174/187152809787582543.
104. Jacobs M, Brown N, Allie N, Ryffel B. 2000. Fatal Mycobacterium bovis BCG infection in TNF-LT-alpha-deficient mice. Clin Immunol 94:192–199. https://doi.org/10.1006/clim.2000.4835.
105. Ehlers S, Benini J, Kutsch S, Endres R, Rietschel ET, Pfeffer K. 1999. Fatal granuloma necrosis without exacerbated mycobacterial growth in tumor necrosis factor receptor p55 gene-deficient mice intravenously infected with Mycobacterium avium. Infect Immun 67:3571–3579. https://doi.org/10.1128/IAI.67.7.3571-3579.1999.
106. Mohan VP, Scanga CA, Yu K, Scott HM, Tanaka KE, Tsang E, Tsai MM, Flynn JL, Chan J. 2001. Effects of tumor necrosis factor alpha on host immune response in chronic persistent tuberculosis: possible role for limiting pathology. Infect Immun 69:1847–1855. https://doi.org/10.1128/IAI.69.3.1847-1855.2001.
107. Chan MJ, Wen YH, Huang YB, Chuang HY, Tain YL, Lily Wang YC, Hsu CN. 2018. Risk of tuberculosis comparison in new users of antitumour necrosis factor-alpha and with existing disease-modifying antirheumatic drug therapy. J Clin Pharm Ther 43:256–264. https://doi.org/10.1111/jcpt.12644.
108. Gómez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD. 2003. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. Arthritis Rheumatism 48:2122–2127. https://doi.org/10.1002/art.11137.
109. Zhang Z, Fan W, Yang G, Xu Z, Wang J, Cheng Q, Yu M. 2017. Risk of tuberculosis in patients treated with TNF-$\alpha$ antagonists: a systematic review and meta-analysis of randomised controlled trials. BMJ Open 7:e012567. https://doi.org/10.1136/bmjopen-2016-012567.
110. Tragiannidis A, Kyriakidis I, Zundorf I, Groll AH. 2017. Invasive fungal infections in pediatric patients treated with tumor necrosis alpha (TNF-alpha) inhibitors. Mycoses 60:222–229. https://doi.org/10.1111/myc.12576.
111. Tsiodras S, Samonis G, Boumpas DT, Kontoyiannis DP. 2008. Fungal infections complicating tumor necrosis factor alpha blockade therapy. Mayo Clin Proc 83:181–194. https://doi.org/10.4065/83.2.181.
112. Marty FM, Lee SJ, Fahey MM, Alyea EP, Soiffer RJ, Antin JH, Baden LR. 2003. Infliximab use in patients with severe graft-versus-host disease and other emerging risk factors of non-Candida invasive fungal infections in allogeneic hematopoietic stem cell transplant recipients: a cohort study. Blood 102:2768–2776. https://doi.org/10.1182/blood-2003-01-0267.
113. Lee JH, Slifman NR, Gershon SK, Edwards ET, Schwieterman WD, Siegel JN, Wise RP, Brown SL, Udall JN, Jr, Braun MM. 2002. Life-threatening histoplasmosis complicating immunotherapy with tumor necrosis factor alpha antagonists infliximab and etanercept. Arthritis Rheum 46:2565–2570. https://doi.org/10.1002/art.10583.
114. Crum NF, Lederman ER, Wallace MR. 2005. Infections associated with tumor necrosis factor-$\alpha$ antagonists. Medicine (Baltimore) 84:291–302. https://doi.org/10.1097/01.md.0000180044.19285.9a.
115. No DJ, Amin M, Wu JJ. 2017. Adalimumab use in patients with psoriasis and hepatitis B: a case series. J Eur Acad Dermatol Venereol 31:e548–e550. https://doi.org/10.1111/jdv.14416.
116. Piaserico S, Dapavo P, Conti A, Gisondi P, Russo FP. 2017. Adalimumab is a safe option for psoriasis patients with concomitant hepatitis B or C infection: a multicentre cohort study of 37 patients and review of the literature. J Eur Acad Dermatol Venereol 31:1853–1859. https://doi.org/10.1111/jdv.14146.
117. Ballanti E, Conigliaro P, Chimenti MS, Kroegler B, Di Muzio G, Guarino MD, Triggianese P, Gigliucci G, Novelli L, Barbato C, Perricone R. 2014. Use of anti-tumor necrosis factor alpha therapy in patients with concurrent rheumatoid arthritis and hepatitis B or hepatitis C: a retrospective analysis of 32 patients. Drug Dev Res 75(Suppl 1):S42–S45. https://doi.org/10.1002/ddr.21193.
118. Laurenti R, Giovannangeli F, Gubinelli E, Viviano MT, Errico A, Leoni L, Ballanti E, Migliore A. 2013. Long-term safety of anti-TNF adalimumab in HBc antibody-positive psoriatic arthritis patients: a retrospective case series of 8 patients. Clin Dev Immunol 2013:410521. https://doi.org/10.1155/2013/410521.
119. Kouba M, Rudolph SE, Hrdlicka P, Zuber MA. 2012. Hepatitis-B reactivation during treatment with tumor necrosis factor-alpha blocker adalimumab in a patient with psoriasis arthritis. Dtsch Med Wochenschr 137:23–26. (In German.) https://doi.org/10.1055/s-0031-1292885.
120. Matsumoto T, Marusawa H, Dogaki M, Suginoshita Y, Inokuma T. 2010. Adalimumab-induced lethal hepatitis B virus reactivation in an HBsAg-negative patient with clinically resolved hepatitis B virus infection. Liver Int 30:1241–1242. https://doi.org/10.1111/j.1478-3231.2010.02238.x.
121. Verhelst X, Orlent H, Colle I, Geerts A, De Vos M, Van Vlierberghe H. 2010. Subfulminant hepatitis B during treatment with adalimumab in a patient with rheumatoid arthritis and chronic hepatitis B. Eur J Gastroenterol Hepatol 22:494–499. https://doi.org/10.1097/meg.0b013e3283329d13.
122. Mori S, Fujiyama S. 2015. Hepatitis B virus reactivation associated with antirheumatic therapy: risk and prophylaxis recommendations. World J Gastroenterol 21:10274–10289. https://doi.org/10.3748/wjg.v21.i36.10274.
123. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, Sharp J, Perez JL, Spencer-Green GT. 2006. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 54:26–37. https://doi.org/10.1002/art.21519.
124. Burmester GR, Mariette X, Montecucco C, Monteagudo-Sáez I, Malaise M, Tzioufas AG, Bijlsma JWJ, Unnebrink K, Kary S, Kupper H. 2007. Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the Research in Active Rheumatoid Arthritis (ReAct) trial. Ann Rheum Dis 66:732–739. https://doi.org/10.1136/ard.2006.066761.
125. Burmester G-R, Kivitz AJ, Kupper H, Arulmani U, Florentinus S, Goss SL, Rathmann SS, Fleischmann RM. 2015. Efficacy and safety of ascending methotrexate dose in combination with adalimumab: the randomised CONCERTO trial. Ann Rheum Dis 74:1037–1044. https://doi.org/10.1136/annrheumdis-2013-204769.
126. Colombel JF, Sandborn WJ, Reinisch W, Peyrin-Biroulet L, Panaccione R, Rutgeerts P, Hanauer SB, Ghosh S, Van Assche G, Robinson AM, Lau W, Maa JF, Huang B, Pappalardo B, Read H. 2018. Long-term safety of adalimumab in clinical trials in adult patients with Crohn's disease or ulcerative colitis. Aliment Pharmacol Ther 47:219–228. https://doi.org/10.1111/apt.14420.
127. Reinisch W, Sandborn WJ, Hommes DW, Haens G, Hanauer S, Schreiber S, Panaccione R, Fedorak RN, Tighe MB, Huang B, Kampman W, Lazar A, Thakkar R. 2011. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut 60:780–787. https://doi.org/10.1136/gut.2010.221127.
128. Kestens C, van Oijen MGH, Mulder CLJ, van Bodegraven AA, Dijkstra G,

de Jong D, Ponsioen C, van Tuyl BAC, Siersema PD, Fidder HH, Oldenburg B. 2013. Adalimumab and infliximab are equally effective for Crohn's disease in patients not previously treated with anti–tumor necrosis factor-$\alpha$ agents. Clin Gastroenterol Hepatol 11:826–831. https://doi.org/10.1016/j.cgh.2013.01.012.
129. Azevedo VF, Pietrovski CF, de Almeida Santos M, Jr. 2010. Acute toxoplasmosis infection in a patient with ankylosing spondylitis treated with adalimumab: a case report. Reumatismo 62:283–285. (In Italian.) https://doi.org/10.4081/reumatismo.2010.283.
130. Díaz F, Urkijo JC, Mendoza F, de la Viuda JM, Blanco M, Unzurrunzaga A, Ayarza R. 2008. Mycobacterium chelonae infection associated with adalimumab therapy. Scand J Rheumatol 37:159–160. https://doi.org/10.1080/03009740701716876.
131. Ray M, Curtis JR, Baddley JW. 2014. A case report of progressive multifocal leucoencephalopathy (PML) associated with adalimumab. Ann Rheum Dis 73:1429–1430. https://doi.org/10.1136/annrheumdis-2013-204978.
132. Catala A, Roe E, Dalmau J, Pomar V, Munoz C, Yelamos O, Puig L. 2015. Anti-tumour necrosis factor-induced visceral and cutaneous leishmaniasis: case report and review of the literature. Dermatology 230:204–207. https://doi.org/10.1159/000370238.
133. Ramasamy BR, Charles P, Johnson D, Frauman A. 2017. Massive splenomegaly due to concurrent primary Epstein-Barr virus and cytomegalovirus infection in a patient on adalimumab. BMJ Case Rep 2017:bcr-2017-220184. https://doi.org/10.1136/bcr-2017-220184.
134. Chang MB, Sri JC, Driscoll M, Gaspari AA. 2011. Mycobacterium fortuitum infection following adalimumab treatment for psoriasis and subsequent complication-free treatment with alternate TNF-a blockers. J Drugs Dermatol 10:914–916.
135. Kolikonda MK, Jayakumar P, Sriramula S, Lippmann S. 2017. Kocuria kristinae infection during adalimumab treatment. Postgrad Med 129:296–298. https://doi.org/10.1080/00325481.2017.1250606.
136. Jain A, Singh JA. 2013. Harms of TNF inhibitors in rheumatic diseases: a focused review of the literature. Immunotherapy 5:265–299. https://doi.org/10.2217/imt.13.10.
137. Schneeweiss S, Korzenik J, Solomon DH, Canning C, Lee J, Bressler B. 2009. Infliximab and other immunomodulating drugs in patients with inflammatory bowel disease and the risk of serious bacterial infections. Aliment Pharmacol Ther 30:253–264. https://doi.org/10.1111/j.1365-2036.2009.04037.x.
138. Baeten D, Kruithof E, Van den Bosch F, Van den Bossche N, Herssens A, Mielants H, De Keyser F, Veys EM. 2003. Systematic safety follow up in a cohort of 107 patients with spondyloarthropathy treated with infliximab: a new perspective on the role of host defence in the pathogenesis of the disease? Ann Rheum Dis 62:829–834. https://doi.org/10.1136/ard.62.9.829.
139. Cooper C, Shafran S, Greenbloom S, Enns R, Farley J, Hilzenrat N, Williams K, Elkashab M, Abadir N, Neuman M. 2014. Single-dose infliximab in hepatitis C genotype 1 treatment-naive patients with high serum tumour necrosis factor-alpha does not influence the efficacy of pegylated interferon alpha-2b/ribavirin therapy. Can J Gastroenterol Hepatol 28:35–40. https://doi.org/10.1155/2014/367131.
140. Parke FA, Reveille JD. 2004. Anti-tumor necrosis factor agents for rheumatoid arthritis in the setting of chronic hepatitis C infection. Arthritis Rheum 51:800–804. https://doi.org/10.1002/art.20702.
141. Oniankitan O, Duvoux C, Challine D, Mallat A, Chevalier X, Pawlotsky JM, Claudepierre P. 2004. Infliximab therapy for rheumatic diseases in patients with chronic hepatitis B or C. J Rheumatol 31:107–109.
142. Campbell S, Ghosh S. 2001. Infliximab therapy for Crohn's disease in the presence of chronic hepatitis C infection. Eur J Gastroenterol Hepatol 13:191–192. https://doi.org/10.1097/00042737-200102000-00016.
143. Aslanidis S, Vassiliadis T, Pyrpasopoulou A, Douloumpakas I, Zamboulis C. 2006. Inhibition of TNFalpha does not induce viral reactivation in patients with chronic hepatitis C infection: two cases. Clin Rheumatol 26:261–264. https://doi.org/10.1007/s10067-006-0394-z.
144. Ferri C, Ferraccioli G, Ferrari D, Galeazzi M, Lapadula G, Montecucco C, Triolo G, Valentini G, Valesini G. 2008. Safety of anti-tumor necrosis factor-alpha therapy in patients with rheumatoid arthritis and chronic hepatitis C virus infection. J Rheumatol 35:1944–1949.
145. Habib SF, Hasan MZ, Salam I. 2009. Infliximab therapy for HIV positive Crohn's disease: a case report. J Crohns Colitis 3:302–304. https://doi.org/10.1016/j.crohns.2009.06.002.
146. Gaylis NB. 2012. Long-term follow-up of an HIV-infected patient with reactive arthritis treated with infliximab. J Clin Rheumatol 18:153–154. https://doi.org/10.1097/RHU.0b013e31824e9151.
147. Sellam J, Bouvard B, Masson C, Rousière M, Villoutreix C, Lacombe K, Khanine V, Chennebault J-M, Leclech C, Audran M, Berenbaum F. 2007. Use of infliximab to treat psoriatic arthritis in HIV-positive patients. Joint Bone Spine 74:197–200. https://doi.org/10.1016/j.jbspin.2006.05.012.
148. Gaylis N. 2003. Infliximab in the treatment of an HIV positive patient with Reiter's syndrome. J Rheumatol 30:407–411.
149. Nakamura M, Abrouk M, Farahnik B, Zhu TH, Bhutani T. 2018. Psoriasis treatment in HIV-positive patients: a systematic review of systemic immunosuppressive therapies. Cutis 101:38.
150. Garcia-Vidal C, Rodríguez-Fernández S, Teijón S, Esteve M, Rodríguez-Carballeira M, Lacasa JM, Salvador G, Garau J. 2009. Risk factors for opportunistic infections in infliximab-treated patients: the importance of screening in prevention. Eur J Clin Microbiol Infect Dis 28:331–337. https://doi.org/10.1007/s10096-008-0628-x.
151. Perdriger A. 2009. Infliximab in the treatment of rheumatoid arthritis. Biologics 3:183–191. https://doi.org/10.2147/btt.2009.3099.
152. Westhovens R, Yocum D, Han J, Berman A, Strusberg I, Geusens P, Rahman MU, START Study Group. 2006. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. Arthritis Rheum 54:1075–1086. https://doi.org/10.1002/art.21734.
153. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, Smolen J, Emery P, Harriman G, Feldmann M, Lipsky P. 1999. Infliximab (chimeric anti-tumour necrosis factor $\alpha$ monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. Lancet 354:1932–1939. https://doi.org/10.1016/S0140-6736(99)05246-0.
154. St Clair EW, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, Keystone E, Schiff M, Kalden JR, Wang B, DeWoody K, Weiss R, Baker D, Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset Study Group. 2004. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum 50:3432–3443. https://doi.org/10.1002/art.20568.
155. Wang Q, Wen Z, Cao Q. 2016. Risk of tuberculosis during infliximab therapy for inflammatory bowel disease, rheumatoid arthritis, and spondyloarthropathy: a meta-analysis. Exp Ther Med 12:1693–1704. https://doi.org/10.3892/etm.2016.3548.
156. Wallis RS, Broder MS, Wong JY, Hanson ME, Beenhouwer DO. 2004. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clin Infect Dis 38:1261–1265. https://doi.org/10.1086/383317.
157. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P. 2002. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 359:1541–1549. https://doi.org/10.1016/S0140-6736(02)08512-4.
158. Sands BE, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, Kamm MA, Korzenik JR, Lashner BA, Onken JE, Rachmilewitz D, Rutgeerts P, Wild G, Wolf DC, Marsters PA, Travers SB, Blank MA, van Deventer SJ. 2004. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med 350:876–885. https://doi.org/10.1056/NEJMoa030815.
159. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJS, Present D, Sands BE, Colombel JF. 2005. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 353:2462–2476. https://doi.org/10.1056/NEJMoa050516.
160. Slifman NR, Gershon SK, Lee JH, Edwards ET, Braun MM. 2003. Listeria monocytogenes infection as a complication of treatment with tumor necrosis factor alpha-neutralizing agents. Arthritis Rheum 48:319–324. https://doi.org/10.1002/art.10758.
161. Vergidis P, Avery RK, Wheat LJ, Dotson JL, Assi MA, Antoun SA, Hamoud KA, Burdette SD, Freifeld AG, McKinsey DS, Money ME, Myint T, Andes DR, Hoey CA, Kaul DA, Dickter JK, Liebers DE, Miller RA, Muth WE, Prakash V, Steiner FT, Walker RC, Hage CA. 2015. Histoplasmosis complicating tumor necrosis factor-alpha blocker therapy: a retrospective analysis of 98 cases. Clin Infect Dis 61:409–417. https://doi.org/10.1093/cid/civ299.

162. Komano Y, Harigai M, Koike R, Sugiyama H, Ogawa J, Saito K, Sekiguchi N, Inoo M, Onishi I, Ohashi H, Amamoto F, Miyata M, Ohtsubo H, Hiramatsu K, Iwamoto M, Minota S, Matsuoka N, Kageyama G, Imaizumi K, Tokuda H, Okochi Y, Kudo K, Tanaka Y, Takeuchi T, Miyasaka N. 2009. Pneumocystis jiroveci pneumonia in patients with rheumatoid arthritis treated with infliximab: a retrospective review and case–control study of 21 patients. Arthritis Rheum 61:305–312. https://doi.org/10.1002/art.24283.
163. Beigel F, Jürgens M, Filik L, Bader L, Lück C, Göke B, Ochsenkühn T, Brand S, Seiderer J. 2009. Severe Legionella pneumophila pneumonia following infliximab therapy in a patient with Crohn's disease. Inflamm Bowel Dis 15:1240–1244. https://doi.org/10.1002/ibd.20866.
164. Seminerio JL, Loftus EV, Jr, Colombel JF, Thapa P, Sandborn WJ. 2013. Infliximab for Crohn's disease: the first 500 patients followed up through 2009. Dig Dis Sci 58:797–806. https://doi.org/10.1007/s10620-012-2405-z.
165. Kesteman T, Yombi JC, Gigi J, Durez P. 2007. Listeria infections associated with infliximab: case reports. Clin Rheumatol 26:2173–2175. https://doi.org/10.1007/s10067-007-0660-8.
166. Malkin J, Shrimpton A, Wiselka M, Barer MR, Duddridge M, Perera N. 2009. Olecranon bursitis secondary to Mycobacterium kansasii infection in a patient receiving infliximab for Behçet's disease. J Med Microbiol 58:371–373. https://doi.org/10.1099/jmm.0.006809-0.
167. Fabre S, Gibert C, Lechiche C, Jorgensen C, Sany J. 2005. Primary cutaneous Nocardia otitidiscaviarum infection in a patient with rheumatoid arthritis treated with infliximab. J Rheumatol 32:2432.
168. Zabana Y, Domènech E, Mañosa M, Garcia-Planella E, Bernal I, Cabré E, Gassull MA. 2010. Infliximab safety profile and long-term applicability in inflammatory bowel disease: 9-year experience in clinical practice. Aliment Pharmacol Ther 31:553–560. https://doi.org/10.1111/j.1365-2036.2009.04206.x.
169. Reichardt P, Dähnert I, Tiller G, Häusler H-J. 2002. Possible activation of an intramyocardial inflammatory process (Staphylococcus aureus) after treatment with infliximab in a boy with Crohn disease. Eur J Pediatr 161:281–283. https://doi.org/10.1007/s00431-002-0925-9.
170. Kling MC, Larian AA, Scordi-Bello I, Emer J, Lebwohl MG. 2010. Fatal influenza A(H1N1) respiratory tract infection in a patient having psoriasis treated with infliximab. Arch Dermatol 146:651–654. https://doi.org/10.1001/archdermatol.2010.96.
171. Keene DL, Legare C, Taylor E, Gallivan J, Cawthorn GM, Vu D. 2011. Monoclonal antibodies and progressive multifocal leukoencephalopathy. Can J Neurol Sci 38:565–571. https://doi.org/10.1017/S0317167100012105.
172. Yoshinari H, Saito K, Nakano K, Fukuyo S, Miyagawa I, Tanaka Y. 2017. A case of rheumatoid arthritis treated with infliximab who developed disseminated Penicillium marneffei infection after visit to Thailand. Mod Rheumatol Case Rep 1:43–48. https://doi.org/10.1080/24725625.2017.1295504.
173. Ting PT, Koo JY. 2006. Use of etanercept in human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) patients. Int J Dermatol 45:689–692. https://doi.org/10.1111/j.1365-4632.2005.02642.x.
174. Aboulafia DM, Bundow D, Wilske K, Ocas UI. 2000. Etanercept for the treatment of human immunodeficiency virus-associated psoriatic arthritis. Mayo Clin Proc 75:1093–1098. https://doi.org/10.4065/75.10.1093.
175. Genovese MC, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC, Wasko MC, Moreland LW, Weaver AL, Markenson J, Cannon GW, Spencer-Green G, Finck BK. 2002. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis Rheum 46:1443–1450. https://doi.org/10.1002/art.10308.
176. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, Mola EM, Pavelka K, Sany J, Settas L, Wajdula J, Pedersen R, Fatenejad S, Sanda M. 2004. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 363:675–681. https://doi.org/10.1016/S0140-6736(04)15640-7.
177. van Riel P, Taggart AJ, Sany J, Gaubitz M, Nab HW, Pedersen R, Freundlich B, MacPeek D, ADORE (Add Enbrel or Replace Methotrexate) Study Investigators. 2006. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: the ADORE study. Ann Rheum Dis 65:1478–1483. https://doi.org/10.1136/ard.2005.043299.
178. Camargo JF, Yakoub D, Cho-Vega JH. 2015. Successful treatment of primary cutaneous mucormycosis complicating anti-TNF therapy with a combination of surgical debridement and oral posaconazole. Mycopathologia 180:187–192. https://doi.org/10.1007/s11046-015-9914-1.
179. Toussi SS, Pan N, Walters HM, Walsh TJ. 2013. Infections in children and adolescents with juvenile idiopathic arthritis and inflammatory bowel disease treated with tumor necrosis factor-alpha inhibitors: systematic review of the literature. Clin Infect Dis 57:1318–1330. https://doi.org/10.1093/cid/cit489.
180. Tanaka M, Sakai R, Koike R, Komano Y, Nanki T, Sakai F, Sugiyama H, Matsushima H, Kojima T, Ohta S, Ishibe Y, Sawabe T, Ota Y, Ohishi K, Miyazato H, Nonomura Y, Saito K, Tanaka Y, Nagasawa H, Takeuchi T, Nakajima A, Ohtsubo H, Onishi M, Goto Y, Dobashi H, Miyasaka N, Harigai M. 2012. Pneumocystis jirovecii pneumonia associated with etanercept treatment in patients with rheumatoid arthritis: a retrospective review of 15 cases and analysis of risk factors. Mod Rheumatol 22:849–858. https://doi.org/10.3109/s10165-012-0615-z.
181. Dare JA, Jahan S, Hiatt K, Torralba KD. 2009. Reintroduction of etanercept during treatment of cutaneous Mycobacterium marinum infection in a patient with ankylosing spondylitis. Arthritis Rheum 61:583–586. https://doi.org/10.1002/art.24095.
182. Levy MS, Polsky D, Davidson A, Strober BE. 2008. Tinea versicolor associated with etanercept therapy. J Am Acad Dermatol 58:S99–S100. https://doi.org/10.1016/j.jaad.2007.01.023.
183. Chavez-Lopez M, Marquez-Diaz F, Aguayo-Leytte G. 2006. Cerebral cryptococcosis associated with etanercept. Enferm Infecc Microbiol Clin 24:288. (In Spanish.). https://doi.org/10.1016/s0213-005x(06)73780-6.
184. Biondo MI, Germano V, Pietrosanti M, Canzoni M, Marignani M, Stroffolini T, Salemi S, D'Amelio R. 2014. Lack of hepatitis B virus reactivation after anti-tumour necrosis factor treatment in potential occult carriers with chronic inflammatory arthropathies. Eur J Intern Med 25:482–484. https://doi.org/10.1016/j.ejim.2013.11.014.
185. Yun H, Xie F, Delzell E, Chen L, Levitan EB, Lewis JD, Saag KG, Beukelman T, Winthrop K, Baddley JW, Curtis JR. 2015. Risks of herpes zoster in patients with rheumatoid arthritis according to biologic disease-modifying therapy. Arthritis Care Res (Hoboken) 67:731–736. https://doi.org/10.1002/acr.22470.
186. Liao T-L, Chen Y-M, Liu H-J, Chen D-Y. 2017. Risk and severity of herpes zoster in patients with rheumatoid arthritis receiving different immunosuppressive medications: a case–control study in Asia. BMJ Open 7:e014032. https://doi.org/10.1136/bmjopen-2016-014032.
187. Kay J, Matteson EL, Dasgupta B, Nash P, Durez P, Hall S, Hsia EC, Han J, Wagner C, Xu Z, Visvanathan S, Rahman MU. 2008. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. Arthritis Rheum 58:964–975. https://doi.org/10.1002/art.23383.
188. Smolen JS, Kay J, Doyle MK, Landewe R, Matteson EL, Wollenhaupt J, Gaylis N, Murphy FT, Neal JS, Zhou Y, Visvanathan S, Hsia EC, Rahman MU. 2009. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet 374:210–221. https://doi.org/10.1016/S0140-6736(09)60506-7.
189. Emery P, Fleischmann RM, Moreland LW, Hsia EC, Strusberg I, Durez P, Nash P, Amante EJ, Churchill M, Park W, Pons-Estel BA, Doyle MK, Visvanathan S, Xu W, Rahman MU. 2009. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis Rheum 60:2272–2283. https://doi.org/10.1002/art.24638.
190. Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, Pazdur J, Bae SC, Palmer W, Zrubek J, Wiekowski M, Visvanathan S, Wu Z, Rahman MU. 2009. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-

FORWARD Study. Ann Rheum Dis 68:789–796. https://doi.org/10.1136/ard.2008.099010.
191. Hsia EC, Cush JJ, Matteson EL, Beutler A, Doyle MK, Hsu B, Xu S, Rahman MU. 2013. Comprehensive tuberculosis screening program in patients with inflammatory arthritides treated with golimumab, a human anti-tumor necrosis factor antibody, in phase III clinical trials. Arthritis Care Res (Hoboken) 65:309–313. https://doi.org/10.1002/acr.21788.
192. Kay J, Fleischmann R, Keystone E, Hsia EC, Hsu B, Mack M, Goldstein N, Braun J, Kavanaugh A. 2015. Golimumab 3-year safety update: an analysis of pooled data from the long-term extensions of randomised, double-blind, placebo-controlled trials conducted in patients with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis. Ann Rheum Dis 74:538–546. https://doi.org/10.1136/annrheumdis-2013-204195.
193. Bonovas S, Fiorino G, Allocca M, Lytras T, Nikolopoulos GK, Peyrin-Biroulet L, Danese S. 2016. Biologic therapies and risk of infection and malignancy in patients with inflammatory bowel disease: a systematic review and network meta-analysis. Clin Gastroenterol Hepatol 14:1385–1397.e10. https://doi.org/10.1016/j.cgh.2016.04.039.
194. Gibson PR, Feagan BG, Sandborn WJ, Marano C, Strauss R, Johanns J, Padgett L, Collins J, Tarabar D, Hebzda Z, Rutgeerts P, Reinisch W. 2016. Maintenance of efficacy and continuing safety of golimumab for active ulcerative colitis: PURSUIT-SC maintenance study extension through 1 year. Clin Transl Gastroenterol 7:e168. https://doi.org/10.1038/ctg.2016.24.
195. Alonso-Sierra M, Calvo M, González-Lama Y. 2016. Nocardia and Aspergillus coinfection in a patient with ulcerative colitis during golimumab therapy. J Crohns Colitis 10:1127–1128. https://doi.org/10.1093/ecco-jcc/jjw064.
196. Iglesias-Plaza A, Iglesias-Sancho M, Quintana-Codina M, Garcia-Miguel J, Salleras-Redonnet M. 2019. Syphilis in the setting of anti-tumor necrosis factor alpha therapy. Reumatol Clin 15:e108–e110. (In Spanish.). https://doi.org/10.1016/j.reuma.2017.12.008.
197. Misra DP, Chengappa KG, Mahadevan A, Jain VK, Negi VS. 2016. Sarcoidosis, neurotoxoplasmosis and golimumab therapy. QJM 109:817–818. https://doi.org/10.1093/qjmed/hcw197.
198. Guarneri C, Bevelacqua V, Patterson JW, Tchernev G. 2017. Cutaneous and visceral leishmaniasis during anti-TNFalpha therapy. Wien Med Wochenschr 167:78–82. https://doi.org/10.1007/s10354-016-0527-1.
199. Bodro M, Paterson DL. 2013. Listeriosis in patients receiving biologic therapies. Eur J Clin Microbiol Infect Dis 32:1225–1230. https://doi.org/10.1007/s10096-013-1873-1.
200. Capogrosso Sansone A, Mantarro S, Tuccori M, Ruggiero E, Montagnani S, Convertino I, Marino A, Fornai M, Antonioli L, Corona T, Garibaldi D, Blandizzi C. 2015. Safety profile of certolizumab pegol in patients with immune-mediated inflammatory diseases: a systematic review and meta-analysis. Drug Saf 38:869–888. https://doi.org/10.1007/s40264-015-0336-2.
201. Bykerk VP, Cush J, Winthrop K, Calabrese L, Lortholary O, de Longueville M, van Vollenhoven R, Mariette X. 2015. Update on the safety profile of certolizumab pegol in rheumatoid arthritis: an integrated analysis from clinical trials. Ann Rheum Dis 74:96–103. https://doi.org/10.1136/annrheumdis-2013-203660.
202. Schreiber S. 2011. Certolizumab pegol for the treatment of Crohn's disease. Therap Adv Gastroenterol 4:375–389. https://doi.org/10.1177/1756283X11413315.
203. Sandborn WJ, Feagan BG, Stoinov S, Honiball PJ, Rutgeerts P, Mason D, Bloomfield R, Schreiber S. 2007. Certolizumab pegol for the treatment of Crohn's disease. N Engl J Med 357:228–238. https://doi.org/10.1056/NEJMoa067594.
204. Mariette X, Vencovsky J, Lortholary O, Gomez-Reino J, de Longueville M, Ralston P, Weinblatt M, van Vollenhoven R. 2015. The incidence of tuberculosis in patients treated with certolizumab pegol across indications: impact of baseline skin test results, more stringent screening criteria and geographic region. RMD Open 1:e000044. https://doi.org/10.1136/rmdopen-2014-000044.
205. Olson TC, Bongartz T, Crowson CS, Roberts GD, Orenstein R, Matteson EL. 2011. Histoplasmosis infection in patients with rheumatoid arthritis, 1998–2009. BMC Infect Dis 11:145. https://doi.org/10.1186/1471-2334-11-145.
206. Nordgaard-Lassen I, Dahlerup JF, Belard E, Gerstoft J, Kjeldsen J, Kragballe K, Ravn P, Sorensen IJ, Theede K, Tjellesen L, Danish Society for Gastroenterology. 2012. Guidelines for screening, prophylaxis and critical information prior to initiating anti-TNF-alpha treatment. Dan Med J 59:C4480.
207. Reid CT, De Gascun C, Hall W, Collins P, Lally A, Kirby B. 2013. Is universal screening for hepatitis C infection prior to commencing antitumour necrosis factor-alpha therapy necessary? Br J Dermatol 169:1319–1321. https://doi.org/10.1111/bjd.12598.
208. Rahier JF, Magro F, Abreu C, Armuzzi A, Ben-Horin S, Chowers Y, Cottone M, de Ridder L, Doherty G, Ehehalt R, Esteve M, Katsanos K, Lees CW, MacMahon E, Moreels T, Reinisch W, Tilg H, Tremblay L, Veereman-Wauters G, Viget N, Yazdanpanah Y, Eliakim R, Colombel JF. 2014. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohns Colitis 8:443–468. https://doi.org/10.1016/j.crohns.2013.12.013.
209. British Thoracic Society Standards of Care Committee. 2005. BTS recommendations for assessing risk and for managing Mycobacterium tuberculosis infection and disease in patients due to start anti-TNF-alpha treatment. Thorax 60:800–805. https://doi.org/10.1136/thx.2005.046797.
210. Salpeter SR. 1993. Fatal isoniazid-induced hepatitis. Its risk during chemoprophylaxis. West J Med 159:560–564.
211. Schechter M, Zajdenverg R, Falco G, Barnes GL, Faulhaber JC, Coberly JS, Moore RD, Chaisson RE. 2006. Weekly rifapentine/isoniazid or daily rifampin/pyrazinamide for latent tuberculosis in household contacts. Am J Respir Crit Care Med 173:922–926. https://doi.org/10.1164/rccm.200512-1953OC.
212. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, Hackman J, Hamilton CD, Menzies D, Kerrigan A, Weis SE, Weiner M, Wing D, Conde MB, Bozeman L, Horsburgh CR, Chaisson RE. 2011. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med 365:2155–2166. https://doi.org/10.1056/NEJMoa1104875.
213. Menzies D, Adjobimey M, Ruslami R, Trajman A, Sow O, Kim H, Obeng Baah J, Marks GB, Long R, Hoeppner V, Elwood K, Al-Jahdali H, Gninafon M, Apriani L, Koesoemadinata RC, Kritski A, Rolla V, Bah B, Camara A, Boakye I, Cook VJ, Goldberg H, Valiquette C, Hornby K, Dion M-J, Li P-Z, Hill PC, Schwartzman K, Benedetti A. 2018. Four months of rifampin or nine months of isoniazid for latent tuberculosis in adults. N Engl J Med 379:440–453. https://doi.org/10.1056/NEJMoa1714283.
214. Lok AS, McMahon BJ. 2007. Chronic hepatitis B. Hepatology 45:507–539. https://doi.org/10.1002/hep.21513.
215. Marzano A. 2009. Management of HBV infection during immunosuppressive treatment. Mediterr J Hematol Infect Dis 1:e2009025. https://doi.org/10.4084/MJHID.2009.025.
216. Gisbert JP, Chaparro M, Esteve M. 2011. Review article: prevention and management of hepatitis B and C infection in patients with inflammatory bowel disease. Aliment Pharmacol Ther 33:619–633. https://doi.org/10.1111/j.1365-2036.2010.04570.x.
217. Wright SA, Taggart AJ. 2004. Pneumococcal vaccination for RA patients on TNF-$\alpha$ antagonists. Rheumatology 43:523–523. https://doi.org/10.1093/rheumatology/keh167.
218. Centers for Disease Control and Prevention. 2012. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 61:816–819.
219. Gisbert JP, Villagrasa JR, Rodriguez-Nogueiras A, Chaparro M. 2012. Efficacy of hepatitis B vaccination and revaccination and factors impacting on response in patients with inflammatory bowel disease. Am J Gastroenterol 107:1460–1466. https://doi.org/10.1038/ajg.2012.79.
220. Perry LM, Winthrop KL, Curtis JR. 2014. Vaccinations for rheumatoid arthritis. Curr Rheumatol Rep 16:431–431. https://doi.org/10.1007/s11926-014-0431-x.
221. Advisory Committee on Immunization Practices. 2009. Recommended adult immunization schedule: United States, 2009*. Ann Intern Med 150:40–44. https://doi.org/10.7326/0003-4819-150-1-200901060-00008.
222. Yatim KM, Lakkis FG. 2015. A brief journey through the immune system. Clin J Am Soc Nephrol 10:1274–1281. https://doi.org/10.2215/CJN.10031014.
223. Ito H, Seishima M. 2010. Regulation of the induction and function of cytotoxic T lymphocytes by natural killer T cell. J Biomed Biotechnol 2010:641757. https://doi.org/10.1155/2010/641757.
224. Voskoboinik I, Whisstock JC, Trapani JA. 2015. Perforin and granzymes:

function, dysfunction and human pathology. Nat Rev Immunol 15:388–400. https://doi.org/10.1038/nri3839.
225. Doucey MA, Legler DF, Faroudi M, Boucheron N, Baumgaertner P, Naeher D, Cebecauer M, Hudrisier D, Ruegg C, Palmer E, Valitutti S, Bron C, Luescher IF. 2003. The beta1 and beta3 integrins promote T cell receptor-mediated cytotoxic T lymphocyte activation. J Biol Chem 278:26983–26991. https://doi.org/10.1074/jbc.M302709200.
226. Ewen CL, Kane KP, Bleackley RC. 2012. A quarter century of granzymes. Cell Death Differ 19:28–35. https://doi.org/10.1038/cdd.2011.153.
227. Gasper DJ, Tejera MM, Suresh M. 2014. CD4 T-cell memory generation and maintenance. Crit Rev Immunol 34:121–146. https://doi.org/10.1615/CritRevImmunol.2014010373.
228. Ye B, Liu X, Li X, Kong H, Tian L, Chen Y. 2015. T-cell exhaustion in chronic hepatitis B infection: current knowledge and clinical significance. Cell Death Dis 6:e1694. https://doi.org/10.1038/cddis.2015.42.
229. Phillips S, Chokshi S, Riva A, Evans A, Williams R, Naoumov NV. 2010. CD8(+) T cell control of hepatitis B virus replication: direct comparison between cytolytic and noncytolytic functions. J Immunol 184:287–295. https://doi.org/10.4049/jimmunol.0902761.
230. Boni C, Fisicaro P, Valdatta C, Amadei B, Di Vincenzo P, Giuberti T, Laccabue D, Zerbini A, Cavalli A, Missale G, Bertoletti A, Ferrari C. 2007. Characterization of hepatitis B virus (HBV)-specific T-cell dysfunction in chronic HBV infection. J Virol 81:4215–4225. https://doi.org/10.1128/JVI.02844-06.
231. Pawlowski A, Jansson M, Sköld M, Rottenberg ME, Källenius G. 2012. Tuberculosis and HIV co-infection. PLoS Pathog 8:e1002464. https://doi.org/10.1371/journal.ppat.1002464.
232. Boom WH. 1996. The role of T-cell subsets in Mycobacterium tuberculosis infection. Infect Agents Dis 5:73–81.
233. Sakai S, Kauffman KD, Schenkel JM, McBerry CC, Mayer-Barber KD, Masopust D, Barber DL. 2014. Cutting edge: control of Mycobacterium tuberculosis infection by a subset of lung parenchyma-homing CD4 T cells. J Immunol 192:2965–2969. https://doi.org/10.4049/jimmunol.1400019.
234. Tubo NJ, Jenkins MK. 2014. CD4+ T cells: guardians of the phagosome. Clin Microbiol Rev 27:200–213. https://doi.org/10.1128/CMR.00097-13.
235. Lin PL, Flynn JL. 2015. CD8 T cells and Mycobacterium tuberculosis infection. Semin Immunopathol 37:239–249. https://doi.org/10.1007/s00281-015-0490-8.
236. Stenger S, Hanson DA, Teitelbaum R, Dewan P, Niazi KR, Froelich CJ, Ganz T, Thoma-Uszynski S, Melian A, Bogdan C, Porcelli SA, Bloom BR, Krensky AM, Modlin RL. 1998. An antimicrobial activity of cytolytic T cells mediated by granulysin. Science 282:121–125. https://doi.org/10.1126/science.282.5386.121.
237. van Pinxteren LA, Cassidy JP, Smedegaard BH, Agger EM, Andersen P. 2000. Control of latent Mycobacterium tuberculosis infection is dependent on CD8 T cells. Eur J Immunol 30:3689–3698. https://doi.org/10.1002/1521-4141(200012)30:12<3689::AID-IMMU3689>3.0.CO;2-4.
238. Anonymous. 2003. Package insert: Simulect (basiliximab), Novartis Pharmaceuticals Company. https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/basnov010203LB.htm. Accessed 7 July 2019.
239. Sun ZJ, Du X, Su LL, Zhang XD, Wang W. 2015. Efficacy and safety of basiliximab versus daclizumab in kidney transplantation: a meta-analysis. Transplant Proc 47:2439–2445. https://doi.org/10.1016/j.transproceed.2015.08.009.
240. Schmidt-Hieber M, Fietz T, Knauf W, Uharek L, Hopfenmuller W, Thiel E, Blau IW. 2005. Efficacy of the interleukin-2 receptor antagonist basiliximab in steroid-refractory acute graft-versus-host disease. Br J Haematol 130:568–574. https://doi.org/10.1111/j.1365-2141.2005.05631.x.
241. Trunečka P, Klempnauer J, Bechstein WO, Pirenne J, Friman S, Zhao A, Isoniemi H, Rostaing L, Settmacher U, Mönch C, Brown M, Undre N, Tisone G, the DIAMOND Study Group. 2015. Renal function in de novo liver transplant recipients receiving different prolonged-release tacrolimus regimens—The DIAMOND Study. Am J Transplant 15:1843–1854. https://doi.org/10.1111/ajt.13182.
242. Clinckart F, Bulpa P, Jamart J, Eucher P, Delaunois L, Evrard P. 2009. Basiliximab as an alternative to antithymocyte globulin for early immunosuppression in lung transplantation. Transplant Proc 41:607–609. https://doi.org/10.1016/j.transproceed.2008.12.028.
243. Kaine JL. 2007. Abatacept for the treatment of rheumatoid arthritis: a review. Curr Ther Res Clin Exp 68:379–399. https://doi.org/10.1016/j.curtheres.2007.12.001.
244. Gron KL, Glintborg B, Norgaard M, Mehnert F, Ostergaard M, Dreyer L, Krogh NS, Bjorner JB, Hetland ML. 2019. Comparative effectiveness of certolizumab pegol, abatacept and biosimilar infliximab in patients with rheumatoid arthritis treated in routine care. Observational data from the Danish DANBIO registry emulating a randomized trial. Arthritis Rheumatol 71:1997–2004. https://doi.org/10.1002/art.41031.
245. Schiff M, Keiserman M, Codding C, Songcharoen S, Berman A, Nayiager S, Saldate C, Li T, Aranda R, Becker JC, Lin C, Cornet PL, Dougados M. 2008. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis 67:1096–1103. https://doi.org/10.1136/ard.2007.080002.
246. Taylor PC. 2009. How do the efficacy and safety of abatacept and infliximab compare in the treatment of active RA? Nat Rev Rheumatol 5:126–127. https://doi.org/10.1038/ncprheum1022.
247. Maxwell LJ, Singh JA. 2010. Abatacept for rheumatoid arthritis: a Cochrane systematic review. J Rheumatol 37:234–245. https://doi.org/10.3899/jrheum.091066.
248. Song I-H, Heldmann F, Rudwaleit M, Haibel H, Weiß A, Braun J, Sieper J. 2011. Treatment of active ankylosing spondylitis with abatacept: an open-label, 24-week pilot study. Ann Rheum Dis 70:1108–1110. https://doi.org/10.1136/ard.2010.145946.
249. Meiners PM, Vissink A, Kroese FG, Spijkervet FK, Smitt-Kamminga NS, Abdulahad WH, Bulthuis-Kuiper J, Brouwer E, Arends S, Bootsma H. 2014. Abatacept treatment reduces disease activity in early primary Sjogren's syndrome (open-label proof of concept ASAP study). Ann Rheum Dis 73:1393–1396. https://doi.org/10.1136/annrheumdis-2013-204653.
250. Hoi A, Littlejohn G. 2014. Is there still a role for abatacept in the treatment of lupus? Expert Opin Biol Ther 14:1345–1350. https://doi.org/10.1517/14712598.2014.935329.
251. Langford CA, Monach PA, Specks U, Seo P, Cuthbertson D, McAlear CA, Ytterberg SR, Hoffman GS, Krischer JP, Merkel PA, Vasculitis Clinical Research Consortium. 2014. An open-label trial of abatacept (CTLA4-IG) in non-severe relapsing granulomatosis with polyangiitis (Wegener's). Ann Rheum Dis 73:1376–1379. https://doi.org/10.1136/annrheumdis-2013-204164.
252. Anonymous. 2011. Full prescribing information: Adcetris (brentuximab vedotin). Reference ID 3662552. Food and Drug Administration, Silver Spring, MD.
253. Nademanee A, Sureda A, Stiff P, Holowiecki J, Abidi M, Hunder N, Pecsok M, Uttarwar M, Purevjal I, Sweetenham J. 2018. Safety analysis of brentuximab vedotin from the phase III AETHERA trial in Hodgkin lymphoma in the post-transplant consolidation setting. Biol Blood Marrow Transplant 24:2354–2359. https://doi.org/10.1016/j.bbmt.2018.05.026.
254. Pro B, Advani R, Brice P, Bartlett NL, Rosenblatt JD, Illidge T, Matous J, Ramchandren R, Fanale M, Connors JM, Yang Y, Sievers EL, Kennedy DA, Shustov A. 2012. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. J Clin Oncol 30:2190–2196. https://doi.org/10.1200/JCO.2011.38.0402.
255. Raisch DW, Rafi JA, Chen C, Bennett CL. 2016. Detection of cases of progressive multifocal leukoencephalopathy associated with new biologicals and targeted cancer therapies from the FDA's adverse event reporting system. Exp Opin Drug Saf 15:1003–1011. https://doi.org/10.1080/14740338.2016.1198775.
256. Tudesq J-J, Vincent L, Lebrun J, Hicheri Y, Gabellier L, Busetto T, Merle C, Fegueux N, Ceballos P, Quittet P, Navarro R, Hillaire-Buys D, Cartron G. 2017. Cytomegalovirus infection with retinitis after brentuximab vedotin treatment for CD30(+) lymphoma. Open Forum Infect Dis 4:ofx091. https://doi.org/10.1093/ofid/ofx091.
257. Osherov M, Milo R. 2017. Daclizumab for the treatment of adults with relapsing forms of multiple sclerosis. Expert Rev Clin Pharmacol 10:1037–1047. https://doi.org/10.1080/17512433.2017.1366854.
258. Brooks M. 2 March 2018. MS drug daclizumab (Zinbryta) pulled from the market. Medscape, New York, NY. https://www.medscape.com/viewarticle/893352. Accessed 10 November 2019.
259. Ellis CN, Krueger GG, Alefacept Clinical Study Group. 2001. Treatment of chronic plaque psoriasis by selective targeting of memory effector

T lymphocytes. N Engl J Med 345:248–255. https://doi.org/10.1056/NEJM200107263450403.
260. Anonymous. 2011. Amevive (alefacept) voluntarily discontinued in the U.S. National Psoriasis Foundation, Portland, OR. https://www.psoriasis.org/media/press-releases/amevive-alefacept-voluntarily-discontinued-us. Accessed 10 November 2019.
261. Reichert JM. 2012. Marketed therapeutic antibodies compendium. MAbs 4:413–415. https://doi.org/10.4161/mabs.19931.
262. Adu D, Cockwell P, Ives NJ, Shaw J, Wheatley K. 2003. Interleukin-2 receptor monoclonal antibodies in renal transplantation: meta-analysis of randomised trials. BMJ 326:789. https://doi.org/10.1136/bmj.326.7393.789.
263. Webster AC, Playford EG, Higgins G, Chapman JR, Craig JC. 2004. Interleukin 2 receptor antagonists for renal transplant recipients: a meta-analysis of randomized trials1. Transplantation 77:166–176. https://doi.org/10.1097/01.TP.0000109643.32659.C4.
264. Keown P, Balshaw R, Khorasheh S, Chong M, Marra C, Kalo Z, Korn A. 2003. Meta-analysis of basiliximab for immunoprophylaxis in renal transplantation. BioDrugs 17:271–279. https://doi.org/10.2165/00063030-200317040-00006.
265. Liu Y, Zhou P, Han M, Xue CB, Hu XP, Li C. 2010. Basiliximab or antithymocyte globulin for induction therapy in kidney transplantation: a meta-analysis. Transplant Proc 42:1667–1670. https://doi.org/10.1016/j.transproceed.2010.02.088.
266. Ponticelli C, Yussim A, Cambi V, Legendre C, Rizzo G, Salvadori M, Kahn D, Kashi H, Salmela K, Fricke L, Heemann U, Garcia-Martinez J, Lechler R, Prestele H, Girault D, Simulect Phase IV Study Group. 2001. A randomized, double-blind trial of basiliximab immunoprophylaxis plus triple therapy in kidney transplant recipients. Transplantation 72:1261–1267. https://doi.org/10.1097/00007890-200110150-00014.
267. Nashan B, Moore R, Amlot P, Schmidt A-G, Abeywickrama K, Soulillou J-P. 1997. Randomised trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients. Lancet 350:1193–1198. https://doi.org/10.1016/S0140-6736(97)09278-7.
268. Kyriakidis I, Tragiannidis A, Zundorf I, Groll AH. 2017. Invasive fungal infections in paediatric patients treated with macromolecular immunomodulators other than tumour necrosis alpha inhibitors. Mycoses 60:493–507. https://doi.org/10.1111/myc.12621.
269. Wang XF, Li JD, Peng Y, Dai Y, Shi G, Xu W. 2010. Interleukin-2 receptor antagonists in liver transplantation: a meta-analysis of randomized trials. Transplant Proc 42:4567–4572. https://doi.org/10.1016/j.transproceed.2010.09.169.
270. Neuhaus P, Clavien PA, Kittur D, Salizzoni M, Rimola A, Abeywickrama K, Ortmann E, Chodoff L, Hall M, Korn A, Nashan B. 2002. Improved treatment response with basiliximab immunoprophylaxis after liver transplantation: results from a double-blind randomized placebo-controlled trial. Liver Transpl 8:132–142. https://doi.org/10.1053/jlts.2002.30302.
271. Mehra MR, Zucker MJ, Wagoner L, Michler R, Boehmer J, Kovarik J, Vasquez A. 2005. A multicenter, prospective, randomized, double-blind trial of basiliximab in heart transplantation. J Heart Lung Transplant 24:1297–1304. https://doi.org/10.1016/j.healun.2004.09.010.
272. Flaman F, Zieroth S, Rao V, Ross H, Delgado DH. 2006. Basiliximab versus rabbit anti-thymocyte globulin for induction therapy in patients after heart transplantation. J Heart Lung Transplant 25:1358–1362. https://doi.org/10.1016/j.healun.2006.09.002.
273. Ansari D, Höglund P, Andersson B, Nilsson J. 2015. Comparison of basiliximab and anti-thymocyte globulin as induction therapy in pediatric heart transplantation: a survival analysis. J Am Heart Assoc 5:e002790. https://doi.org/10.1161/JAHA.115.002790.
274. Butts RJ, Dipchand AI, Sutcliffe D, Bano M, Dimas V, Morrow R, Das B, Kirk R. 2018. Comparison of basiliximab vs antithymocyte globulin for induction in pediatric heart transplant recipients: an analysis of the International Society for Heart and Lung Transplantation database. Pediatr Transplant 22:e13190. https://doi.org/10.1111/petr.13190.
275. Borro JM, De la Torre M, Míguelez C, Fernandez R, Gonzalez D, Lemos C. 2005. Comparative study of basiliximab treatment in lung transplantation. Transplant Proc 37:3996–3998. https://doi.org/10.1016/j.transproceed.2005.09.192.
276. Whited LK, Latran MJ, Hashmi ZA, Wang IW, Wozniak TC, Duncan MD, Roe DW, Baz MA, Hage CA. 2015. Evaluation of alemtuzumab versus basiliximab induction: a retrospective cohort study in lung transplant recipients. Transplantation 99:2190–2195. https://doi.org/10.1097/TP.0000000000000687.
277. Furuya Y, Jayarajan SN, Taghavi S, Cordova FC, Patel N, Shiose A, Leotta E, Criner GJ, Guy TS, Wheatley GH, Kaiser LR, Toyoda Y. 2016. The impact of alemtuzumab and basiliximab induction on patient survival and time to bronchiolitis obliterans syndrome in double lung transplantation recipients. Am J Transplant 16:2334–2341. https://doi.org/10.1111/ajt.13739.
278. Zinzani PL, Sasse S, Radford J, Shonukan O, Bonthapally V. 2015. Experience of brentuximab vedotin in relapsed/refractory Hodgkin lymphoma and relapsed/refractory systemic anaplastic large-cell lymphoma in the Named Patient Program: review of the literature. Crit Rev Oncol Hematol 95:359–369. https://doi.org/10.1016/j.critrevonc.2015.03.011.
279. Gandolfi L, Pellegrini C, Casadei B, Stefoni V, Broccoli A, Tonialini L, Morigi A, Argnani L, Zinzani PL. 2016. Long-term responders after brentuximab vedotin: single-center experience on relapsed and refractory Hodgkin lymphoma and anaplastic large cell lymphoma patients. Oncologist 21:1436–1441. https://doi.org/10.1634/theoncologist.2016-0112.
280. Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, Birbara C, Box J, Natarajan K, Nuamah I, Li T, Aranda R, Hagerty DT, Dougados M. 2005. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med 353:1114–1123. https://doi.org/10.1056/NEJMoa050524.
281. Weinblatt M, Combe B, Covucci A, Aranda R, Becker JC, Keystone E. 2006. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and non-biologic disease-modifying antirheumatic drugs: a one-year randomized, placebo-controlled study. Arthritis Rheum 54:2807–2816. https://doi.org/10.1002/art.22070.
282. Weinblatt M, Schiff M, Goldman A, Kremer J, Luggen M, Li T, Chen D, Becker JC. 2006. Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: a randomised clinical trial. Ann Rheum Dis 66:228–234. https://doi.org/10.1136/ard.2006.055111.
283. Khraishi M, Russell A, Olszynski WP. 2010. Safety profile of abatacept in rheumatoid arthritis: a review. Clin Ther 32:1855–1870. https://doi.org/10.1016/j.clinthera.2010.10.011.
284. Montastruc F, Renoux C, Hudson M, Dell'Aniello S, Simon TA, Suissa S. 2019. Abatacept initiation in rheumatoid arthritis and the risk of serious infection: a population-based cohort study. Semin Arthritis Rheum 48:1053–1058. https://doi.org/10.1016/j.semarthrit.2019.01.009.
285. Fanouriakis A, Vassilopoulos D, Repa A, Boumpas DT, Sidiropoulos P. 2014. Hepatitis B reactivation following treatment with abatacept in a patient with past hepatitis B virus infection. Rheumatology (Oxford) 53:195–196. https://doi.org/10.1093/rheumatology/ket221.
286. Germanidis G, Hytiroglou P, Zakalka M, Settas L. 2012. Reactivation of occult hepatitis B virus infection, following treatment of refractory rheumatoid arthritis with abatacept. J Hepatol 56:1420–1421. https://doi.org/10.1016/j.jhep.2011.10.011.
287. Talotta R, Atzeni F, Sarzi Puttini P. 2016. Reactivation of occult hepatitis B virus infection under treatment with abatacept: a case report. BMC Pharmacol Toxicol 17:17. https://doi.org/10.1186/s40360-016-0060-2.
288. Padovan M, Filippini M, Tincani A, Lanciano E, Bruschi E, Epis O, Garau P, Mathieu A, Celletti E, Giani L, Tomietto P, Atzeni F, Sarzi Puttini P, Zuliani F, De Vita S, Trotta F, Grilli A, Puoti M, Govoni M. 2016. Safety of abatacept in rheumatoid arthritis with serologic evidence of past or present hepatitis B virus infection. Arthritis Care Res (Hoboken) 68:738–743. https://doi.org/10.1002/acr.22786.
289. Kim PS, Ho GY, Prete PE, Furst DE. 2012. Safety and efficacy of abatacept in eight rheumatoid arthritis patients with chronic hepatitis B. Arthritis Care Res (Hoboken) 64:1265–1268. https://doi.org/10.1002/acr.21654.
290. Bigbee CL, Gonchoroff DG, Vratsanos G, Nadler SG, Haggerty HG, Flynn JL. 2007. Abatacept treatment does not exacerbate chronic Mycobacterium tuberculosis infection in mice. Arthritis Rheum 56:2557–2565. https://doi.org/10.1002/art.22750.
291. Cantini F, Niccoli L, Goletti D. 2014. Tuberculosis risk in patients treated with non-anti-tumor necrosis factor-alpha (TNF-alpha) targeted biologics and recently licensed TNF-alpha inhibitors: data from clinical trials and national registries. J Rheumatol Suppl 91:56–64. https://doi.org/10.3899/jrheum.140103.
292. Lim CH, Chen HH, Chen YH, Chen DY, Huang WN, Tsai JJ, Hsieh TY,

Hsieh CW, Hung WT, Lin CT, Lai KL, Tang KT, Tseng CW, Chen YM. 2017. The risk of tuberculosis disease in rheumatoid arthritis patients on biologics and targeted therapy: a 15-year real world experience in Taiwan. PLoS One 12:e0178035. https://doi.org/10.1371/journal.pone.0178035.
293. Kawabe A, Nakano K, Miyata H, Shibuya R, Matsuyama A, Ogoshi T, Tanaka Y. 2019. Fatal chronic active Epstein-Barr virus infection in a rheumatoid arthritis patient treated with abatacept. Intern Med 58:585–591. https://doi.org/10.2169/internalmedicine.1280-18.
294. Dalal RS, LeGolvan MP, Stachurski DR, Goldberg LR. 2014. Epstein-Barr virus associated hemophagocytic lymphohistiocytosis in a rheumatic patient receiving abatacept therapy. R I Med J (2013) 97:28–31.
295. Nakajima H, Takayama A, Ito T, Yoshikawa T. 2013. Acute encephalomyelitis with multiple herpes viral reactivations during abatacept therapy. BMJ Case Rep 2013:bcr2013009731. https://doi.org/10.1136/bcr-2013-009731.
296. Balandraud N, Texier G, Massy E, Muis-Pistor O, Martin M, Auger I, Guzian MC, Guis S, Pham T, Roudier J. 2017. Long term treatment with abatacept or tocilizumab does not increase Epstein-Barr virus load in patients with rheumatoid arthritis—a three years retrospective study. PLoS One 12:e0171623. https://doi.org/10.1371/journal.pone.0171623.
297. Issa NC, Fishman JA, Snydman DR. 2009. Infectious complications of antilymphocyte therapies in solid organ transplantation. Clin Infect Dis 48:772–786. https://doi.org/10.1086/597089.
298. Cooper MD, Peterson RD, Good RA. 1965. Delineation of the thymic and bursal lymphoid systems in the chicken. Nature 205:143–146. https://doi.org/10.1038/205143a0.
299. LeBien TW, Tedder TF. 2008. B lymphocytes: how they develop and function. Blood 112:1570–1580. https://doi.org/10.1182/blood-2008-02-078071.
300. Forthal DN. 2014. Functions of antibodies. Microbiol Spectr 2:AID-0019-2014. https://doi.org/10.1128/microbiolspec.AID-0019-2014.
301. Chen X, Jensen PE. 2008. The role of B lymphocytes as antigen-presenting cells. Arch Immunol Ther Exp 56:77–83. https://doi.org/10.1007/s00005-008-0014-5.
302. Rivera A, Chen CC, Ron N, Dougherty JP, Ron Y. 2001. Role of B cells as antigen-presenting cells in vivo revisited: antigen-specific B cells are essential for T cell expansion in lymph nodes and for systemic T cell responses to low antigen concentrations. Int Immunol 13:1583–1593. https://doi.org/10.1093/intimm/13.12.1583.
303. Bouaziz J-D, Yanaba K, Venturi GM, Wang Y, Tisch RM, Poe JC, Tedder TF. 2007. Therapeutic B cell depletion impairs adaptive and autoreactive CD4(+) T cell activation in mice. Proc Natl Acad Sci U S A 104:20878–20883. https://doi.org/10.1073/pnas.0709205105.
304. Stavnezer J, Schrader CE. 2014. Ig heavy chain class switch recombination: mechanism and regulation. J Immunol 193:5370–5378. https://doi.org/10.4049/jimmunol.1401849.
305. Lykken JM, DiLillo DJ, Weimer ET, Roser-Page S, Heise MT, Grayson JM, Weitzmann MN, Tedder TF. 2014. Acute and chronic B cell depletion disrupts CD4(+) and CD8(+) T cell homeostasis and expansion during acute viral infection in mice. J Immunol 193:746–756. https://doi.org/10.4049/jimmunol.1302848.
306. Misumi I, Whitmire JK. 2014. B cell depletion curtails CD4+ T cell memory and reduces protection against disseminating virus infection. J Immunol 192:1597–1608. https://doi.org/10.4049/jimmunol.1302661.
307. Mazanec MB, Coudret CL, Fletcher DR. 1995. Intracellular neutralization of influenza virus by immunoglobulin A anti-hemagglutinin monoclonal antibodies. J Virol 69:1339–1343. https://doi.org/10.1128/JVI.69.2.1339-1343.1995.
308. Mazanec MB, Kaetzel CS, Lamm ME, Fletcher D, Nedrud JG. 1992. Intracellular neutralization of virus by immunoglobulin A antibodies. Proc Natl Acad Sci U S A 89:6901–6905. https://doi.org/10.1073/pnas.89.15.6901.
309. Baumgarth N. 2013. How specific is too specific? B-cell responses to viral infections reveal the importance of breadth over depth. Immunol Rev 255:82–94. https://doi.org/10.1111/imr.12094.
310. Xu X, Shang Q, Chen X, Nie W, Zou Z, Huang A, Meng M, Jin L, Xu R, Zhang J-Y, Fu J, Wang L, Tang Z, Xie Y, Yang X, Zhang Z, Wang F-S. 2015. Reversal of B-cell hyperactivation and functional impairment is associated with HBsAg seroconversion in chronic hepatitis B patients. Cell Mol Immunol 12:309–316. https://doi.org/10.1038/cmi.2015.25.
311. Wang G, Liu Y, Huang R, Jia B, Su R, Sun Z, Tian C, Xiong Y, Xia J, Yan X, Zhang Z, Wu C. 2017. Characteristics of regulatory B cells in patients with chronic hepatitis B virus infection in different immune phases. Discov Med 23:295–304.
312. Sugalski JM, Rodriguez B, Moir S, Anthony DD. 2010. Peripheral blood B cell subset skewing is associated with altered cell cycling and intrinsic resistance to apoptosis and reflects a state of immune activation in chronic hepatitis C virus infection. J Immunol 185:3019–3027. https://doi.org/10.4049/jimmunol.1000879.
313. Racanelli V, Frassanito MA, Leone P, Galiano M, De Re V, Silvestris F, Dammacco F. 2006. Antibody production and in vitro behavior of CD27-defined B-cell subsets: persistent hepatitis C virus infection changes the rules. J Virol 80:3923–3934. https://doi.org/10.1128/JVI.80.8.3923-3934.2006.
314. Dai B, Chen AY, Corkum CP, Peroutka RJ, Landon A, Houng S, Muniandy PA, Zhang Y, Lehrmann E, Mazan-Mamczarz K, Steinhardt J, Shlyak M, Chen QC, Becker KG, Livak F, Michalak TI, Talwani R, Gartenhaus RB. 2016. Hepatitis C virus upregulates B-cell receptor signaling: a novel mechanism for HCV-associated B-cell lymphoproliferative disorders. Oncogene 35:2979–2990. https://doi.org/10.1038/onc.2015.364.
315. Lavillette D, Morice Y, Germanidis G, Donot P, Soulier A, Pagkalos E, Sakellariou G, Intrator L, Bartosch B, Pawlotsky JM, Cosset FL. 2005. Human serum facilitates hepatitis C virus infection, and neutralizing responses inversely correlate with viral replication kinetics at the acute phase of hepatitis C virus infection. J Virol 79:6023–6034. https://doi.org/10.1128/JVI.79.10.6023-6034.2005.
316. Pestka JM, Zeisel MB, Blaser E, Schurmann P, Bartosch B, Cosset FL, Patel AH, Meisel H, Baumert J, Viazov S, Rispeter K, Blum HE, Roggendorf M, Baumert TF. 2007. Rapid induction of virus-neutralizing antibodies and viral clearance in a single-source outbreak of hepatitis C. Proc Natl Acad Sci U S A 104:6025–6030. https://doi.org/10.1073/pnas.0607026104.
317. Dowd KA, Netski DM, Wang XH, Cox AL, Ray SC. 2009. Selection pressure from neutralizing antibodies drives sequence evolution during acute infection with hepatitis C virus. Gastroenterology 136:2377–2386. https://doi.org/10.1053/j.gastro.2009.02.080.
318. Tomaras GD, Yates NL, Liu P, Qin L, Fouda GG, Chavez LL, Decamp AC, Parks RJ, Ashley VC, Lucas JT, Cohen M, Eron J, Hicks CB, Liao HX, Self SG, Landucci G, Forthal DN, Weinhold KJ, Keele BF, Hahn BH, Greenberg ML, Morris L, Karim SS, Blattner WA, Montefiori DC, Shaw GM, Perelson AS, Haynes BF. 2008. Initial B-cell responses to transmitted human immunodeficiency virus type 1: virion-binding immunoglobulin M (IgM) and IgG antibodies followed by plasma anti-gp41 antibodies with ineffective control of initial viremia. J Virol 82:12449–12463. https://doi.org/10.1128/JVI.01708-08.
319. Mouquet H. 2014. Antibody B cell responses in HIV-1 infection. Trends Immunol 35:549–561. https://doi.org/10.1016/j.it.2014.08.007.
320. Richman DD, Wrin T, Little SJ, Petropoulos CJ. 2003. Rapid evolution of the neutralizing antibody response to HIV type 1 infection. Proc Natl Acad Sci U S A 100:4144–4149. https://doi.org/10.1073/pnas.0630530100.
321. Gray ES, Madiga MC, Hermanus T, Moore PL, Wibmer CK, Tumba NL, Werner L, Mlisana K, Sibeko S, Williamson C, Abdool Karim SS, Morris L, CAPRISA002 Study Team. 2011. The neutralization breadth of HIV-1 develops incrementally over four years and is associated with CD4+ T cell decline and high viral load during acute infection. J Virol 85:4828–4840. https://doi.org/10.1128/JVI.00198-11.
322. Binley JM, Lybarger EA, Crooks ET, Seaman MS, Gray E, Davis KL, Decker JM, Wycuff D, Harris L, Hawkins N, Wood B, Nathe C, Richman D, Tomaras GD, Bibollet-Ruche F, Robinson JE, Morris L, Shaw GM, Montefiori DC, Mascola JR. 2008. Profiling the specificity of neutralizing antibodies in a large panel of plasmas from patients chronically infected with human immunodeficiency virus type 1 subtypes B and C. J Virol 82:11651–11668. https://doi.org/10.1128/JVI.01762-08.
323. Hraber P, Seaman MS, Bailer RT, Mascola JR, Montefiori DC, Korber BT. 2014. Prevalence of broadly neutralizing antibody responses during chronic HIV-1 infection. AIDS 28:163–169. https://doi.org/10.1097/QAD.0000000000000106.
324. Simek MD, Rida W, Priddy FH, Pung P, Carrow E, Laufer DS, Lehrman JK, Boaz M, Tarragona-Fiol T, Miiro G, Birungi J, Pozniak A, McPhee DA, Manigart O, Karita E, Inwoley A, Jaoko W, DeHovitz J, Bekker L-G, Pitisuttithum P, Paris R, Walker LM, Poignard P, Wrin T, Fast PE, Burton DR, Koff WC. 2009. Human immunodeficiency virus type 1 elite neutralizers: individuals with broad and potent neutralizing activity

identified by using a high-throughput neutralization assay together with an analytical selection algorithm. J Virol 83:7337–7348. https://doi.org/10.1128/JVI.00110-09.
325. Goo L, Chohan V, Nduati R, Overbaugh J. 2014. Early development of broadly neutralizing antibodies in HIV-1–infected infants. Nat Med 20:655–658. https://doi.org/10.1038/nm.3565.
326. Mabuka J, Nduati R, Odem-Davis K, Peterson D, Overbaugh J. 2012. HIV-specific antibodies capable of ADCC are common in breastmilk and are associated with reduced risk of transmission in women with high viral loads. PLoS Pathog 8:e1002739. https://doi.org/10.1371/journal.ppat.1002739.
327. Baum LL, Cassutt KJ, Knigge K, Khattri R, Margolick J, Rinaldo C, Kleeberger CA, Nishanian P, Henrard DR, Phair J. 1996. HIV-1 gp120-specific antibody-dependent cell-mediated cytotoxicity correlates with rate of disease progression. J Immunol 157:2168.
328. Halper-Stromberg A, Lu CL, Klein F, Horwitz JA, Bournazos S, Nogueira L, Eisenreich TR, Liu C, Gazumyan A, Schaefer U, Furze RC, Seaman MS, Prinjha R, Tarakhovsky A, Ravetch JV, Nussenzweig MC. 2014. Broadly neutralizing antibodies and viral inducers decrease rebound from HIV-1 latent reservoirs in humanized mice. Cell 158:989–999. https://doi.org/10.1016/j.cell.2014.07.043.
329. Ng CT, Jaworski JP, Jayaraman P, Sutton WF, Delio P, Kuller L, Anderson D, Landucci G, Richardson BA, Burton DR, Forthal DN, Haigwood NL. 2010. Passive neutralizing antibody controls SHIV viremia and enhances B cell responses in infant macaques. Nat Med 16:1117–1119. https://doi.org/10.1038/nm.2233.
330. Winkelstein JA, Marino MC, Lederman HM, Jones SM, Sullivan K, Burks AW, Conley ME, Cunningham-Rundles C, Ochs HD. 2006. X-linked agammaglobulinemia: report on a United States registry of 201 patients. Medicine (Baltimore) 85:193–202. https://doi.org/10.1097/01.md.0000229482.27398.ad.
331. Casadevall A. 2003. Antibody-mediated immunity against intracellular pathogens: two-dimensional thinking comes full circle. Infect Immun 71:4225–4228. https://doi.org/10.1128/IAI.71.8.4225-4228.2003.
332. Chan J, Mehta S, Bharrhan S, Chen Y, Achkar JM, Casadevall A, Flynn J. 2014. The role of B cells and humoral immunity in Mycobacterium tuberculosis infection. Semin Immunol 26:588–600. https://doi.org/10.1016/j.smim.2014.10.005.
333. Maglione PJ, Chan J. 2009. How B cells shape the immune response against Mycobacterium tuberculosis. Eur J Immunol 39:676–686. https://doi.org/10.1002/eji.200839148.
334. Casadevall A, Pirofski LA. 2006. A reappraisal of humoral immunity based on mechanisms of antibody-mediated protection against intracellular pathogens. Adv Immunol 91:1–44. https://doi.org/10.1016/S0065-2776(06)91001-3.
335. Martinez LR, Casadevall A. 2005. Specific antibody can prevent fungal biofilm formation and this effect correlates with protective efficacy. Infect Immun 73:6350–6362. https://doi.org/10.1128/IAI.73.10.6350-6362.2005.
336. Brena S, Omaetxebarria MJ, Elguezabal N, Cabezas J, Moragues MD, Ponton J. 2007. Fungicidal monoclonal antibody C7 binds to Candida albicans Als3. Infect Immun 75:3680–3682. https://doi.org/10.1128/IAI.01840-06.
337. Moragues MD, Omaetxebarria MJ, Elguezabal N, Sevilla MJ, Conti S, Polonelli L, Ponton J. 2003. A monoclonal antibody directed against a Candida albicans cell wall mannoprotein exerts three anti-C. albicans activities. Infect Immun 71:5273–5279. https://doi.org/10.1128/IAI.71.9.5273-5279.2003.
338. Nabavi N, Murphy JW. 1986. Antibody-dependent natural killer cell-mediated growth inhibition of Cryptococcus neoformans. Infect Immun 51:556–562. https://doi.org/10.1128/IAI.51.2.556-562.1986.
339. Shapiro S, Beenhouwer DO, Feldmesser M, Taborda C, Carroll MC, Casadevall A, Scharff MD. 2002. Immunoglobulin G monoclonal antibodies to Cryptococcus neoformans protect mice deficient in complement component C3. Infect Immun 70:2598–2604. https://doi.org/10.1128/IAI.70.5.2598-2604.2002.
340. Schlageter AM, Kozel TR. 1990. Opsonization of Cryptococcus neoformans by a family of isotype-switch variant antibodies specific for the capsular polysaccharide. Infect Immun 58:1914–1918. https://doi.org/10.1128/IAI.58.6.1914-1918.1990.
341. Brena S, Cabezas-Olcoz J, Moragues MD, Fernández de Larrinoa I, Domínguez A, Quindós G, Pontón J. 2011. Fungicidal monoclonal antibody C7 interferes with iron acquisition in Candida albicans. Antimicrob Agents Chemother 55:3156–3163. https://doi.org/10.1128/AAC.00892-10.
342. Rivera J, Zaragoza O, Casadevall A. 2005. Antibody-mediated protection against Cryptococcus neoformans pulmonary infection is dependent on B cells. Infect Immun 73:1141–1150. https://doi.org/10.1128/IAI.73.2.1141-1150.2005.
343. Subramaniam KS, Datta K, Quintero E, Manix C, Marks MS, Pirofski LA. 2010. The absence of serum IgM enhances the susceptibility of mice to pulmonary challenge with Cryptococcus neoformans. J Immunol 184:5755–5767. https://doi.org/10.4049/jimmunol.0901638.
344. Harris N, Gause WC. 2011. B cell function in the immune response to helminths. Trends Immunol 32:80–88. https://doi.org/10.1016/j.it.2010.11.005.
345. Horsnell WG, Darby MG, Hoving JC, Nieuwenhuizen N, McSorley HJ, Ndlovu H, Bobat S, Kimberg M, Kirstein F, Cutler AJ, Dewals B, Cunningham AF, Brombacher F. 2013. IL-4Ralpha-associated antigen processing by B cells promotes immunity in Nippostrongylus brasiliensis infection. PLoS Pathog 9:e1003662. https://doi.org/10.1371/journal.ppat.1003662.
346. Lantz CS, Boesiger J, Song CH, Mach N, Kobayashi T, Mulligan RC, Nawa Y, Dranoff G, Galli SJ. 1998. Role for interleukin-3 in mast-cell and basophil development and in immunity to parasites. Nature 392:90–93. https://doi.org/10.1038/32190.
347. Caughey GH. 2011. Mast cell proteases as protective and inflammatory mediators. Adv Exp Med Biol 716:212–234. https://doi.org/10.1007/978-1-4419-9533-9_12.
348. Schwartz LB, Austen KF. 1980. Enzymes of the mast cell granule. J Invest Dermatol 74:349–353. https://doi.org/10.1111/1523-1747.ep12543620.
349. Kanzaki M, Lindorfer MA, Garrison JC, Kojima I. 1997. Activation of the calcium-permeable cation channel CD20 by alpha subunits of the Gi protein. J Biol Chem 272:14733–14739. https://doi.org/10.1074/jbc.272.23.14733.
350. Riley JK, Sliwkowski MX. 2000. CD20: a gene in search of a function. Semin Oncol 27:17–24.
351. Anonymous. 2010. Rituxan (rituximab). Full prescribing information. Food and Drug Administration, Silver Spring, MD. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103705s5311lbl.pdf.
352. Marco H, Smith RM, Jones RB, Guerry M-J, Catapano F, Burns S, Chaudhry AN, Smith KGC, Jayne D. 2014. The effect of rituximab therapy on immunoglobulin levels in patients with multisystem autoimmune disease. BMC Musculoskelet Disord 15:178. https://doi.org/10.1186/1471-2474-15-178.
353. Martin F, Chan AC. 2006. B cell immunobiology in disease: evolving concepts from the clinic. Annu Rev Immunol 24:467–496. https://doi.org/10.1146/annurev.immunol.24.021605.090517.
354. Hoelzer D, Walewski J, Döhner H, Viardot A, Hiddemann W, Spiekermann K, Serve H, Dührsen U, Hüttmann A, Thiel E, Dengler J, Kneba M, Schaich M, Schmidt-Wolf IGH, Beck J, Hertenstein B, Reichle A, Domanska-Czyz K, Fietkau R, Horst H-A, Rieder H, Schwartz S, Burmeister T, Gökbuget N. 2014. Improved outcome of adult Burkitt lymphoma/leukemia with rituximab and chemotherapy: report of a large prospective multicenter trial. Blood 124:3870–3879. https://doi.org/10.1182/blood-2014-03-563627.
355. Holdhoff M, Ambady P, Abdelaziz A, Sarai G, Bonekamp D, Blakeley J, Grossman SA, Ye X. 2014. High-dose methotrexate with or without rituximab in newly diagnosed primary CNS lymphoma. Neurology 83:235–239. https://doi.org/10.1212/WNL.0000000000000593.
356. Kalpadakis C, Pangalis GA, Angelopoulou MK, Sachanas S, Kontopidou FN, Yiakoumis X, Kokoris SI, Dimitriadou EM, Dimopoulou MN, Moschogiannis M, Korkolopoulou P, Kyrtsonis MC, Siakantaris MP, Papadaki T, Tsaftaridis P, Plata E, Papadaki HE, Vassilakopoulos TP. 2013. Treatment of splenic marginal zone lymphoma with rituximab monotherapy: progress report and comparison with splenectomy. Oncologist 18:190–197. https://doi.org/10.1634/theoncologist.2012-0251.
357. Martinelli G, Laszlo D, Ferreri AJ, Pruneri G, Ponzoni M, Conconi A, Crosta C, Pedrinis E, Bertoni F, Calabrese L, Zucca E. 2005. Clinical activity of rituximab in gastric marginal zone non-Hodgkin's lymphoma resistant to or not eligible for anti-Helicobacter pylori therapy. J Clin Oncol 23:1979–1983. https://doi.org/10.1200/JCO.2005.08.128.
358. Trappe R, Oertel S, Leblond V, Mollee P, Sender M, Reinke P, Neuhaus R, Lehmkuhl H, Horst HA, Salles G, Morschhauser F, Jaccard A, Lamy T, Leithauser M, Zimmermann H, Anagnostopoulos I, Raphael M, Riess H,

Choquet S. 2012. Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicentre phase 2 PTLD-1 trial. Lancet Oncol 13:196–206. https://doi.org/10.1016/S1470-2045(11)70300-X.
359. Dimopoulos MA, Garcia-Sanz R, Gavriatopoulou M, Morel P, Kyrtsonis MC, Michalis E, Kartasis Z, Leleu X, Palladini G, Tedeschi A, Gika D, Merlini G, Kastritis E, Sonneveld P. 2013. Primary therapy of Waldenstrom macroglobulinemia (WM) with weekly bortezomib, low-dose dexamethasone, and rituximab (BDR): long-term results of a phase 2 study of the European Myeloma Network (EMN). Blood 122:3276–3282. https://doi.org/10.1182/blood-2013-05-503862.
360. Yamout BI, El-Ayoubi NK, Nicolas J, El Kouzi Y, Khoury SJ, Zeineddine MM. 2018. Safety and efficacy of rituximab in multiple sclerosis: a retrospective observational study. J Immunol Res 2018:9084759. https://doi.org/10.1155/2018/9084759.
361. Zecca C, Bovis F, Novi G, Capobianco M, Lanzillo R, Frau J, Repice AM, Hakiki B, Realmuto S, Bonavita S, Curti E, Brambilla L, Mataluni G, Cavalla P, Di Sapio A, Signoriello E, Barone S, Maniscalco GT, Maietta I, Maraffi I, Boffa G, Malucchi S, Nozzolillo A, Coghe G, Mechi C, Salemi G, Gallo A, Sacco R, Cellerino M, Malentacchi M, De Angelis M, Lorefice L, Magnani E, Prestipino E, Sperli F, Brescia Morra V, Fenu G, Barilaro A, Abbadessa G, Signori A, Granella F, Amato MP, Uccelli A, Gobbi C, Sormani MP. 2019. Treatment of multiple sclerosis with rituximab: a multicentric Italian-Swiss experience. Mult Scler 2019:1352458519872889. https://doi.org/10.1177/1352458519872889:1352458519872889.
362. Scully M, McDonald V, Cavenagh J, Hunt BJ, Longair I, Cohen H, Machin SJ. 2011. A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura. Blood 118:1746–1753. https://doi.org/10.1182/blood-2011-03-341131.
363. Sayani FA, Abrams CS. 2015. How I treat refractory thrombotic thrombocytopenic purpura. Blood 125:3860–3867. https://doi.org/10.1182/blood-2014-11-551580.
364. Zaja F, Vianelli N, Volpetti S, Battista ML, Defina M, Palmieri S, Bocchia M, Medeot M, De Luca S, Ferrara F, Isola M, Baccarani M, Fanin R. 2010. Low-dose rituximab in adult patients with primary immune thrombocytopenia. Eur J Haematol 85:329–334. https://doi.org/10.1111/j.1600-0609.2010.01486.x.
365. Tandan R, Hehir MK, Waheed W, Howard DB. 2017. Rituximab treatment of myasthenia gravis: a systematic review. Muscle Nerve 56:185–196. https://doi.org/10.1002/mus.25597.
366. Damato V, Evoli A, Iorio R. 2016. Efficacy and safety of rituximab therapy in neuromyelitis optica spectrum disorders: a systematic review and meta-analysis. JAMA Neurol 73:1342–1348. https://doi.org/10.1001/jamaneurol.2016.1637.
367. Vigna-Perez M, Hernández-Castro B, Paredes-Saharopulos O, Portales-Pérez D, Baranda L, Abud-Mendoza C, González-Amaro R. 2006. Clinical and immunological effects of Rituximab in patients with lupus nephritis refractory to conventional therapy: a pilot study. Arthritis Res Ther 8:R83. https://doi.org/10.1186/ar1954.
368. Dahan K, Debiec H, Plaisier E, Cachanado M, Rousseau A, Wakselman L, Michel PA, Mihout F, Dussol B, Matignon M, Mousson C, Simon T, Ronco P, GEMRITUX Study Group. 2017. Rituximab for severe membranous nephropathy: a 6-month trial with extended follow-up. J Am Soc Nephrol 28:348–358. https://doi.org/10.1681/ASN.2016040449.
369. Reynaud Q, Durieu I, Dutertre M, Ledochowski S, Durupt S, Michallet AS, Vital-Durand D, Lega JC. 2015. Efficacy and safety of rituximab in auto-immune hemolytic anemia: a meta-analysis of 21 studies. Autoimmun Rev 14:304–313. https://doi.org/10.1016/j.autrev.2014.11.014.
370. Wolff D, Schleuning M, von Harsdorf S, Bacher U, Gerbitz A, Stadler M, Ayuk F, Kiani A, Schwerdtfeger R, Vogelsang GB, Kobbe G, Gramatzki M, Lawitschka A, Mohty M, Pavletic SZ, Greinix H, Holler E. 2011. Consensus Conference on Clinical Practice in Chronic GVHD: second-line treatment of chronic graft-versus-host disease. Biol Blood Marrow Transplant 17:1–17. https://doi.org/10.1016/j.bbmt.2010.05.011.
371. Keystone E, Fleischmann R, Emery P, Furst DE, van Vollenhoven R, Bathon J, Dougados M, Baldassare A, Ferraccioli G, Chubick A, Udell J, Cravets MW, Agarwal S, Cooper S, Magrini F. 2007. Safety and efficacy of additional courses of rituximab in patients with active rheumatoid arthritis: an open-label extension analysis. Arthritis Rheum 56:3896–3908. https://doi.org/10.1002/art.23059.
372. Muhammad K, Roll P, Einsele H, Dorner T, Tony HP. 2009. Delayed acquisition of somatic hypermutations in repopulated IGD+CD27+ memory B cell receptors after rituximab treatment. Arthritis Rheum 60:2284–2293. https://doi.org/10.1002/art.24722.
373. Anonymous. 2009. Arzerra (ofatumumab). Full prescribing information. Reference ID 3490691. Food and Drug Administration, Silver Spring, MD.
374. Anonymous. 2017. Ocrevus (ocrelizumab). Full prescribing information. Reference ID 4076448. Food and Drug Administration, Silver Spring, MD.
375. Emery P, Rigby W, Tak PP, Dorner T, Olech E, Martin C, Millar L, Travers H, Fisheleva E. 2014. Safety with ocrelizumab in rheumatoid arthritis: results from the ocrelizumab phase III program. PLoS One 9:e87379. https://doi.org/10.1371/journal.pone.0087379.
376. Mysler EF, Spindler AJ, Guzman R, Bijl M, Jayne D, Furie RA, Houssiau FA, Drappa J, Close D, Maciuca R, Rao K, Shahdad S, Brunetta P. 2013. Efficacy and safety of ocrelizumab in active proliferative lupus nephritis: results from a randomized, double-blind, phase III study. Arthritis Rheum 65:2368–2379. https://doi.org/10.1002/art.38037.
377. Anonymous. 2013. Gazyva (obinutuzumab). Full prescribing information. Reference ID 3893320. Food and Drug Administration, Silver Spring, MD.
378. Anonymous. 2011. Benlysta (belimumab). Full prescribing information. Reference ID 4281596. Food and Drug Administration, Silver Spring, MD.
379. Chen D, Gallagher S, Monson NL, Herbst R, Wang Y. 2016. Inebilizumab, a B cell-depleting anti-CD19 antibody for the treatment of autoimmune neurological diseases: insights from preclinical studies. J Clin Med 5:E107. https://doi.org/10.3390/jcm5120107.
380. Cree BAC, Bennett JL, Kim HJ, Weinshenker BG, Pittock SJ, Wingerchuk DM, Fujihara K, Paul F, Cutter GR, Marignier R, Green AJ, Aktas O, Hartung HP, Lublin FD, Drappa J, Barron G, Madani S, Ratchford JN, She D, Cimbora D, Katz E, N-MOmentum study Investigators. 2019. Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): a double-blind, randomised placebo-controlled phase 2/3 trial. Lancet 394:1352–1363. https://doi.org/10.1016/S0140-6736(19)31817-3.
381. Agius MA, Klodowska-Duda G, Maciejowski M, Potemkowski A, Li J, Patra K, Wesley J, Madani S, Barron G, Katz E, Flor A. 2019. Safety and tolerability of inebilizumab (MEDI-551), an anti-CD19 monoclonal antibody, in patients with relapsing forms of multiple sclerosis: results from a phase 1 randomised, placebo-controlled, escalating intravenous and subcutaneous dose study. Mult Scler 25:235–245. https://doi.org/10.1177/1352458517740641.
382. Ohmachi K, Ogura M, Suehiro Y, Ando K, Uchida T, Choi I, Ogawa Y, Kobayashi M, Fukino K, Yokoi Y, Okamura J. 2019. A multicenter phase I study of inebilizumab, a humanized anti-CD19 monoclonal antibody, in Japanese patients with relapsed or refractory B-cell lymphoma and multiple myeloma. Int J Hematol 109:657–664. https://doi.org/10.1007/s12185-019-02635-9.
383. Anonymous. 2003. Bexxar (tositumomab and iodine I 131 tositumomab). Full prescribing information. Food and Drug Administration, Silver Spring, MD. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125011s102lbl.pdf.
384. Kaminski MS, Tuck M, Estes J, Kolstad A, Ross CW, Zasadny K, Regan D, Kison P, Fisher S, Kroll S, Wahl RL. 2005. 131I-tositumomab therapy as initial treatment for follicular lymphoma. N Engl J Med 352:441–449. https://doi.org/10.1056/NEJMoa041511.
385. Aksoy S, Dizdar Ö, Hayran M, Harputluoğlu H. 2009. Infectious complications of rituximab in patients with lymphoma during maintenance therapy: a systematic review and meta-analysis. Leuk Lymphoma 50:357–365. https://doi.org/10.1080/10428190902730219.
386. Vidal L, Gafter-Gvili A, Leibovici L, Dreyling M, Ghielmini M, Hsu Schmitz S-F, Cohen A, Shpilberg O. 2009. Rituximab maintenance for the treatment of patients with follicular lymphoma: systematic review and meta-analysis of randomized trials. J Natl Cancer Inst 101:248–255. https://doi.org/10.1093/jnci/djn478.
387. Lanini S, Molloy AC, Prentice AG, Ippolito G, Kibbler CC. 2013. Infections in patients taking rituximab for hematologic malignancies: two-year cohort study. BMC Infect Dis 13:317–317. https://doi.org/10.1186/1471-2334-13-317.
388. Kamar N, Milioto O, Puissant-Lubrano B, Esposito L, Pierre MC, Mohamed AO, Lavayssiere L, Cointault O, Ribes D, Cardeau I, Nogier MB, Durand D, Abbal M, Blancher A, Rostaing L. 2010. Incidence and predictive factors for infectious disease after rituximab therapy in

kidney-transplant patients. Am J Transplant 10:89–98. https://doi.org/10.1111/j.1600-6143.2009.02785.x.
389. Grim SA, Pham T, Thielke J, Sankary H, Oberholzer J, Benedetti E, Clark NM. 2007. Infectious complications associated with the use of rituximab for ABO-incompatible and positive cross-match renal transplant recipients. Clin Transplant 21:628–632. https://doi.org/10.1111/j.1399-0012.2007.00700.x.
390. Gulleroglu K, Baskin E, Moray G, Ozdemir H, Arslan H, Haberal M. 2016. Rituximab therapy and infection risk in pediatric renal transplant patients. Exp Clin Transplant 14:172–175. https://doi.org/10.6002/ect.2014.0156.
391. Cohen SB, Emery P, Greenwald MW, Dougados M, Furie RA, Genovese MC, Keystone EC, Loveless JE, Burmester GR, Cravets MW, Hessey EW, Shaw T, Totoritis MC, REFLEX Trial Group. 2006. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum 54:2793–2806. https://doi.org/10.1002/art.22025.
392. Edwards JCW, Szczepański L, Szechiński J, Filipowicz-Sosnowska A, Emery P, Close DR, Stevens RM, Shaw T. 2004. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med 350:2572–2581. https://doi.org/10.1056/NEJMoa032534.
393. Strand V, Balbir-Gurman A, Pavelka K, Emery P, Li N, Yin M, Lehane PB, Agarwal S. 2006. Sustained benefit in rheumatoid arthritis following one course of rituximab: improvements in physical function over 2 years. Rheumatology (Oxford) 45:1505–1513. https://doi.org/10.1093/rheumatology/kel358.
394. Emery P, Fleischmann R, Filipowicz-Sosnowska A, Schechtman J, Szczepanski L, Kavanaugh A, Racewicz AJ, van Vollenhoven RF, Li NF, Agarwal S, Hessey EW, Shaw TM, DANCER Study Group. 2006. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. Arthritis Rheum 54:1390–1400. https://doi.org/10.1002/art.21778.
395. Salliot C, Dougados M, Gossec L. 2009. Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. Ann Rheum Dis 68:25–32. https://doi.org/10.1136/ard.2007.083188.
396. van Vollenhoven RF, Fleischmann RM, Furst DE, Lacey S, Lehane PB. 2015. Longterm safety of rituximab: final report of the Rheumatoid Arthritis Global Clinical Trial Program over 11 years. J Rheumatol 42:1761–1766. https://doi.org/10.3899/jrheum.150051.
397. Garcia-Rodriguez MJ, Canales MA, Hernandez-Maraver D, Hernandez-Navarro F. 2008. Late reactivation of resolved hepatitis B virus infection: an increasing complication post rituximab-based regimens treatment? Am J Hematol 83:673–675. https://doi.org/10.1002/ajh.21214.
398. Win LL, Powis J, Shah H, Feld JJ, Wong DK. 2013. Death from liver failure despite lamivudine prophylaxis during R-CHOP chemotherapy due to rapid emergence M204 mutations. Case Reports Hepatol 2013:454897. https://doi.org/10.1155/2013/454897.
399. Villadolid J, LaPlant KD, Markham MJ, Nelson DR, George TJ. 2010. Hepatitis B reactivation and rituximab in the oncology practice. Oncologist 15:1113–1121. https://doi.org/10.1634/theoncologist.2010-0106.
400. Yamada T, Nannya Y, Suetsugu A, Shimizu S, Sugihara J, Shimizu M, Seishima M, Tsurumi H. 2017. Late reactivation of hepatitis B virus after chemotherapies for hematological malignancies: a case report and review of the literature. Intern Med 56:115–118. https://doi.org/10.2169/internalmedicine.56.7468.
401. Muraishi J, Shibata M, Honma Y, Hiura M, Abe S, Harada M. 2017. Reactivation of occult hepatitis B virus infection 27 months after the end of chemotherapy including rituximab for malignant lymphoma. Intern Med 56:1967–1971. https://doi.org/10.2169/internalmedicine.56.8233.
402. Yeo W, Chan TC, Leung NW, Lam WY, Mo FK, Chu MT, Chan HL, Hui EP, Lei KI, Mok TS, Chan PK. 2009. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. J Clin Oncol 27:605–611. https://doi.org/10.1200/JCO.2008.18.0182.
403. Gutierrez Garcia ML, Alonso Lopez S, Martin Rios MD, Sanmartin Fenollera P, Agudo Fernandez S, Fernandez Rodriguez CM. 2015. Hepatitis B virus reactivation in rituximab-treated patients: incidence and risk factors. Gastroenterol Hepatol 38:1–6. (In Spanish.) https://doi.org/10.1016/j.gastrohep.2014.05.008.
404. Yeo W, Chan PK, Zhong S, Ho WM, Steinberg JL, Tam JS, Hui P, Leung NW, Zee B, Johnson PJ. 2000. Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: a prospective study of 626 patients with identification of risk factors. J Med Virol 62:299–307. https://doi.org/10.1002/1096-9071(200011)62:3<299::AID-JMV1>3.0.CO;2-0.
405. Matsue K, Kimura S, Takanashi Y, Iwama K, Fujiwara H, Yamakura M, Takeuchi M. 2010. Reactivation of hepatitis B virus after rituximab-containing treatment in patients with CD20-positive B-cell lymphoma. Cancer 116:4769–4776. https://doi.org/10.1002/cncr.25253.
406. Aksoy S, Harputluoglu H, Kilickap S, Dede DS, Dizdar O, Altundag K, Barista I. 2007. Rituximab-related viral infections in lymphoma patients. Leuk Lymphoma 48:1307–1312. https://doi.org/10.1080/10428190701411441.
407. Liang R. 2009. How I treat and monitor viral hepatitis B infection in patients receiving intensive immunosuppressive therapies or undergoing hematopoietic stem cell transplantation. Blood 113:3147–3153. https://doi.org/10.1182/blood-2008-10-163493.
408. Kusumoto S, Tanaka Y, Ueda R, Mizokami M. 2011. Reactivation of hepatitis B virus following rituximab-plus-steroid combination chemotherapy. J Gastroenterol 46:9–16. https://doi.org/10.1007/s00535-010-0331-4.
409. Evens AM, Jovanovic BD, Su YC, Raisch DW, Ganger D, Belknap SM, Dai MS, Chiu BCC, Fintel B, Cheng Y, Chuang SS, Lee MY, Chen TY, Lin SF, Kuo CY. 2011. Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports. Ann Oncol 22:1170–1180. https://doi.org/10.1093/annonc/mdq583.
410. Lok AS, Liang RH, Chiu EK, Wong KL, Chan TK, Todd D. 1991. Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Report of a prospective study. Gastroenterology 100:182–188. https://doi.org/10.1016/0016-5085(91)90599-G.
411. Nakamura Y, Motokura T, Fujita A, Yamashita T, Ogata E. 1996. Severe hepatitis related to chemotherapy in hepatitis B virus carriers with hematologic malignancies. Survey in Japan, 1987–1991. Cancer 78:2210–2215. https://doi.org/10.1002/(SICI)1097-0142(19961115)78:10<2210::AID-CNCR24>3.0.CO;2-0.
412. Kim SJ, Hsu C, Song YQ, Tay K, Hong XN, Cao J, Kim JS, Eom HS, Lee JH, Zhu J, Chang KM, Reksodiputro AH, Tan D, Goh YT, Lee J, Intragumtornchai T, Chng WJ, Cheng AL, Lim ST, Suh C, Kwong YL, Kim WS. 2013. Hepatitis B virus reactivation in B-cell lymphoma patients treated with rituximab: analysis from the Asia Lymphoma Study Group. Eur J Cancer 49:3486–3496. https://doi.org/10.1016/j.ejca.2013.07.006.
413. Koo YX, Tay M, Teh YE, Teng D, Tan DS, Tan IB, Tai DW, Quek R, Tao M, Lim ST. 2011. Risk of hepatitis B virus (HBV) reactivation in hepatitis B surface antigen negative/hepatitis B core antibody positive patients receiving rituximab-containing combination chemotherapy without routine antiviral prophylaxis. Ann Hematol 90:1219–1223. https://doi.org/10.1007/s00277-011-1241-0.
414. Seto WK, Chan TS, Hwang YY, Wong DK, Fung J, Liu KS, Gill H, Lam YF, Lie AK, Lai CL, Kwong YL, Yuen MF. 2014. Hepatitis B reactivation in patients with previous hepatitis B virus exposure undergoing rituximab-containing chemotherapy for lymphoma: a prospective study. J Clin Oncol 32:3736–3743. https://doi.org/10.1200/JCO.2014.56.7081.
415. Giordano TP, Henderson L, Landgren O, Chiao EY, Kramer JR, El-Serag H, Engels EA. 2007. Risk of non-Hodgkin lymphoma and lymphoproliferative precursor diseases in US veterans with hepatitis C virus. JAMA 297:2010–2017. https://doi.org/10.1001/jama.297.18.2010.
416. Sagnelli E, Pisaturo M, Sagnelli C, Coppola N. 2012. Rituximab-based treatment, HCV replication, and hepatic flares. Clin Dev Immunol 2012:1–5. https://doi.org/10.1155/2012/945950.
417. Torres HA, Hosry J, Mahale P, Economides MP, Jiang Y, Lok AS. 2018. Hepatitis C virus reactivation in patients receiving cancer treatment: a prospective observational study. Hepatology 67:36–47. https://doi.org/10.1002/hep.29344.
418. Ennishi D, Maeda Y, Niitsu N, Kojima M, Izutsu K, Takizawa J, Kusumoto S, Okamoto M, Yokoyama M, Takamatsu Y, Sunami K, Miyata A, Murayama K, Sakai A, Matsumoto M, Shinagawa K, Takaki A, Matsuo K, Kinoshita T, Tanimoto M. 2010. Hepatic toxicity and prognosis in hepatitis C virus-infected patients with diffuse large B-cell lymphoma

treated with rituximab-containing chemotherapy regimens: a Japanese multicenter analysis. Blood 116:5119–5125. https://doi.org/10.1182/blood-2010-06-289231.
419. Fink DL, Hedley L, Miller RF. 2017. Systematic review of the efficacy and safety of biological therapy for inflammatory conditions in HIV-infected individuals. Int J STD AIDS 28:110–119. https://doi.org/10.1177/0956462416675109.
420. Kaplan LD, Lee JY, Ambinder RF, Sparano JA, Cesarman E, Chadburn A, Levine AM, Scadden DT. 2005. Rituximab does not improve clinical outcome in a randomized phase 3 trial of CHOP with or without rituximab in patients with HIV-associated non-Hodgkin lymphoma: AIDS-Malignancies Consortium Trial 010. Blood 106:1538–1543. https://doi.org/10.1182/blood-2005-04-1437.
421. Ribera J-M, Oriol A, Morgades M, González-Barca E, Miralles P, López-Guillermo A, Gardella S, López A, Abella E, García M, PETHEMA, GELTAMO, GELCAB, and GESIDA Groups. 2008. Safety and efficacy of cyclophosphamide, adriamycin, vincristine, prednisone and rituximab in patients with human immunodeficiency virus-associated diffuse large B-cell lymphoma: results of a phase II trial. Br J Haematol 140:411–419. https://doi.org/10.1111/j.1365-2141.2007.06943.x.
422. Sparano JA, Lee JY, Kaplan LD, Levine AM, Ramos JC, Ambinder RF, Wachsman W, Aboulafia D, Noy A, Henry DH, Von Roenn J, Dezube BJ, Remick SC, Shah MH, Leichman L, Ratner L, Cesarman E, Chadburn A, Mitsuyasu R, AIDS Malignancy Consortium. 2010. Rituximab plus concurrent infusional EPOCH chemotherapy is highly effective in HIV-associated B-cell non-Hodgkin lymphoma. Blood 115:3008–3016. https://doi.org/10.1182/blood-2009-08-231613.
423. Barta SK, Xue X, Wang D, Tamari R, Lee JY, Mounier N, Kaplan LD, Ribera J-M, Spina M, Tirelli U, Weiss R, Galicier L, Boue F, Wilson WH, Wyen C, Oriol A, Navarro J-T, Dunleavy K, Little RF, Ratner L, Garcia O, Morgades M, Remick SC, Noy A, Sparano JA. 2013. Treatment factors affecting outcomes in HIV-associated non-Hodgkin lymphomas: a pooled analysis of 1546 patients. Blood 122:3251–3262. https://doi.org/10.1182/blood-2013-04-498964.
424. Brunnberg U, Hentrich M, Hoffmann C, Wolf T, Hubel K. 2017. HIV-associated malignant lymphoma. Oncol Res Treat 40:82–87. https://doi.org/10.1159/000456036.
425. Carson KR, Evens AM, Richey EA, Habermann TM, Focosi D, Seymour JF, Laubach J, Bawn SD, Gordon LI, Winter JN, Furman RR, Vose JM, Zelenetz AD, Mamtani R, Raisch DW, Dorshimer GW, Rosen ST, Muro K, Gottardi-Littell NR, Talley RL, Sartor O, Green D, Major EO, Bennett CL. 2009. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. Blood 113:4834–4840. https://doi.org/10.1182/blood-2008-10-186999.
426. Zaheer F, Berger JR. 2012. Treatment-related progressive multifocal leukoencephalopathy: current understanding and future steps. Ther Adv Drug Saf 3:227–239. https://doi.org/10.1177/2042098612453849.
427. Berger JR, Malik V, Lacey S, Brunetta P, Lehane PB. 2018. Progressive multifocal leukoencephalopathy in rituximab-treated rheumatic diseases: a rare event. J Neurovirol 24:323–331. https://doi.org/10.1007/s13365-018-0615-7.
428. Gea-Banacloche JC. 2010. Rituximab-associated infections. Semin Hematol 47:187–198. https://doi.org/10.1053/j.seminhematol.2010.01.002.
429. Johansen KK, Torp SH, Rydland J, Aasly JO. 2013. Progressive multifocal leukoencephalopathy in an immunocompetent patient? Case Rep Neurol 5:149–154. https://doi.org/10.1159/000354828.
430. Cortese I, Muranski P, Enose-Akahata Y, Ha SK, Smith B, Monaco M, Ryschkewitsch C, Major EO, Ohayon J, Schindler MK, Beck E, Reoma LB, Jacobson S, Reich DS, Nath A. 2019. Pembrolizumab treatment for progressive multifocal leukoencephalopathy. N Engl J Med 380:1597–1605. https://doi.org/10.1056/NEJMoa1815039.
431. Stathis A, La Rosa S, Proserpio I, Micello D, Chini C, Pinotti G. 2009. Cytomegalovirus infection of endocrine system in a patient with diffuse large B-cell lymphoma. Report of a Case. Tumori 95:119–122. https://doi.org/10.1177/030089160909500123.
432. Suzan F, Ammor M, Ribrag V. 2001. Fatal reactivation of cytomegalovirus infection after use of rituximab for a post-transplantation lymphoproliferative disorder. N Engl J Med 345:1000. https://doi.org/10.1056/NEJM200109273451315.
433. Vallet S, Tempescul A, Tran A, Legrand-Quillien MC, Narbonne V, Berthou C. 2005. Cytomegalovirus-associated meningoradiculoneuritis after treatment of mantle cell lymphoma with a combination of chemotherapy and rituximab. Ann Hematol 84:545–547. https://doi.org/10.1007/s00277-005-1038-0.
434. Polprasert C, Wongjitrat C, Wisedopas N. 2011. Case report: severe CMV colitis in a patient with follicular lymphoma after chemotherapy. J Med Assoc Thai 94:498–500.
435. Hasegawa Y, Goto A, Nishimura S, Sukawa Y, Fujii K, Suzuki K, Yonezawa K, Abe T, Shinomura Y, Yoshida Y. 2009. Cytomegalovirus gastritis after treatment with rituximab. Endoscopy 41(Suppl 2):E199–E199. https://doi.org/10.1055/s-0029-1214855.
436. Goldberg SL, Pecora AL, Alter RS, Kroll MS, Rowley SD, Waintraub SE, Imrit K, Preti RA. 2002. Unusual viral infections (progressive multifocal leukoencephalopathy and cytomegalovirus disease) after high-dose chemotherapy with autologous blood stem cell rescue and peritransplantation rituximab. Blood 99:1486–1488. https://doi.org/10.1182/blood.V99.4.1486.
437. Libby E, Movva S, Quintana D, Abdul-Jaleel M, Das A. 2010. Cytomegalovirus retinitis during chemotherapy with rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone. J Clin Oncol 28:e661–e662.2. https://doi.org/10.1200/JCO.2010.29.6467.
438. Le Clech L, Ianotto J-C, Quintin-Roue I, Tempescul A. 2013. Severe CMV complication following maintenance therapy with rituximab. BMJ Case Rep 2013:bcr2012006672. https://doi.org/10.1136/bcr-2012-006672.
439. Siakantaris MP, Argyropoulos KV, Ioannou S, Papadopoulou V, Tzeletas G, Tsonis J, Dimitrakopoulou A, Yiannopoulou KG, Pangalis GA, Vaiopoulos G. 2015. Cytomegalovirus meningoencephalitis after rituximab treatment for primary central nervous system lymphoma. Neurologist 19:35–37. https://doi.org/10.1097/NRL.0b013e318287fde0.
440. Tay MR, Lim ST, Tao M, Quek RH, Tay K, Tan TT. 2014. Cytomegalovirus infection and end-organ disease in Asian patients with lymphoma receiving chemotherapy. Leuk Lymphoma 55:182–187. https://doi.org/10.3109/10428194.2013.798867.
441. Vallet H, Houitte R, Azria A, Mariette X. 2011. Cytomegalovirus colitis and hypo-IgG after rituximab therapy for rheumatoid arthritis. J Rheumatol 38:965–966. https://doi.org/10.3899/jrheum.100818.
442. Chiu YM, Tang CH, Hung ST, Yang YW, Fang CH, Lin HY. 2017. A real-world risk analysis of biological treatment (adalimumab and etanercept) in a country with a high prevalence of tuberculosis and chronic liver disease: a nationwide population-based study. Scand J Rheumatol 46:236–240. https://doi.org/10.1080/03009742.2016.1202318.
443. Chang H, Tang TC, Hung YS, Lin TL, Kuo MC, Wang PN. 2011. Cytomegalovirus infection in non-transplant patients with hematologic neoplasms: a case series. Chang Gung Med J 34:65–74.
444. Marchesi F, Pimpinelli F, Ensoli F, Mengarelli A. 2018. Cytomegalovirus infection in hematologic malignancy settings other than the allogeneic transplant. Hematol Oncol 36:381–391. https://doi.org/10.1002/hon.2453.
445. Lanini S, Molloy AC, Fine PE, Prentice AG, Ippolito G, Kibbler CC. 2011. Risk of infection in patients with lymphoma receiving rituximab: systematic review and meta-analysis. BMC Med 9:36–36. https://doi.org/10.1186/1741-7015-9-36.
446. Avilés A, Neri N, Huerta-Guzmán J, de Jesús Nambo M. 2010. ESHAP versus rituximab-ESHAP in frail patients with refractory diffuse large B-cell lymphoma. Clin Lymphoma Myeloma Leuk 10:125–128. https://doi.org/10.3816/CLML.2010.n.017.
447. Lee MY, Chiou TJ, Hsiao LT, Yang MH, Lin PC, Poh SB, Yen CC, Liu JH, Teng HW, Chao TC, Wang WS, Chen PM. 2008. Rituximab therapy increased post-transplant cytomegalovirus complications in Non-Hodgkin's lymphoma patients receiving autologous hematopoietic stem cell transplantation. Ann Hematol 87:285–289. https://doi.org/10.1007/s00277-007-0397-0.
448. Nishida H, Ishida H, Tanaka T, Amano H, Omoto K, Shirakawa H, Shimizu T, Iida S, Toki D, Yamaguchi Y, Tanabe K. 2009. Cytomegalovirus infection following renal transplantation in patients administered low-dose rituximab induction therapy. Transpl Int 22:961–969. https://doi.org/10.1111/j.1432-2277.2009.00903.x.
449. Ishihara H, Ishida H, Toki D, Omoto K, Sirakawa H, Shimizu T, Okumi M, Tanabe K. 2015. Effects of low-dose rituximab therapy in patients with primary cytomegalovirus infection. Exp Clin Transplant 13:573–580.
450. Tsuji H, Yoshifuji H, Fujii T, Matsuo T, Nakashima R, Imura Y, Yukawa N, Ohmura K, Sumiyoshi S, Mimori T. 2017. Visceral disseminated varicella zoster virus infection after rituximab treatment for granulo-

matosis with polyangiitis. Mod Rheumatol 27:155–161. https://doi.org/10.3109/14397595.2014.948981.
451. Bermudez A, Marco F, Conde E, Mazo E, Recio M, Zubizarreta A. 2000. Fatal visceral varicella-zoster infection following rituximab and chemotherapy treatment in a patient with follicular lymphoma. Haematologica 85:894–895.
452. McIlwaine LM, Fitzsimons EJ, Soutar RL. 2001. Inappropriate antidiuretic hormone secretion, abdominal pain and disseminated varicella-zoster virus infection: an unusual and fatal triad in a patient 13 months post Rituximab and autologous stem cell transplantation. Clin Lab Haematol 23:253–254. https://doi.org/10.1046/j.1365-2257.2001.00397.x.
453. Cho S-F, Wu W-H, Yang Y-H, Liu Y-C, Hsiao H-H, Chang C-S. 2015. Longitudinal risk of herpes zoster in patients with non-Hodgkin lymphoma receiving chemotherapy: a nationwide population-based study. Sci Rep 5:14008. https://doi.org/10.1038/srep14008.
454. Merrill JT, Neuwelt CM, Wallace DJ, Shanahan JC, Latinis KM, Oates JC, Utset TO, Gordon C, Isenberg DA, Hsieh HJ, Zhang D, Brunetta PG. 2010. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. Arthritis Rheum 62:222–233. https://doi.org/10.1002/art.27233.
455. Patel SJ, Devos JM, Knight RJ, Dawson KL, Suki WN, Gonzalez JM, Abdellatif AA, Gaber AO. 2013. Effects of rituximab on the development of viral and fungal infections in renal transplant recipients. Int Sch Res Notices 2013:819025. https://doi.org/10.5402/2013/819025.
456. Chiu HY, Chang CY, Hsiao CH, Wang LF. 2013. Concurrent cytomegalovirus and herpes simplex virus infection in pemphigus vulgaris treated with rituximab and prednisolone. Acta Derm Venereol 93:200–201. https://doi.org/10.2340/00015555-1429.
457. Guerrero MD, Swenson KK. 2014. Herpes simplex virus-related oral mucositis in patients with lymphoma. Oncol Nurs Forum 41:327–330. https://doi.org/10.1188/14.ONF.327-330.
458. Yang SH, Lin LW, Fang YJ, Cheng AL, Kuo SH. 2012. Parvovirus B19 infection-related acute hepatitis after rituximab-containing regimen for treatment of diffuse large B-cell lymphoma. Ann Hematol 91:291–294. https://doi.org/10.1007/s00277-011-1238-8.
459. Giraud C, Tatar Z, Soubrier M. 2016. Agranulocytosis under biotherapy in rheumatoid arthritis: three cases hypothesis of parvovirus B19 involvement in agranulocytosis observed under tocilizumab and rituximab for the treatment of rheumatoid arthritis. Clin Rheumatol 35:2615–2618. https://doi.org/10.1007/s10067-016-3379-6.
460. Sharma VR, Fleming DR, Slone SP. 2000. Pure red cell aplasia due to parvovirus B19 in a patient treated with rituximab. Blood 96:1184–1186. https://doi.org/10.1182/blood.V96.3.1184.015k54_1184_1186.
461. Klepfish A, Rachmilevitch E, Schattner A. 2006. Parvovirus B19 reactivation presenting as neutropenia after rituximab treatment. Eur J Intern Med 17:505–507. https://doi.org/10.1016/j.ejim.2006.05.002.
462. Mawhorter SD, Sierk A, Staugaitis SM, Avery RK, Sobecks R, Prayson RA, Procop GW, Yen-Lieberman B. 2005. Fatal West Nile virus infection after rituximab/fludarabine-induced remission for non-Hodgkin's lymphoma. Clin Lymphoma Myeloma 6:248–250. https://doi.org/10.3816/CLM.2005.n.053.
463. Morjaria S, Arguello E, Taur Y, Sepkowitz K, Hatzoglou V, Nemade A, Rosenblum M, Cavalcanti MS, Palomba ML, Kaltsas A. 2015. West Nile virus central nervous system infection in patients treated with rituximab: implications for diagnosis and prognosis, with a review of literature. Open Forum Infect Dis 2:ofv136. https://doi.org/10.1093/ofid/ofv136.
464. Levi ME, Quan D, Ho JT, Kleinschmidt-DeMasters BK, Tyler KL, Grazia TJ. 2010. Impact of rituximab-associated B-cell defects on West Nile virus meningoencephalitis in solid organ transplant recipients. Clin Transplant 24:223–228. https://doi.org/10.1111/j.1399-0012.2009.01044.x.
465. Nissen JC, Hummel M, Brade J, Kruth J, Hofmann W-K, Buchheidt D, Reinwald M. 2014. The risk of infections in hematologic patients treated with rituximab is not influenced by cumulative rituximab dosage—a single center experience. BMC Infect Dis 14:364. https://doi.org/10.1186/1471-2334-14-364.
466. Trivin C, Tran A, Moulin B, Choukroun G, Gatault P, Courivaud C, Augusto J-F, Ficheux M, Vigneau C, Thervet E, Karras A. 2017. Infectious complications of a rituximab-based immunosuppressive regimen in patients with glomerular disease. Clin Kidney J 10:461–469.
467. Heusele M, Clerson P, Guery B, Lambert M, Launay D, Lefevre G, Morell-Dubois S, Maillard H, Le Gouellec N, Hatron P-Y, Hachulla E. 2014. Risk factors for severe bacterial infections in patients with systemic autoimmune diseases receiving rituximab. Clin Rheumatol 33:799–805.
468. Ottaviani S, Tiendrebeogo J, Choudat L, Gill G, Palazzo E, Meyer O, Dieude P. 2013. Knee tuberculosis under rituximab therapy for rheumatoid arthritis. Joint Bone Spine 80:435–436. https://doi.org/10.1016/j.jbspin.2012.10.018.
469. Teramura Y, Kameda K, Kanda J, Gomyo A, Hayakawa J, Akahoshi Y, Komiya Y, Harada N, Ugai T, Ishihara Y, Kawamura K, Sakamoto K, Sato M, Wada H, Terasako-Saito K, Kimura S, Kikuchi M, Nakasone H, Kako S, Kanda Y. 2016. Development tuberculous meningitis during chemotherapy for CD5-positive diffuse large B-cell lymphoma. Rinsho Ketsueki 57:597–601. https://doi.org/10.11406/rinketsu.57.597.
470. Cantini F, Nannini C, Niccoli L, Petrone L, Ippolito G, Goletti D. 2017. Risk of tuberculosis reactivation in patients with rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis receiving non-anti-TNF-targeted biologics. Mediators Inflamm 2017:8909834. https://doi.org/10.1155/2017/8909834.
471. Xanthouli P, Sailer S, Fiehn C. 2012. Rituximab (RTX) as an alternative to TNF-alpha antagonists in patients with rheumatoid arthritis and high risk of severe infections: a systematic analysis of the experience in one center. Open Rheumatol 6:286–289. https://doi.org/10.2174/1874312901206010286.
472. Pehlivan Y, Kisacik B, Bosnak VK, Onat AM. 2013. Rituximab seems to be a safer alternative in patients with active rheumatoid arthritis with tuberculosis. BMJ Case Rep 2013:bcr2012006585. https://doi.org/10.1136/bcr-2012-006585.
473. Gottenberg JE, Ravaud P, Bardin T, Cacoub P, Cantagrel A, Combe B, Dougados M, Flipo RM, Godeau B, Guillevin L, Le Loet X, Hachulla E, Schaeverbeke T, Sibilia J, Baron G, Mariette X. 2010. Risk factors for severe infections in patients with rheumatoid arthritis treated with rituximab in the autoimmunity and rituximab registry. Arthritis Rheum 62:2625–2632. https://doi.org/10.1002/art.27555.
474. Jung N, Owczarczyk K, Hellmann M, Lehmann C, Fatkenheuer G, Hallek M, Rubbert A. 2008. Efficacy and safety of rituximab in a patient with active rheumatoid arthritis and chronic disseminated pulmonary aspergillosis and history of tuberculosis. Rheumatology (Oxford) 47:932–933. https://doi.org/10.1093/rheumatology/ken143.
475. Kimby E. 2005. Tolerability and safety of rituximab (MabThera). Cancer Treat Rev 31:456–473. https://doi.org/10.1016/j.ctrv.2005.05.007.
476. Buch MH, Smolen JS, Betteridge N, Breedveld FC, Burmester G, Dorner T, Ferraccioli G, Gottenberg JE, Isaacs J, Kvien TK, Mariette X, Martin-Mola E, Pavelka K, Tak PP, van der Heijde D, van Vollenhoven RF, Emery P, Rituximab Consensus Expert Committee. 2011. Updated consensus statement on the use of rituximab in patients with rheumatoid arthritis. Ann Rheum Dis 70:909–920. https://doi.org/10.1136/ard.2010.144998.
477. Lim K-H, Yoon H-I, Kang YA, Lee K-W, Kim JH, Bang S-M, Lee JH, Lee C-T, Lee JS. 2010. Severe pulmonary adverse effects in lymphoma patients treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen plus rituximab. Korean J Intern Med 25:86–92. https://doi.org/10.3904/kjim.2010.25.1.86.
478. Scemla A, Loupy A, Candon S, Mamzer MF, Martinez F, Zuber J, Sberro R, Legendre C, Thervet E. 2010. Incidence of infectious complications in highly sensitized renal transplant recipients treated by rituximab: a case-controlled study. Transplantation 90:1180–1184. https://doi.org/10.1097/TP.0b013e3181fa941b.
479. Zarkhin V, Li L, Kambham N, Sigdel T, Salvatierra O, Sarwal MM. 2008. A randomized, prospective trial of rituximab for acute rejection in pediatric renal transplantation. Am J Transplant 8:2607–2617. https://doi.org/10.1111/j.1600-6143.2008.02411.x.
480. Kaposztas Z, Podder H, Mauiyyedi S, Illoh O, Kerman R, Reyes M, Pollard V, Kahan BD. 2009. Impact of rituximab therapy for treatment of acute humoral rejection. Clin Transplant 23:63–73. https://doi.org/10.1111/j.1399-0012.2008.00902.x.
481. Tyden G, Genberg H, Tollemar J, Ekberg H, Persson NH, Tufveson G, Wadstrom J, Gabel M, Mjornstedt L. 2009. A randomized, doubleblind, placebo-controlled, study of single-dose rituximab as induction in renal transplantation. Transplantation 87:1325–1329. https://doi.org/10.1097/TP.0b013e3181a235fd.
482. Martin-Garrido I, Carmona EM, Specks U, Limper AH. 2013. Pneumo-

cystis pneumonia in patients treated with rituximab. Chest 144:258–265. https://doi.org/10.1378/chest.12-0477.
483. Katsuya H, Suzumiya J, Sasaki H, Ishitsuka K, Shibata T, Takamatsu Y, Tamura K. 2009. Addition of rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisolone therapy has a high risk of developing interstitial pneumonia in patients with non-Hodgkin lymphoma. Leuk Lymphoma 50:1818–1823. https://doi.org/10.3109/10428190903258780.
484. Elsegeiny W, Eddens T, Chen K, Kolls JK. 2015. Anti-CD20 antibody therapy and susceptibility to pneumocystis pneumonia. Infect Immun 83:2043–2052. https://doi.org/10.1128/IAI.03099-14.
485. Jiang X, Mei X, Feng D, Wang X. 2015. Prophylaxis and treatment of Pneumocystis jiroveci pneumonia in lymphoma patients subjected to rituximab-contained therapy: a systemic review and meta-analysis. PLoS One 10:e0122171. https://doi.org/10.1371/journal.pone.0122171.
486. Krause PJ, Gewurz BE, Hill D, Marty FM, Vannier E, Foppa IM, Furman RR, Neuhaus E, Skowron G, Gupta S, McCalla C, Pesanti EL, Young M, Heiman D, Hsue G, Gelfand JA, Wormser GP, Dickason J, Bia FJ, Hartman B, Telford SR, Christianson D, Dardick K, Coleman M, Girotto JE, Spielman A. 2008. Persistent and relapsing babesiosis in immunocompromised patients. Clin Infect Dis 46:370–376. https://doi.org/10.1086/525852.
487. Lutman C, Finocchiaro G, Abate E, Milo M, Morassi P, Sinagra G. 2014. Purulent pericarditis in rheumatoid arthritis treated with rituximab and methotrexate. J Cardiovasc Med (Hagerstown) 15:880–882. https://doi.org/10.2459/JCM.0000000000000160.
488. Rouil A, Pollet S, Martin A, Tattevin P, Perdriger A. 2013. Severe Pasteurella multocida infection in a patient on rituximab therapy for rheumatoid arthritis. Joint Bone Spine 80:224–225. https://doi.org/10.1016/j.jbspin.2012.07.011.
489. Chen YC, Jou R, Huang WL, Huang ST, Liu KC, Lay CJ, Chang SM, Tseng CE, Lai CL, Su YC. 2008. Bacteremia caused by Mycobacterium wolinskyi. Emerg Infect Dis 14:1818–1819. https://doi.org/10.3201/eid1411.080003.
490. Lutt JR, Pisculli ML, Weinblatt ME, Deodhar A, Winthrop KL. 2008. Severe nontuberculous mycobacterial infection in 2 patients receiving rituximab for refractory myositis. J Rheumatol 35:1683–1685.
491. Wingfield T, Jani M, Krutikov M, Mayer J, Uriel A, Marks J, Ustianowski AP. 2011. Cryptococcal meningitis in an HIV-negative patient with rheumatoid arthritis treated with rituximab. Rheumatology (Oxford) 50:1725–1727. https://doi.org/10.1093/rheumatology/ker210.
492. Padate BP, Keidan J. 2006. Enteroviral meningoencephalitis in a patient with non-Hodgkin's lymphoma treated previously with rituximab. Clin Lab Haematol 28:69–71. https://doi.org/10.1111/j.1365-2257.2006.00751.x.
493. Ganjoo KN, Raman R, Sobel RA, Pinto HA. 2009. Opportunistic enteroviral meningoencephalitis: an unusual treatable complication of rituximab therapy. Leuk Lymphoma 50:673–675. https://doi.org/10.1080/10428190902782210.
494. Ng HJ, Lim LC. 2001. Fulminant hepatitis B virus reactivation with concomitant listeriosis after fludarabine and rituximab therapy: case report. Ann Hematol 80:549–552. https://doi.org/10.1007/s002770100346.
495. Steininger PA, Bobinger T, Dietrich W, Lee DH, Knott M, Bogdan C, Korn K, Lang R. 2017. Two cases of severe tick-borne encephalitis in rituximab-treated patients in Germany: implications for diagnosis and prevention. Open Forum Infect Dis 4:ofx204. https://doi.org/10.1093/ofid/ofx204.
496. Incani RN, Hernandez M, Gonzalez ME. 2010. Hyperinfection by Strongyloides stercoralis probably associated with rituximab in a patient with mantle cell lymphoma and hyper eosinophilia. Rev Inst Med Trop Sao Paulo 52:221–224. https://doi.org/10.1590/S0036-46652010000400011.
497. Kappos L, Li D, Calabresi PA, O'Connor P, Bar-Or A, Barkhof F, Yin M, Leppert D, Glanzman R, Tinbergen J, Hauser SL. 2011. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. Lancet 378:1779–1787. https://doi.org/10.1016/S0140-6736(11)61649-8.
498. Chaudhuri A. 2012. Ocrelizumab in multiple sclerosis: risks and benefits. Lancet 379:1196. (Letter). https://doi.org/10.1016/S0140-6736(12)60508-X. (Reply, 379:1197. https://doi.org/10.1016/S0140-6736(12)60509-1.)
499. Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung H-P, Hemmer B, Lublin F, Montalban X, Rammohan KW, Selmaj K, Traboulsee A, Wolinsky JS, Arnold DL, Klingelschmitt G, Masterman D, Fontoura P, Belachew S, Chin P, Mairon N, Garren H, Kappos L. 2017. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med 376:221–234. https://doi.org/10.1056/NEJMoa1601277.
500. 500.Naismith R, Cascione M, Grimaldi LM, Hauser S, Kappos L, Montalban X, Wolinsky J, Chin P, Garren H, Julian L, Model F, Honeycutt D. 2017. Preliminary Results of the OPERA I and OPERA II open-label extension study. Neurology 88(16 Suppl):S31.004.
501. Coiffier B, Lepretre S, Pedersen LM, Gadeberg O, Fredriksen H, van Oers MH, Wooldridge J, Kloczko J, Holowiecki J, Hellmann A, Walewski J, Flensburg M, Petersen J, Robak T. 2008. Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: a phase 1–2 study. Blood 111:1094–1100. https://doi.org/10.1182/blood-2007-09-111781.
502. Wierda WG, Kipps TJ, Mayer J, Stilgenbauer S, Williams CD, Hellmann A, Robak T, Furman RR, Hillmen P, Trneny M, Dyer MJ, Padmanabhan S, Piotrowska M, Kozak T, Chan G, Davis R, Losic N, Wilms J, Russell CA, Osterborg A. 2010. Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol 28:1749–1755. https://doi.org/10.1200/JCO.2009.25.3187.
503. Byrd JC, Brown JR, O'Brien S, Barrientos JC, Kay NE, Reddy NM, Coutre S, Tam CS, Mulligan SP, Jaeger U, Devereux S, Barr PM, Furman RR, Kipps TJ, Cymbalista F, Pocock C, Thornton P, Caligaris-Cappio F, Robak T, Delgado J, Schuster SJ, Montillo M, Schuh A, de Vos S, Gill D, Bloor A, Dearden C, Moreno C, Jones JJ, Chu AD, Fardis M, McGreivy J, Clow F, James DF, Hillmen P, RESONATE Investigators. 2014. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med 371:213–223. https://doi.org/10.1056/NEJMoa1400376.
504. Wierda WG, Kipps TJ, Durig J, Griskevicius L, Stilgenbauer S, Mayer J, Smolej L, Hess G, Griniute R, Hernandez-Ilizaliturri FJ, Padmanabhan S, Gorczyca M, Chang CN, Chan G, Gupta I, Nielsen TG, Russell CA. 2011. Chemoimmunotherapy with O-FC in previously untreated patients with chronic lymphocytic leukemia. Blood 117:6450–6458. https://doi.org/10.1182/blood-2010-12-323980.
505. Goede V, Fischer K, Busch R, Engelke A, Eichhorst B, Wendtner CM, Chagorova T, de la Serna J, Dilhuydy MS, Illmer T, Opat S, Owen CJ, Samoylova O, Kreuzer KA, Stilgenbauer S, Dohner H, Langerak AW, Ritgen M, Kneba M, Asikanius E, Humphrey K, Wenger M, Hallek M. 2014. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med 370:1101–1110. https://doi.org/10.1056/NEJMoa1313984.
506. Demitrovicova L, Mikuskova E, Oravcova I, Cingelova S, Drgona L, Mladosievicova B. 2017. Infectious complications in chronic lymphocytic leukemia—a retrospective analysis: single institution experience. Neoplasma 64:474–481. https://doi.org/10.4149/neo_2017_320.
507. Marcus R, Davies A, Ando K, Klapper W, Opat S, Owen C, Phillips E, Sangha R, Schlag R, Seymour JF, Townsend W, Trněný M, Wenger M, Fingerle-Rowson G, Rufibach K, Moore T, Herold M, Hiddemann W. 2017. Obinutuzumab for the first-line treatment of follicular lymphoma. N Engl J Med 377:1331–1344. https://doi.org/10.1056/NEJMoa1614598.
508. Wallace DJ, Navarra S, Petri MA, Gallacher A, Thomas M, Furie R, Levy RA, van Vollenhoven RF, Cooper S, Zhong ZJ, Freimuth W, Cervera R, BLISS-52 and -76 and LBSL02 Study Groups. 2013. Safety profile of belimumab: pooled data from placebo-controlled phase 2 and 3 studies in patients with systemic lupus erythematosus. Lupus 22:144–154. https://doi.org/10.1177/0961203312469259.
509. Borba HH, Wiens A, de Souza TT, Correr CJ, Pontarolo R. 2014. Efficacy and safety of biologic therapies for systemic lupus erythematosus treatment: systematic review and meta-analysis. BioDrugs 28:211–228. https://doi.org/10.1007/s40259-013-0074-x.
510. Navarra SV, Guzman RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, Li EK, Thomas M, Kim HY, Leon MG, Tanasescu C, Nasonov E, Lan JL, Pineda L, Zhong ZJ, Freimuth W, Petri MA. 2011. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet 377:721–731. https://doi.org/10.1016/S0140-6736(10)61354-2.
511. Furie R, Petri M, Zamani O, Cervera R, Wallace DJ, Tegzova D, Sanchez-Guerrero J, Schwarting A, Merrill JT, Chatham WW, Stohl W, Ginzler EM, Hough DR, Zhong ZJ, Freimuth W, van Vollenhoven RF, BLISS-76 Study Group. 2011. A phase III, randomized, placebo-controlled study

of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum 63:3918–3930. https://doi.org/10.1002/art.30613.
512. Merrill JT, LBSL02/99 Study Group, Ginzler EM, Wallace DJ, McKay JD, Lisse JR, Aranow C, Wellborne FR, Burnette M, Condemi J, Zhong ZJ, Pineda L, Klein J, Freimuth WW. 2012. Long-term safety profile of belimumab plus standard therapy in patients with systemic lupus erythematosus. Arthritis Rheum 64:3364–3373. https://doi.org/10.1002/art.34564.
513. Ginzler EM, Wallace DJ, Merrill JT, Furie RA, Stohl W, Chatham WW, Weinstein A, McKay JD, McCune WJ, Zhong ZJ, Freimuth WW, Petri MA, LBSL02/99 Study Group. 2014. Disease control and safety of belimumab plus standard therapy over 7 years in patients with systemic lupus erythematosus. J Rheumatol 41:300–309. https://doi.org/10.3899/jrheum.121368.
514. Hwang JP, Somerfield MR, Alston-Johnson DE, Cryer DR, Feld JJ, Kramer BS, Sabichi AL, Wong SL, Artz AS. 2015. Hepatitis B virus screening for patients with cancer before therapy: American Society of Clinical Oncology provisional clinical opinion update. J Clin Oncol 33:2212–2220. https://doi.org/10.1200/JCO.2015.61.3745.
515. Doyle J, Raggatt M, Slavin M, McLachlan SA, Strasser SI, Sasadeusz JJ, Howell J, Hajkowicz K, Nandurkar H, Johnston A, Bak N, Thompson AJ. 2019. Hepatitis B management during immunosuppression for haematological and solid organ malignancies: an Australian consensus statement. Med J Aust 210:462–468. https://doi.org/10.5694/mja2.50160.
516. Pattullo V. 2016. Prevention of hepatitis B reactivation in the setting of immunosuppression. Clin Mol Hepatol 22:219–237. https://doi.org/10.3350/cmh.2016.0024.
517. Hui CK, Cheung WW, Zhang HY, Au WY, Yueng YH, Leung AY, Leung N, Luk JM, Lie AK, Kwong YL, Liang R, Lau GK. 2006. Kinetics and risk of de novo hepatitis B infection in HBsAg-negative patients undergoing cytotoxic chemotherapy. Gastroenterology 131:59–68. https://doi.org/10.1053/j.gastro.2006.04.015.
518. Lok AS, McMahon BJ. 2004. Chronic hepatitis B: update of recommendations. Hepatology 39:857–861. https://doi.org/10.1002/hep.20110.
519. Gauthier J, Bourne EJ, Lutz MW, Crowther LM, Dienstag JL, Brown NA, Condreay LD. 1999. Quantitation of hepatitis B viremia and emergence of YMDD variants in patients with chronic hepatitis B treated with lamivudine. J Infect Dis 180:1757–1762. https://doi.org/10.1086/315147.
520. Huang H, Li X, Zhu J, Ye S, Zhang H, Wang W, Wu X, Peng J, Xu B, Lin Y, Cao Y, Li H, Lin S, Liu Q, Lin T. 2014. Entecavir vs lamivudine for prevention of hepatitis B virus reactivation among patients with untreated diffuse large B-cell lymphoma receiving R-CHOP chemotherapy: a randomized clinical trial. JAMA 312:2521–2530. https://doi.org/10.1001/jama.2014.15704.
521. Buensalido JA, Chandrasekar PH. 2014. Prophylaxis against hepatitis B reactivation among patients with lymphoma receiving rituximab. Expert Rev Anti Infect Ther 12:151–154. https://doi.org/10.1586/14787210.2014.870473.
522. Pham T, Fautrel B, Gottenberg J-E, Goupille P, Hachulla E, Masson C, Morel J, Mouthon L, Saraux A, Schaeverbeke T, Wendling D, Mariette X, Sibilia J. 2008. Rituximab (MabThera) therapy and safety management. Clinical tool guide. Joint Bone Spine 75(Suppl 1):S2–S99. https://doi.org/10.1016/S1297-319X(08)73620-0.
523. Nazi I, Kelton JG, Larché M, Snider DP, Heddle NM, Crowther MA, Cook RJ, Tinmouth AT, Mangel J, Arnold DM. 2013. The effect of rituximab on vaccine responses in patients with immune thrombocytopenia. Blood 122:1946–1953. https://doi.org/10.1182/blood-2013-04-494096.
524. Anonymous. 2001. Lemtrada (alemtuzumab). Full prescribing information. Reference ID 4163684. Food and Drug Administration, Silver Spring, MD.
525. Hill-Cawthorne GA, Button T, Tuohy O, Jones JL, May K, Somerfield J, Green A, Giovannoni G, Compston DA, Fahey MT, Coles AJ. 2012. Long term lymphocyte reconstitution after alemtuzumab treatment of multiple sclerosis. J Neurol Neurosurg Psychiatry 83:298–304. https://doi.org/10.1136/jnnp-2011-300826.
526. Coles AJ. 2013. Alemtuzumab therapy for multiple sclerosis. Neurotherapeutics 10:29–33. https://doi.org/10.1007/s13311-012-0159-0.
527. Hillmen P, Skotnicki AB, Robak T, Jaksic B, Dmoszynska A, Wu J, Sirard C, Mayer J. 2007. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. J Clin Oncol 25:5616–5623. https://doi.org/10.1200/JCO.2007.12.9098.
528. Keating MJ, Cazin B, Coutre S, Birhiray R, Kovacsovics T, Langer W, Leber B, Maughan T, Rai K, Tjonnfjord G, Bekradda M, Itzhaki M, Herait P. 2002. Campath-1H treatment of T-cell prolymphocytic leukemia in patients for whom at least one prior chemotherapy regimen has failed. J Clin Oncol 20:205–213. https://doi.org/10.1200/JCO.2002.20.1.205.
529. Lundin J, Hagberg H, Repp R, Cavallin-Ståhl E, Fredén S, Juliusson G, Rosenblad E, Tjønnfjord G, Wiklund T, Österborg A. 2003. Phase 2 study of alemtuzumab (anti-CD52 monoclonal antibody) in patients with advanced mycosis fungoides/Sezary syndrome. Blood 101:4267–4272. https://doi.org/10.1182/blood-2002-09-2802.
530. Scheinberg P, Nunez O, Weinstein B, Scheinberg P, Wu CO, Young NS. 2012. Activity of alemtuzumab monotherapy in treatment-naive, relapsed, and refractory severe acquired aplastic anemia. Blood 119:345–354. https://doi.org/10.1182/blood-2011-05-352328.
531. Osterborg A, Foa R, Bezares RF, Dearden C, Dyer MJ, Geisler C, Lin TS, Montillo M, van Oers MH, Wendtner CM, Rai KR. 2009. Management guidelines for the use of alemtuzumab in chronic lymphocytic leukemia. Leukemia 23:1980–1988. https://doi.org/10.1038/leu.2009.146.
532. Schnitzler M, Hasskarl J, Egger M, Bertz H, Finke J. 2009. Successful treatment of severe acute intestinal graft-versus-host resistant to systemic and topical steroids with alemtuzumab. Biol Blood Marrow Transplant 15:910–918. https://doi.org/10.1016/j.bbmt.2009.04.002.
533. Marsh RA, Allen CE, McClain KL, Weinstein JL, Kanter J, Skiles J, Lee ND, Khan SP, Lawrence J, Mo JQ, Bleesing JJ, Filipovich AH, Jordan MB. 2013. Salvage therapy of refractory hemophagocytic lymphohistiocytosis with alemtuzumab. Pediatr Blood Cancer 60:101–109. https://doi.org/10.1002/pbc.24188.
534. Teuteberg JJ, Shullo MA, Zomak R, Toyoda Y, McNamara DM, Bermudez C, Kormos RL, McCurry KR. 2010. Alemtuzumab induction prior to cardiac transplantation with lower intensity maintenance immunosuppression: one-year outcomes. Am J Transplant 10:382–388. https://doi.org/10.1111/j.1600-6143.2009.02856.x.
535. Haynes R, Harden P, Judge P, Blackwell L, Emberson J, Landray MJ, Baigent C, Friend PJ. 2014. Alemtuzumab-based induction treatment versus basiliximab-based induction treatment in kidney transplantation (the 3C Study): a randomised trial. Lancet 384:1684–1690.
536. Hassoun L, Eisele J, Thomas K, Ziemssen T. 2016. Hands on alemtuzumab—experience from clinical practice: whom and how to treat. Mult Scler Demyelinating Disord 1:10. https://doi.org/10.1186/s40893-016-0011-1.
537. Epstein DJ, Dunn J, Deresinski S. 2018. Infectious complications of multiple sclerosis therapies: implications for screening, prophylaxis, and management. Open Forum Infect Dis 5:ofy174. https://doi.org/10.1093/ofid/ofy174.
538. Kim SJ, Moon JH, Kim H, Kim JS, Hwang YY, Intragumtornchai T, Issaragrisil S, Kwak JY, Lee JJ, Won JH, Reksodiputro AH, Lim ST, Cheng AL, Kim WS, Kwong YL. 2012. Non-bacterial infections in Asian patients treated with alemtuzumab: a retrospective study of the Asian Lymphoma Study Group. Leuk Lymphoma 53:1515–1524. https://doi.org/10.3109/10428194.2012.659735.
539. Mastroianni CM, Lichtner M, Citton R, Del Borgo C, Rago A, Martini HCG, Vullo V. 2011. Current trends in management of hepatitis B virus reactivation in the biologic therapy era. World J Gastroenterol 17:3881–3887. https://doi.org/10.3748/wjg.v17.i34.3881.
540. Mikulska M, Lanini S, Gudiol C, Drgona L, Ippolito G, Fernandez-Ruiz M, Salzberger B. 2018. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (agents targeting lymphoid cells surface antigens [I]: CD19, CD20 and CD52). Clin Microbiol Infect 24(Suppl 2):S71–S82. https://doi.org/10.1016/j.cmi.2018.02.003.
541. Ruxrungtham K, Sirivichayakul S, Buranapraditkun S, Krause W. 2016. Alemtuzumab-induced elimination of HIV-1-infected immune cells. J Virus Erad 2:12–18.
542. Rasmussen TA, McMahon J, Chang JJ, Symons J, Roche M, Dantanarayana A, Okoye A, Hiener B, Palmer S, Lee WS, Kent SJ, Van Der Weyden C, Prince HM, Cameron PU, Lewin SR. 2017. Impact of alemtuzumab on HIV persistence in an HIV-infected individual on antiretroviral therapy with Sezary syndrome. AIDS 31:1839–1845. https://doi.org/10.1097/QAD.0000000000001540.
543. Coles AJ, Compston DA, Selmaj KW, Lake SL, Moran S, Margolin DH,

Norris K, Tandon PK. 2008. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N Engl J Med 359:1786–1801.
544. Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP, Havrdova E, Selmaj KW, Weiner HL, Fisher E, Brinar VV, Giovannoni G, Stojanovic M, Ertik BI, Lake SL, Margolin DH, Panzara MA, Compston DA. 2012. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet 380:1819–1828. https://doi.org/10.1016/S0140-6736(12)61769-3.
545. Brownlee WJ, Chataway J. 2017. Opportunistic infections after alemtuzumab: new cases of norcardial infection and cytomegalovirus syndrome. Mult Scler 23:876–877. https://doi.org/10.1177/1352458517693440.
546. Yann K, Jackson F, Sharaf N, Mihalova T, Talbot P, Rog D, Pace A. 2017. Acute respiratory distress syndrome following alemtuzumab therapy for relapsing multiple sclerosis. Mult Scler Relat Disord 14:1–3. https://doi.org/10.1016/j.msard.2017.03.001.
547. O'Brien S, Ravandi F, Riehl T, Wierda W, Huang X, Tarrand J, O'Neal B, Kantarjian H, Keating M. 2008. Valganciclovir prevents cytomegalovirus reactivation in patients receiving alemtuzumab-based therapy. Blood 111:1816–1819. https://doi.org/10.1182/blood-2007-03-080010.
548. Ng AP, Worth L, Chen L, Seymour JF, Prince HM, Slavin M, Thursky K. 2005. Cytomegalovirus DNAemia and disease: incidence, natural history and management in settings other than allogeneic stem cell transplantation. Haematologica 90:1672–1679.
549. Smolej L, Prochazka V, Spacek M, Obrtlikova P, Gumulec J, Vokurka S, Doubek M. 2012. Guidelines for alemtuzumab treatment in chronic lymphocytic leukaemia (CLL). Vnitr Lek 58:232–236. (In Czech.)
550. Berger T, Elovaara I, Fredrikson S, McGuigan C, Moiola L, Myhr K-M, Oreja-Guevara C, Stoliarov I, Zettl UK. 2017. Alemtuzumab use in clinical practice: recommendations from European Multiple Sclerosis Experts. CNS Drugs 31:33–50. https://doi.org/10.1007/s40263-016-0394-8.
551. Piccinni C, Sacripanti C, Poluzzi E, Motola D, Magro L, Moretti U, Conforti A, Montanaro N. 2010. Stronger association of drug-induced progressive multifocal leukoencephalopathy (PML) with biological immunomodulating agents. Eur J Clin Pharmacol 66:199–206. https://doi.org/10.1007/s00228-009-0739-z.
552. Baghban A, Azar MM, Bernardo RM, Malinis M. 2016. Disseminated Mycobacterium tuberculosis following renal transplant with alemtuzumab induction. BMJ Case Rep 2016:bcr2016217998. https://doi.org/10.1136/bcr-2016-217998.
553. Au WY, Leung AY, Tse EW, Cheung WW, Shek TW, Kwong YL. 2008. High incidence of tuberculosis after alemtuzumab treatment in Hong Kong Chinese patients. Leuk Res 32:547–551. https://doi.org/10.1016/j.leukres.2007.06.010.
554. Walsh R, Ortiz J, Foster P, Palma-Vargas J, Rosenblatt S, Wright F. 2008. Fungal and mycobacterial infections after Campath (alemtuzumab) induction for renal transplantation. Transpl Infect Dis 10:236–239. https://doi.org/10.1111/j.1399-3062.2007.00292.x.
555. Guarnera C, Bramanti P, Mazzon E. 2017. Alemtuzumab: a review of efficacy and risks in the treatment of relapsing remitting multiple sclerosis. Ther Clin Risk Manag 13:871–879. https://doi.org/10.2147/TCRM.S134398.
556. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, Bousvaros A, Dhanireddy S, Sung L, Keyserling H, Kang I. 2014. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 58:309–318. https://doi.org/10.1093/cid/cit816.
557. Buonomo AR, Sacca F, Zappulo E, De Zottis F, Lanzillo R, Gentile I, Carotenuto A, Borgia G, Russo CV. 2019. Bacterial and CMV pneumonia in a patient treated with alemtuzumab for multiple sclerosis. Mult Scler Relat Disord 27:44–45. https://doi.org/10.1016/j.msard.2018.09.031.
558. Boyle S, Olive G, Townell N, Henderson A, Bowler S, Blum S. 2017. Legionella longbeachae pneumonia as a complication of alemtuzumab therapy. J Clin Neurosci 46:67–69. https://doi.org/10.1016/j.jocn.2017.08.051.
559. Penkert H, Delbridge C, Wantia N, Wiestler B, Korn T. 2016. Fulminant central nervous system nocardiosis in a patient treated with alemtuzumab for relapsing-remitting multiple sclerosis. JAMA Neurol 73:757–759. https://doi.org/10.1001/jamaneurol.2016.0146.
560. Sheikh-Taha M, Corman LC. 2017. Pulmonary Nocardia beijingensis infection associated with the use of alemtuzumab in a patient with multiple sclerosis. Mult Scler 23:872–874. https://doi.org/10.1177/1352458517694431.
561. Holmoy T, von der Lippe H, Leegaard TM. 2017. Listeria monocytogenes infection associated with alemtuzumab—a case for better preventive strategies. BMC Neurol 17:65. https://doi.org/10.1186/s12883-017-0848-8.
562. Anonymous. 2014. Blincyto (blinatumomab). Full prescribing information. Reference ID 4123274. Food and Drug Administration, Silver Spring, MD.
563. Zugmaier G, Topp MS, Alekar S, Viardot A, Horst HA, Neumann S, Stelljes M, Bargou RC, Goebeler M, Wessiepe D, Degenhard E, Gokbuget N, Klinger M. 2014. Long-term follow-up of serum immunoglobulin levels in blinatumomab-treated patients with minimal residual disease-positive B-precursor acute lymphoblastic leukemia. Blood Cancer J 4:244. https://doi.org/10.1038/bcj.2014.64.
564. Kantarjian H, Stein A, Gökbuget N, Fielding AK, Schuh AC, Ribera J-M, Wei A, Dombret H, Foà R, Bassan R, Arslan Ö, Sanz MA, Bergeron J, Demirkan F, Lech-Maranda E, Rambaldi A, Thomas X, Horst H-A, Brüggemann M, Klapper W, Wood BL, Fleishman A, Nagorsen D, Holland C, Zimmerman Z, Topp MS. 2017. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med 376:836–847. https://doi.org/10.1056/NEJMoa1609783.
565. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, Stemmler HJ, Schlößer HA, Schlaak M, Kochanek M, Böll B, von Bergwelt-Baildon MS. 2018. Cytokine release syndrome. J Immunother Cancer 6:56. https://doi.org/10.1186/s40425-018-0343-9.
566. So W, Pandya S, Quilitz R, Quilitz R, Greene J. 2018. Infectious risks and complications in adult leukemic patients receiving blinatumomab. Mediterr J Hematol Infect Dis 10:e2018029. https://doi.org/10.4084/mjhid.2018.029.
567. Anonymous. 2015. Darzalex (daratumumab). Full prescribing information. Reference ID 4016996. Food and Drug Administration, Silver Spring, MD.
568. Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, Spicka I, Hungria V, Munder M, Mateos MV, Mark TM, Qi M, Schecter J, Amin H, Qin X, Deraedt W, Ahmadi T, Spencer A, Sonneveld P. 2016. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. N Engl J Med 375:754–766. https://doi.org/10.1056/NEJMoa1606038.
569. Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, Rabin N, Orlowski RZ, Komarnicki M, Suzuki K, Plesner T, Yoon S-S, Ben Yehuda D, Richardson PG, Goldschmidt H, Reece D, Lisby S, Khokhar NZ, O'Rourke L, Chiu C, Qin X, Guckert M, Ahmadi T, Moreau P. 2016. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 375:1319–1331. https://doi.org/10.1056/NEJMoa1607751.
570. Drgona L, Gudiol C, Lanini S, Salzberger B, Ippolito G, Mikulska M. 2018. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (agents targeting lymphoid or myeloid cells surface antigens [II]: CD22, CD30, CD33, CD38, CD40, SLAMF-7 and CCR4). Clin Microbiol Infect 24(Suppl 2):S83–S94. https://doi.org/10.1016/j.cmi.2018.03.022.
571. Magen H, Muchtar E. 2016. Elotuzumab: the first approved monoclonal antibody for multiple myeloma treatment. Ther Adv Hematol 7:187–195. https://doi.org/10.1177/2040620716652862.
572. Anonymous. 2015. Empliciti (elotuzumab). Full prescribing information. Reference ID 3853154. Food and Drug Administration, Silver Spring, MD.
573. van Rhee F, Szmania SM, Dillon M, van Abbema AM, Li X, Stone MK, Garg TK, Shi J, Moreno-Bost AM, Yun R, Balasa B, Ganguly B, Chao D, Rice AG, Zhan F, Shaughnessy JD, Jr, Barlogie B, Yaccoby S, Afar DE. 2009. Combinatorial efficacy of anti-CS1 monoclonal antibody elotuzumab (HuLuc63) and bortezomib against multiple myeloma. Mol Cancer Ther 8:2616–2624. https://doi.org/10.1158/1535-7163.MCT-09-0483.
574. Hsi ED, Steinle R, Balasa B, Szmania S, Draksharapu A, Shum BP, Huseni M, Powers D, Nanisetti A, Zhang Y, Rice AG, van Abbema A, Wong M, Liu G, Zhan F, Dillon M, Chen S, Rhodes S, Fuh F, Tsurushita N, Kumar S, Vexler V, Shaughnessy JD, Jr, Barlogie B, van Rhee F, Hussein M, Afar DE, Williams MB. 2008. CS1, a potential new therapeutic antibody target for the treatment of multiple myeloma. Clin Cancer Res 14:2775–2784. https://doi.org/10.1158/1078-0432.CCR-07-4246.

575. Lonial S, Dimopoulos M, Palumbo A, White D, Grosicki S, Spicka I, Walter-Croneck A, Moreau P, Mateos M-V, Magen H, Belch A, Reece D, Beksac M, Spencer A, Oakervee H, Orlowski RZ, Taniwaki M, Röllig C, Einsele H, Wu KL, Singhal A, San-Miguel J, Matsumoto M, Katz J, Bleickardt E, Poulart V, Anderson KC, Richardson P. 2015. Elotuzumab therapy for relapsed or refractory multiple myeloma. N Engl J Med 373:621–631. https://doi.org/10.1056/NEJMoa1505654.
576. Dimopoulos MA, Lonial S, White D, Moreau P, Palumbo A, San Miguel J, Shpilberg O, Anderson KC, Grosicki S, Spicka I, Walter-Croneck A, Magen-Nativ H, Mateos M-V, Belch A, Reece D, Beksac M, Bleickhardt E, Poulart V, Katz J, Singhal AK, Richardson PG. 2015. Eloquent-2 update: a phase 3, randomized, open-label study of elotuzumab in combination with lenalidomide/dexamethasone in patients with relapsed/refractory multiple myeloma—3-year safety and efficacy follow-up. Blood 126:28–28. https://doi.org/10.1182/blood.V126.23.28.28.
577. Dinarello CA. 2018. Overview of the IL-1 family in innate inflammation and acquired immunity. Immunol Rev 281:8–27. https://doi.org/10.1111/imr.12621.
578. Hahn M, Frey S, Hueber AJ. 2017. The novel interleukin-1 cytokine family members in inflammatory diseases. Curr Opin Rheumatol 29:208–213. https://doi.org/10.1097/BOR.0000000000000361.
579. Chen IY, Moriyama M, Chang MF, Ichinohe T. 2019. Severe acute respiratory syndrome coronavirus viroporin 3a activates the NLRP3 inflammasome. Front Microbiol 10:50. https://doi.org/10.3389/fmicb.2019.00050.
580. Khazim K, Azulay EE, Kristal B, Cohen I. 2018. Interleukin 1 gene polymorphism and susceptibility to disease. Immunol Rev 281:40–56. https://doi.org/10.1111/imr.12620.
581. Weigt SS, Palchevskiy V, Belperio JA. 2017. Inflammasomes and IL-1 biology in the pathogenesis of allograft dysfunction. J Clin Invest 127:2022–2029. https://doi.org/10.1172/JCI93537.
582. Sims JE, Smith DE. 2010. The IL-1 family: regulators of immunity. Nat Rev Immunol 10:89–102. https://doi.org/10.1038/nri2691.
583. Bresnihan B, Alvaro-Gracia JM, Cobby M, Doherty M, Domljan Z, Emery P, Nuki G, Pavelka K, Rau R, Rozman B, Watt I, Williams B, Aitchison R, McCabe D, Musikic P. 1998. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. Arthritis Rheum 41:2196–2204. https://doi.org/10.1002/1529-0131(199812)41:12<2196::AID-ART15>3.0.CO;2-2.
584. Yang BB, Baughman S, Sullivan JT. 2003. Pharmacokinetics of anakinra in subjects with different levels of renal function. Clin Pharmacol Ther 74:85–94. https://doi.org/10.1016/S0009-9236(03)00094-8.
585. Rothman AM, Morton AC, Crossman DC, MRC-ILA Heart Investigators. 2018. Canakinumab for atherosclerotic disease. N Engl J Med 378:197–198. https://doi.org/10.1056/NEJMc1714635.
586. De Benedetti F, Gattorno M, Anton J, Ben-Chetrit E, Frenkel J, Hoffman HM, Kone-Paut I, Lachmann HJ, Ozen S, Simon A, Zeft A, Calvo Penades I, Moutschen M, Quartier P, Kasapcopur O, Shcherbina A, Hofer M, Hashkes PJ, Van der Hilst J, Hara R, Bujan-Rivas S, Constantin T, Gul A, Livneh A, Brogan P, Cattalini M, Obici L, Lheritier K, Speziale A, Junge G. 2018. Canakinumab for the treatment of autoinflammatory recurrent fever syndromes. N Engl J Med 378:1908–1919. https://doi.org/10.1056/NEJMoa1706314.
587. Winthrop KL, Mariette X, Silva JT, Benamu E, Calabrese LH, Dumusc A, Smolen JS, Aguado JM, Fernandez-Ruiz M. 2018. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (soluble immune effector molecules [II]: agents targeting interleukins, immunoglobulins and complement factors). Clin Microbiol Infect 24(Suppl 2):S21–S40. https://doi.org/10.1016/j.cmi.2018.02.002.
588. Hoffman HM, Throne ML, Amar NJ, Sebai M, Kivitz AJ, Kavanaugh A, Weinstein SP, Belomestnov P, Yancopoulos GD, Stahl N, Mellis SJ. 2008. Efficacy and safety of rilonacept (interleukin-1 Trap) in patients with cryopyrin-associated periodic syndromes: results from two sequential placebo-controlled studies. Arthritis Rheum 58:2443–2452. https://doi.org/10.1002/art.23687.
589. Terkeltaub R, Sundy JS, Schumacher HR, Murphy F, Bookbinder S, Biedermann S, Wu R, Mellis S, Radin A. 2009. The interleukin 1 inhibitor rilonacept in treatment of chronic gouty arthritis: results of a placebo-controlled, monosequence crossover, non-randomised, single-blind pilot study. Ann Rheum Dis 68:1613–1617. https://doi.org/10.1136/ard.2009.108936.
590. Feist E, Quartier P, Fautrel B, Schneider R, Sfriso P, Efthimiou P, Cantarini L, Lheritier K, Leon K, Karyekar CS, Speziale A. 2018. Efficacy and safety of canakinumab in patients with Still's disease: exposure-response analysis of pooled systemic juvenile idiopathic arthritis data by age groups. Clin Exp Rheumatol 36:668–675.
591. Dinarello CA, van der Meer JW. 2013. Treating inflammation by blocking interleukin-1 in humans. Semin Immunol 25:469–484. https://doi.org/10.1016/j.smim.2013.10.008.
592. van der Hilst JC, Bodar EJ, Barron KS, Frenkel J, Drenth JP, van der Meer JW, Simon A, International HIDS Study Group. 2008. Long-term follow-up, clinical features, and quality of life in a series of 103 patients with hyperimmunoglobulinemia D syndrome. Medicine (Baltimore) 87:301–310. https://doi.org/10.1097/MD.0b013e318190cfb7.
593. Gentileschi S, Rigante D, Vitale A, Sota J, Frediani B, Galeazzi M, Cantarini L. 2017. Efficacy and safety of anakinra in tumor necrosis factor receptor-associated periodic syndrome (TRAPS) complicated by severe renal failure: a report after long-term follow-up and review of the literature. Clin Rheumatol 36:1687–1690. https://doi.org/10.1007/s10067-017-3688-4.
594. Jesus AA, Goldbach-Mansky R. 2014. IL-1 blockade in autoinflammatory syndromes. Annu Rev Med 65:223–244. https://doi.org/10.1146/annurev-med-061512-150641.
595. Nikfar S, Saiyarsarai P, Tigabu BM, Abdollahi M. 2018. Efficacy and safety of interleukin-1 antagonists in rheumatoid arthritis: a systematic review and meta-analysis. Rheumatol Int 38:1363–1383. https://doi.org/10.1007/s00296-018-4041-1.
596. Horneff G, Schulz AC, Klotsche J, Hospach A, Minden K, Foeldvari I, Trauzeddel R, Ganser G, Weller-Heinemann F, Haas JP. 2017. Experience with etanercept, tocilizumab and interleukin-1 inhibitors in systemic onset juvenile idiopathic arthritis patients from the BIKER registry. Arthritis Res Ther 19:256. https://doi.org/10.1186/s13075-017-1462-2.
597. Thueringer JT, Doll NK, Gertner E. 2015. Anakinra for the treatment of acute severe gout in critically ill patients. Semin Arthritis Rheum 45:81–85. https://doi.org/10.1016/j.semarthrit.2015.02.006.
598. Tran AP, Edelman J. 2011. Interleukin-1 inhibition by anakinra in refractory chronic tophaceous gout. Int J Rheum Dis 14:e33–e37. https://doi.org/10.1111/j.1756-185X.2011.01629.x.
599. Schlesinger N, Alten RE, Bardin T, Schumacher HR, Bloch M, Gimona A, Krammer G, Murphy V, Richard D, So AK. 2012. Canakinumab for acute gouty arthritis in patients with limited treatment options: results from two randomised, multicentre, active-controlled, double-blind trials and their initial extensions. Ann Rheum Dis 71:1839–1848. https://doi.org/10.1136/annrheumdis-2011-200908.
600. Sivera F, Wechalekar MD, Andres M, Buchbinder R, Carmona L. 2014. Interleukin-1 inhibitors for acute gout. Cochrane Database Syst Rev 2014:CD009993. https://doi.org/10.1002/14651858.CD009993.
601. Fabiani C, Vitale A, Emmi G, Lopalco G, Vannozzi L, Guerriero S, Gentileschi S, Bacherini D, Franceschini R, Frediani B, Galeazzi M, Iannone F, Tosi GM, Cantarini L. 2017. Interleukin (IL)-1 inhibition with anakinra and canakinumab in Behcet's disease-related uveitis: a multicenter retrospective observational study. Clin Rheumatol 36:191–197. https://doi.org/10.1007/s10067-016-3506-4.
602. Cantarini L, Talarico R, Generali E, Emmi G, Lopalco G, Costa L, Silvestri E, Caso F, Franceschini R, Cimaz R, Iannone F, Galeazzi M, Selmi C. 2017. Safety profile of biologic agents for Behcet's disease in a multicenter observational cohort study. Int J Rheum Dis 20:103–108. https://doi.org/10.1111/1756-185X.12732.
603. Diamantopoulos AP, Brodin C, Hetland H, Haugeberg G. 2012. Interleukin 1beta blockade improves signs and symptoms of chronic calcium pyrophosphate crystal arthritis resistant to treatment. J Clin Rheumatol 18:310–311. https://doi.org/10.1097/RHU.0b013e31826149a2.
604. Brucato A, Emmi G, Cantarini L, Di Lenarda A, Gattorno M, Lopalco G, Marcolongo R, Imazio M, Martini A, Prisco D. 2018. Management of idiopathic recurrent pericarditis in adults and in children: a role for IL-1 receptor antagonism. Intern Emerg Med 13:475–489. https://doi.org/10.1007/s11739-018-1842-x.
605. Buckley LF, Viscusi MM, Van Tassell BW, Abbate A. 2018. Interleukin-1 blockade for the treatment of pericarditis. Eur Heart J Cardiovasc Pharmacother 4:46–53. https://doi.org/10.1093/ehjcvp/pvx018.
606. Acquitter M, Plantin P, Kupfer I, Auvinet H, Marhadour T. 2015. Anakinra improves pyoderma gangrenosum in psoriatic arthritis: a case report. Ann Intern Med 163:70–71. https://doi.org/10.7326/L15-5107.

607. Kluger N, Gil-Bistes D, Guillot B, Bessis D. 2011. Efficacy of anti-interleukin-1 receptor antagonist anakinra (Kineret) in a case of refractory Sweet's syndrome. Dermatology 222:123–127. https://doi.org/10.1159/000326112.
608. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ. 2017. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 377:1119–1131. https://doi.org/10.1056/NEJMoa1707914.
609. Ridker PM, MacFadyen JG, Everett BM, Libby P, Thuren T, Glynn RJ, CANTOS Trial Group. 2018. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. Lancet 391:319–328. https://doi.org/10.1016/S0140-6736(17)32814-3.
610. Tugal-Tutkun I, Pavesio C, De Cordoue A, Bernard-Poenaru O, Gül A. 2018. Use of gevokizumab in patients with Behcet's disease uveitis: an international, randomized, double-masked, placebo-controlled study and open-label extension study. Ocul Immunol Inflamm 26:1023–1033. https://doi.org/10.1080/09273948.2017.1421233.
611. Terkeltaub RA, Schumacher HR, Carter JD, Baraf HS, Evans RR, Wang J, King-Davis S, Weinstein SP. 2013. Rilonacept in the treatment of acute gouty arthritis: a randomized, controlled clinical trial using indomethacin as the active comparator. Arthritis Res Ther 15:R25. https://doi.org/10.1186/ar4159.
612. So A, De Meulemeester M, Pikhlak A, Yucel AE, Richard D, Murphy V, Arulmani U, Sallstig P, Schlesinger N. 2010. Canakinumab for the treatment of acute flares in difficult-to-treat gouty arthritis: results of a multicenter, phase II, dose-ranging study. Arthritis Rheum 62:3064–3076. https://doi.org/10.1002/art.27600.
613. Cohen S, Hurd E, Cush J, Schiff M, Weinblatt ME, Moreland LW, Kremer J, Bear MB, Rich WJ, McCabe D. 2002. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 46:614–624. https://doi.org/10.1002/art.10141.
614. Fleischmann RM, Tesser J, Schiff MH, Schechtman J, Burmester GR, Bennett R, Modafferi D, Zhou L, Bell D, Appleton B. 2006. Safety of extended treatment with anakinra in patients with rheumatoid arthritis. Ann Rheum Dis 65:1006–1012. https://doi.org/10.1136/ard.2005.048371.
615. Nuki G, Bresnihan B, Bear MB, McCabe D, European Group Of Clinical Investigators. 2002. Long-term safety and maintenance of clinical improvement following treatment with anakinra (recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis: extension phase of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 46:2838–2846. https://doi.org/10.1002/art.10578.
616. Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA, Tanjong Ghogomu E, Tugwell P. 2009. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Cochrane Database Syst Rev 2009:CD007848. https://doi.org/10.1002/14651858.CD007848.
617. Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, Horneff G, Brik R, McCann L, Kasapcopur O, Rutkowska-Sak L, Schneider R, Berkun Y, Calvo I, Erguven M, Goffin L, Hofer M, Kallinich T, Oliveira SK, Uziel Y, Viola S, Nistala K, Wouters C, Cimaz R, Ferrandiz MA, Flato B, Gamir ML, Kone-Paut I, Grom A, Magnusson B, Ozen S, Sztajnbok F, Lheritier K, Abrams K, Kim D, Martini A, Lovell DJ. 2012. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. N Engl J Med 367:2396–2406. https://doi.org/10.1056/NEJMoa1205099.
618. Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat NM, Horneff G, Kasapcopur O, Schneider R, Anton J, Barash J, Berner R, Corona F, Cuttica R, Fouillet-Desjonqueres M, Fischbach M, Foster HE, Foell D, Radominski SC, Ramanan AV, Trauzeddel R, Unsal E, Levy J, Vritzali E, Martini A, Lovell DJ, Paediatric Rheumatology International Trials Organisation (PRINTO) and Pediatric Rheumatology Collaborative Study Group (PRCSG). 2018. Canakinumab in patients with systemic juvenile idiopathic arthritis and active systemic features: results from the 5-year long-term extension of the phase III pivotal trials. Ann Rheum Dis 77:1710–1719. https://doi.org/10.1136/annrheumdis-2018-213150.
619. Hong D, Yang Z, Han S, Liang X, Ma K, Zhang X. 2014. Interleukin 1 inhibition with anakinra in adult-onset Still disease: a meta-analysis of its efficacy and safety. Drug Des Devel Ther 8:2345–2357. https://doi.org/10.2147/DDDT.S73428.
620. Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, Leslie KS, Hachulla E, Quartier P, Gitton X, Widmer A, Patel N, Hawkins PN. 2009. Use of canakinumab in the cryopyrin-associated periodic syndrome. N Engl J Med 360:2416–2425. https://doi.org/10.1056/NEJMoa0810787.
621. Brik R, Butbul-Aviel Y, Lubin S, Ben Dayan E, Rachmilewitz-Minei T, Tseng L, Hashkes PJ. 2014. Canakinumab for the treatment of children with colchicine-resistant familial Mediterranean fever: a 6-month open-label, single-arm pilot study. Arthritis Rheumatol 66:3241–3243. https://doi.org/10.1002/art.38777.
622. Kuemmerle-Deschner JB, Hachulla E, Cartwright R, Hawkins PN, Tran TA, Bader-Meunier B, Hoyer J, Gattorno M, Gul A, Smith J, Leslie KS, Jimenez S, Morell-Dubois S, Davis N, Patel N, Widmer A, Preiss R, Lachmann HJ. 2011. Two-year results from an open-label, multicentre, phase III study evaluating the safety and efficacy of canakinumab in patients with cryopyrin-associated periodic syndrome across different severity phenotypes. Ann Rheum Dis 70:2095–2102. https://doi.org/10.1136/ard.2011.152728.
623. Gattorno M, Obici L, Cattalini M, Tormey V, Abrams K, Davis N, Speziale A, Bhansali SG, Martini A, Lachmann HJ. 2017. Canakinumab treatment for patients with active recurrent or chronic TNF receptor-associated periodic syndrome (TRAPS): an open-label, phase II study. Ann Rheum Dis 76:173–178. https://doi.org/10.1136/annrheumdis-2015-209031.
624. Arostegui JI, Anton J, Calvo I, Robles A, Iglesias E, López-Montesinos B, Banchereau R, Hong S, Joubert Y, Junge G, Pascual V, Yagüe J. 2017. Open-label, phase II study to assess the efficacy and safety of canakinumab treatment in active hyperimmunoglobulinemia D with periodic fever syndrome. Arthritis Rheumatol 69:1679–1688. https://doi.org/10.1002/art.40146.
625. Kullenberg T, Lofqvist M, Leinonen M, Goldbach-Mansky R, Olivecrona H. 2016. Long-term safety profile of anakinra in patients with severe cryopyrin-associated periodic syndromes. Rheumatology (Oxford) 55:1499–1506. https://doi.org/10.1093/rheumatology/kew208.
626. Sibley CH, Chioato A, Felix S, Colin L, Chakraborty A, Plass N, Rodriguez-Smith J, Brewer C, King K, Zalewski C, Kim HJ, Bishop R, Abrams K, Stone D, Chapelle D, Kost B, Snyder C, Butman JA, Wesley R, Goldbach-Mansky R. 2015. A 24-month open-label study of canakinumab in neonatal-onset multisystem inflammatory disease. Ann Rheum Dis 74:1714–1719. https://doi.org/10.1136/annrheumdis-2013-204877.
627. Russo RA, Melo-Gomes S, Lachmann HJ, Wynne K, Rajput K, Eleftheriou D, Edelsten C, Hawkins PN, Brogan PA. 2014. Efficacy and safety of canakinumab therapy in paediatric patients with cryopyrin-associated periodic syndrome: a single-centre, real-world experience. Rheumatology (Oxford) 53:665–670. https://doi.org/10.1093/rheumatology/ket415.
628. Hashkes PJ, Spalding SJ, Giannini EH, Huang B, Johnson A, Park G, Barron KS, Weisman MH, Pashinian N, Reiff AO, Samuels J, Wright DA, Kastner DL, Lovell DJ. 2012. Rilonacept for colchicine-resistant or -intolerant familial Mediterranean fever: a randomized trial. Ann Intern Med 157:533–541. https://doi.org/10.7326/0003-4819-157-8-201210160-00003.
629. Anonymous. 2010. Updated recommendations for prevention of invasive pneumococcal disease among adults using the 23-valent pneumococcal polysaccharide vaccine (PPSV23). MMWR Morb Mortal Wkly Rep 59:1102–1106.
630. van Assen S, Agmon-Levin N, Elkayam O, Cervera R, Doran MF, Dougados M, Emery P, Geborek P, Ioannidis JP, Jayne DR, Kallenberg CG, Muller-Ladner U, Shoenfeld Y, Stojanovich L, Valesini G, Wulffraat NM, Bijl M. 2011. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis 70:414–422. https://doi.org/10.1136/ard.2010.137216.
631. Jaeger VK, Hoffman HM, van der Poll T, Tilson H, Seibert J, Speziale A, Junge G, Franke K, Vritzali E, Hawkins PN, Kuemmerle-Deschner J, Walker UA. 2017. Safety of vaccinations in patients with cryopyrin-associated periodic syndromes: a prospective registry based study. Rheumatology (Oxford) 56:1484–1491. https://doi.org/10.1093/rheumatology/kex185.
632. McCormick SM, Heller NM. 2015. Commentary: IL-4 and IL-13 recep-

tors and signaling. Cytokine 75:38–50. https://doi.org/10.1016/j.cyto.2015.05.023.
633. Sastre J, Davila I. 2018. Dupilumab: a new paradigm for the treatment of allergic diseases. J Invest Allergol Clin Immunol 28:139–150. https://doi.org/10.18176/jiaci.0254.
634. May RD, Fung M. 2015. Strategies targeting the IL-4/IL-13 axes in disease. Cytokine 75:89–116. https://doi.org/10.1016/j.cyto.2015.05.018.
635. Gour N, Wills-Karp M. 2015. IL-4 and IL-13 signaling in allergic airway disease. Cytokine 75:68–78. https://doi.org/10.1016/j.cyto.2015.05.014.
636. Junttila IS, Creusot RJ, Moraga I, Bates DL, Wong MT, Alonso MN, Suhoski MM, Lupardus P, Meier-Schellersheim M, Engleman EG, Utz PJ, Fathman CG, Paul WE, Garcia KC. 2012. Redirecting cell-type specific cytokine responses with engineered interleukin-4 superkines. Nat Chem Biol 8:990–998. https://doi.org/10.1038/nchembio.1096.
637. Thomson J, Wernham AGH, Williams HC. 2018. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a critical appraisal. Br J Dermatol 178:897–902. https://doi.org/10.1111/bjd.16317.
638. Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D, Simpson EL, Papp KA, Hong HC, Rubel D, Foley P, Prens E, Griffiths CEM, Etoh T, Pinto PH, Pujol RM, Szepietowski JC, Ettler K, Kemeny L, Zhu X, Akinlade B, Hultsch T, Mastey V, Gadkari A, Eckert L, Amin N, Graham NMH, Pirozzi G, Stahl N, Yancopoulos GD, Shumel B. 2017. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet 389:2287–2303. https://doi.org/10.1016/S0140-6736(17)31191-1.
639. Beck LA, Thaci D, Hamilton JD, Graham NM, Bieber T, Rocklin R, Ming JE, Ren H, Kao R, Simpson E, Ardeleanu M, Weinstein SP, Pirozzi G, Guttman-Yassky E, Suarez-Farinas M, Hager MD, Stahl N, Yancopoulos GD, Radin AR. 2014. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. N Engl J Med 371:130–139. https://doi.org/10.1056/NEJMoa1314768.
640. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, Silverberg JI, Deleuran M, Kataoka Y, Lacour JP, Kingo K, Worm M, Poulin Y, Wollenberg A, Soo Y, Graham NM, Pirozzi G, Akinlade B, Staudinger H, Mastey V, Eckert L, Gadkari A, Stahl N, Yancopoulos GD, Ardeleanu M. 2016. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med 375:2335–2348. https://doi.org/10.1056/NEJMoa1610020.
641. Thaci D, Simpson EL, Beck LA, Bieber T, Blauvelt A, Papp K, Soong W, Worm M, Szepietowski JC, Sofen H, Kawashima M, Wu R, Weinstein SP, Graham NM, Pirozzi G, Teper A, Sutherland ER, Mastey V, Stahl N, Yancopoulos GD, Ardeleanu M. 2016. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. Lancet 387:40–52. https://doi.org/10.1016/S0140-6736(15)00388-8.
642. Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, Zhu H, Hamilton JD, Swanson BN, Khan A, Chao J, Staudinger H, Pirozzi G, Antoni C, Amin N, Ruddy M, Akinlade B, Graham NMH, Stahl N, Yancopoulos GD, Teper A. 2018. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med 378:2475–2485. https://doi.org/10.1056/NEJMoa1804093.
643. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, Busse WW, Ford L, Sher L, FitzGerald JM, Katelaris C, Tohda Y, Zhang B, Staudinger H, Pirozzi G, Amin N, Ruddy M, Akinlade B, Khan A, Chao J, Martincova R, Graham NMH, Hamilton JD, Swanson BN, Stahl N, Yancopoulos GD, Teper A. 2018. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med 378:2486–2496. https://doi.org/10.1056/NEJMoa1804092.
644. Busse WW, Maspero JF, Rabe KF, Papi A, Wenzel SE, Ford LB, Pavord ID, Zhang B, Staudinger H, Pirozzi G, Amin N, Akinlade B, Eckert L, Chao J, Graham NMH, Teper A. 2018. Liberty Asthma QUEST: phase 3 randomized, double-blind, placebo-controlled, parallel-group study to evaluate dupilumab efficacy/safety in patients with uncontrolled, moderate-to-severe asthma. Adv Ther 35:737–748. https://doi.org/10.1007/s12325-018-0702-4.
645. Wenzel S, Castro M, Corren J, Maspero J, Wang L, Zhang B, Pirozzi G, Sutherland ER, Evans RR, Joish VN, Eckert L, Graham NM, Stahl N, Yancopoulos GD, Louis-Tisserand M, Teper A. 2016. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting beta2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. Lancet 388:31–44. https://doi.org/10.1016/S0140-6736(16)30307-5.
646. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, Wang L, Kirkesseli S, Rocklin R, Bock B, Hamilton J, Ming JE, Radin A, Stahl N, Yancopoulos GD, Graham N, Pirozzi G. 2013. Dupilumab in persistent asthma with elevated eosinophil levels. N Engl J Med 368:2455–2466. https://doi.org/10.1056/NEJMoa1304048.
647. Drazen JM, Harrington D. 2018. New biologics for asthma. N Engl J Med 378:2533–2534. https://doi.org/10.1056/NEJMe1806037.
648. Weinstein SF, Katial R, Jayawardena S, Pirozzi G, Staudinger H, Eckert L, Joish VN, Amin N, Maroni J, Rowe P, Graham NMH, Teper A. 2018. Efficacy and safety of dupilumab in perennial allergic rhinitis and comorbid asthma. J Allergy Clin Immunol 142:171–177.e1. https://doi.org/10.1016/j.jaci.2017.11.051.
649. Bachert C, Mannent L, Naclerio RM, Mullol J, Ferguson BJ, Gevaert P, Hellings P, Jiao L, Wang L, Evans RR, Pirozzi G, Graham NM, Swanson B, Hamilton JD, Radin A, Gandhi NA, Stahl N, Yancopoulos GD, Sutherland ER. 2016. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. JAMA 315:469–479. https://doi.org/10.1001/jama.2015.19330.
650. Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE, Mullol J, Greos LS, Bosso JV, Laidlaw TM, Cervin AU, Maspero JF, Hopkins C, Olze H, Canonica GW, Paggiaro P, Cho SH, Fokkens WJ, Fujieda S, Zhang M, Lu X, Fan C, Draikiwicz S, Kamat SA, Khan A, Pirozzi G, Patel N, Graham NMH, Ruddy M, Staudinger H, Weinreich D, Stahl N, Yancopoulos GD, Mannent LP. 2019. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. Lancet 394:1638–1650. https://doi.org/10.1016/S0140-6736(19)31881-1. [Erratum, 394:1618, 2019, https://doi.org/10.1016/S0140-6736(19)32218-4.]
651. Reference deleted.
652. Hirano I, Dellon ES, Hamilton JD, Collins MH, Peterson K, Chehade M, Schoepfer AM, Safroneeva E, Rothenberg ME, Falk GW, Assouline-Dayan Y, Zhao Q, Chen Z, Swanson BN, Pirozzi G, Mannent L, Graham NMH, Akinlade B, Stahl N, Yancopoulos GD, Radin A. 2020. Efficacy of dupilumab in a phase 2 randomized trial of adults with active eosinophilic esophagitis. Gastroenterology 158:111–122.e10. https://doi.org/10.1053/j.gastro.2019.09.042.
653. Ou Z, Chen C, Chen A, Yang Y, Zhou W. 2018. Adverse events of dupilumab in adults with moderate-to-severe atopic dermatitis: a meta-analysis. Int Immunopharmacol 54:303–310. https://doi.org/10.1016/j.intimp.2017.11.031.
654. Fleming P, Drucker AM. 2018. Risk of infection in patients with atopic dermatitis treated with dupilumab: a meta-analysis of randomized controlled trials. J Am Acad Dermatol 78:62–69.e1. https://doi.org/10.1016/j.jaad.2017.09.052.
655. Barnes AC, Blandford AD, Perry JD. 2017. Cicatricial ectropion in a patient treated with dupilumab. Am J Ophthalmol Case Rep 7:120–122. https://doi.org/10.1016/j.ajoc.2017.06.017.
656. Wollenberg A, Ariens L, Thurau S, van Luijk C, Seegraber M, de Bruin-Weller M. 2018. Conjunctivitis occurring in atopic dermatitis patients treated with dupilumab—clinical characteristics and treatment. J Allergy Clin Immunol Pract 6:1778–1780.e1. https://doi.org/10.1016/j.jaip.2018.01.034.
657. Nussbaum JC, Van Dyken SJ, von Moltke J, Cheng LE, Mohapatra A, Molofsky AB, Thornton EE, Krummel MF, Chawla A, Liang HE, Locksley RM. 2013. Type 2 innate lymphoid cells control eosinophil homeostasis. Nature 502:245–248. https://doi.org/10.1038/nature12526.
658. Fallon PG, Ballantyne SJ, Mangan NE, Barlow JL, Dasvarma A, Hewett DR, McIlgorm A, Jolin HE, McKenzie AN. 2006. Identification of an interleukin (IL)-25-dependent cell population that provides IL-4, IL-5, and IL-13 at the onset of helminth expulsion. J Exp Med 203:1105–1116. https://doi.org/10.1084/jem.20051615.
659. Varricchi G, Canonica GW. 2016. The role of interleukin 5 in asthma. Expert Rev Clin Immunol 12:903–905. https://doi.org/10.1080/1744666X.2016.1208564.
660. Esnault S, Kelly EA. 2016. Essential mechanisms of differential

activation of eosinophils by IL-3 compared to GM-CSF and IL-5. Crit Rev Immunol 36:429–444. https://doi.org/10.1615/CritRevImmunol.2017020172.
661. Ochi H, De Jesus NH, Hsieh FH, Austen KF, Boyce JA. 2000. IL-4 and -5 prime human mast cells for different profiles of IgE-dependent cytokine production. Proc Natl Acad Sci U S A 97:10509–10513. https://doi.org/10.1073/pnas.180318697.
662. DeKruyff RH, Yu S, Kim HY, Umetsu DT. 2014. Innate immunity in the lung regulates the development of asthma. Immunol Rev 260:235–248. https://doi.org/10.1111/imr.12187.
663. Varricchi G, Bagnasco D, Borriello F, Heffler E, Canonica GW. 2016. Interleukin-5 pathway inhibition in the treatment of eosinophilic respiratory disorders: evidence and unmet needs. Curr Opin Allergy Clin Immunol 16:186–200. https://doi.org/10.1097/ACI.0000000000000251.
664. Esnault S, Kelly EA, Shen ZJ, Johansson MW, Malter JS, Jarjour NN. 2015. IL-3 maintains activation of the p90S6K/RPS6 pathway and increases translation in human eosinophils. J Immunol 195:2529–2539. https://doi.org/10.4049/jimmunol.1500871.
665. Gregory B, Kirchem A, Phipps S, Gevaert P, Pridgeon C, Rankin SM, Robinson DS. 2003. Differential regulation of human eosinophil IL-3, IL-5, and GM-CSF receptor alpha-chain expression by cytokines: IL-3, IL-5, and GM-CSF down-regulate IL-5 receptor alpha expression with loss of IL-5 responsiveness, but up-regulate IL-3 receptor alpha expression. J Immunol 170:5359–5366. https://doi.org/10.4049/jimmunol.170.11.5359.
666. Weissler JC. 2017. Eosinophilic lung disease. Am J Med Sci 354:339–349. https://doi.org/10.1016/j.amjms.2017.03.020.
667. Weller PF, Spencer LA. 2017. Functions of tissue-resident eosinophils. Nat Rev Immunol 17:746–760. https://doi.org/10.1038/nri.2017.95.
668. Simpson JL, Scott R, Boyle MJ, Gibson PG. 2006. Inflammatory subtypes in asthma: assessment and identification using induced sputum. Respirology 11:54–61. https://doi.org/10.1111/j.1440-1843.2006.00784.x.
669. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, Wardlaw AJ, Green RH. 2008. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med 178:218–224. https://doi.org/10.1164/rccm.200711-1754OC.
670. Pavord ID, Chanez P, Criner GJ, Kerstjens HAM, Korn S, Lugogo N, Martinot JB, Sagara H, Albers FC, Bradford ES, Harris SS, Mayer B, Rubin DB, Yancey SW, Sciurba FC. 2017. Mepolizumab for eosinophilic chronic obstructive pulmonary disease. N Engl J Med 377:1613–1629. https://doi.org/10.1056/NEJMoa1708208.
671. Wechsler ME, Akuthota P, Jayne D, Khoury P, Klion A, Langford CA, Merkel PA, Moosig F, Specks U, Cid MC, Luqmani R, Brown J, Mallett S, Philipson R, Yancey SW, Steinfeld J, Weller PF, Gleich GJ. 2017. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. N Engl J Med 376:1921–1932. https://doi.org/10.1056/NEJMoa1702079.
672. Greco A, Rizzo MI, De Virgilio A, Gallo A, Fusconi M, Ruoppolo G, Altissimi G, De Vincentiis M. 2015. Churg-Strauss syndrome. Autoimmun Rev 14:341–348. https://doi.org/10.1016/j.autrev.2014.12.004.
673. Rothenberg ME, Klion AD, Roufosse FE, Kahn JE, Weller PF, Simon HU, Schwartz LB, Rosenwasser LJ, Ring J, Griffin EF, Haig AE, Frewer PI, Parkin JM, Gleich GJ. 2008. Treatment of patients with the hypereosinophilic syndrome with mepolizumab. N Engl J Med 358:1215–1228. https://doi.org/10.1056/NEJMoa070812.
674. Galli SJ, Tsai M. 2012. IgE and mast cells in allergic disease. Nat Med 18:693–704. https://doi.org/10.1038/nm.2755.
675. Navinés-Ferrer A, Serrano-Candelas E, Molina-Molina G-J, Martín M. 2016. IgE-related chronic diseases and anti-IgE-based treatments. J Immunol Res 2016:1–12. https://doi.org/10.1155/2016/8163803.
676. Gould HJ, Sutton BJ. 2008. IgE in allergy and asthma today. Nat Rev Immunol 8:205–217. https://doi.org/10.1038/nri2273.
677. Takizawa F, Adamczewski M, Kinet JP. 1992. Identification of the low affinity receptor for immunoglobulin E on mouse mast cells and macrophages as Fc gamma RII and Fc gamma RIII. J Exp Med 176:469–475. https://doi.org/10.1084/jem.176.2.469.
678. Li H, Nowak-Wegrzyn A, Charlop-Powers Z, Shreffler W, Chehade M, Thomas S, Roda G, Dahan S, Sperber K, Berin MC. 2006. Transcytosis of IgE-antigen complexes by CD23a in human intestinal epithelial cells and its role in food allergy. Gastroenterology 131:47–58. https://doi.org/10.1053/j.gastro.2006.03.044.
679. Thomson NC, Chaudhuri R. 2012. Omalizumab: clinical use for the management of asthma. Clin Med Insights Circ Respir Pulm Med 6:27–40. https://doi.org/10.4137/CCRPM.S7793.
680. Kawakami T, Blank U. 2016. From IgE to Omalizumab. J Immunol 197:4187–4192. https://doi.org/10.4049/jimmunol.1601476.
681. Dunican EM, Fahy JV. 2015. The role of type 2 inflammation in the pathogenesis of asthma exacerbations. Ann Am Thorac Soc 12(Suppl 2):S144–S149.
682. Asero R, Tedeschi A, Marzano AV, Cugno M. 2017. Chronic urticaria: a focus on pathogenesis. F1000Res 6:1095. https://doi.org/10.12688/f1000research.11546.1.
683. Yanase Y, Takahagi S, Hide M. 2018. Chronic spontaneous urticaria and the extrinsic coagulation system. Allergol Int 67:191–194. https://doi.org/10.1016/j.alit.2017.09.003.
684. Kolkhir P, Church MK, Weller K, Metz M, Schmetzer O, Maurer M. 2017. Autoimmune chronic spontaneous urticaria: what we know and what we do not know. J Allergy Clin Immunol 139:1772–1781.e1. https://doi.org/10.1016/j.jaci.2016.08.050.
685. Fahy JV, Fleming HE, Wong HH, Liu JT, Su JQ, Reimann J, Fick RB, Jr, Boushey HA. 1997. The effect of an anti-IgE monoclonal antibody on the early- and late-phase responses to allergen inhalation in asthmatic subjects. Am J Respir Crit Care Med 155:1828–1834. https://doi.org/10.1164/ajrccm.155.6.9196082.
686. Wu Y, Li JJ, Kim HJ, Liu X, Liu W, Akhgar A, Bowen MA, Spitz S, Jiang XR, Roskos LK, White WI. 2015. A neutralizing antibody assay based on a reporter of antibody-dependent cell-mediated cytotoxicity. AAPS J 17:1417–1426. https://doi.org/10.1208/s12248-015-9798-5.
687. Flood-Page PT, Menzies-Gow AN, Kay AB, Robinson DS. 2003. Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes numbers in asthmatic airway. Am J Respir Crit Care Med 167:199–204. https://doi.org/10.1164/rccm.200208-789OC.
688. Farne HA, Wilson A, Powell C, Bax L, Milan SJ. 2017. Anti-IL5 therapies for asthma. Cochrane Database Syst Rev 9:CD010834. https://doi.org/10.1002/14651858.CD010834.pub3.
689. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, Marshall RP, Bradding P, Green RH, Wardlaw AJ, Pavord ID. 2009. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med 360:973–984. https://doi.org/10.1056/NEJMoa0808991.
690. Nair P, Pizzichini MM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, Hargreave FE, O'Byrne PM. 2009. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. N Engl J Med 360:985–993. https://doi.org/10.1056/NEJMoa0805435.
691. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, Ortega H, Chanez P. 2012. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet 380:651–659. https://doi.org/10.1016/S0140-6736(12)60988-X.
692. Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, Sproule S, Gilmartin G, Aurivillius M, Werkstrom V, Goldman M. 2016. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet 388:2115–2127. https://doi.org/10.1016/S0140-6736(16)31324-1.
693. Brightling CE, Bleecker ER, Panettieri RA, Jr, Bafadhel M, She D, Ward CK, Xu X, Birrell C, van der Merwe R. 2014. Benralizumab for chronic obstructive pulmonary disease and sputum eosinophilia: a randomised, double-blind, placebo-controlled, phase 2a study. Lancet Respir Med 2:891–901. https://doi.org/10.1016/S2213-2600(14)70187-0.
694. Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M. 2016. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomized phase 3 study. Chest 150:789–798. https://doi.org/10.1016/j.chest.2016.03.032.
695. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, Murphy K, Maspero JF, O'Brien C, Korn S. 2015. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med 3:355–366. https://doi.org/10.1016/S2213-2600(15)00042-9.
696. Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, Wilkins HJ, Henkel T, Nair P. 2011. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. Am J Respir Crit Care Med 184:1125–1132. https://doi.org/10.1164/rccm.201103-0396OC.
697. Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. 2016. Phase 3 study of reslizumab in patients with poorly controlled asthma: effects across

a broad range of eosinophil counts. Chest 150:799–810. https://doi.org/10.1016/j.chest.2016.03.018.
698. Castro M, Wenzel SE, Bleecker ER, Pizzichini E, Kuna P, Busse WW, Gossage DL, Ward CK, Wu Y, Wang B, Khatry DB, van der Merwe R, Kolbeck R, Molfino NA, Raible DG. 2014. Benralizumab, an anti-interleukin 5 receptor alpha monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. Lancet Respir Med 2:879–890. https://doi.org/10.1016/S2213-2600(14)70201-2.
699. Nowak RM, Parker JM, Silverman RA, Rowe BH, Smithline H, Khan F, Fiening JP, Kim K, Molfino NA. 2015. A randomized trial of benralizumab, an antiinterleukin 5 receptor alpha monoclonal antibody, after acute asthma. Am J Emerg Med 33:14–20. https://doi.org/10.1016/j.ajem.2014.09.036.
700. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, Ferguson GT, Busse WW, Barker P, Sproule S, Gilmartin G, Werkstrom V, Aurivillius M, Goldman M. 2016. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 388:2128–2141. https://doi.org/10.1016/S0140-6736(16)31322-8.
701. Ferguson GT, FitzGerald JM, Bleecker ER, Laviolette M, Bernstein D, LaForce C, Mansfield L, Barker P, Wu Y, Jison M, Goldman M, Chouinard G, FitzGerald JM, Rostami M, Oosthuizen J, Pek B, Patel D, Houle P-A, Laviolette M, Khattak S, Killorn P, Keller C, Schenkenberger I, Zielen S, Ballenberger S, Hoffmann M, Kirschner J, Papp M, Kecskés T, Póczi M, Molnár L, Radeczky É, Schlezák J, Springer E, Balicka V, Kaczmarek J, Madra-Rogacka D, Pisarczyk-Bogacka E, Zurowska-Gebala M, Marczak M, Napora P, Pomiecko W, Pribulova E, Kurthova S, Drugdova M, Kavkova D, Frajtova L, Golubov A, Paulinyova D, Hasicova D, et al. 2017. Benralizumab for patients with mild to moderate, persistent asthma (BISE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med 5:568–576. https://doi.org/10.1016/S2213-2600(17)30190-X.
702. Cabon Y, Molinari N, Marin G, Vachier I, Gamez AS, Chanez P, Bourdin A. 2017. Comparison of anti-interleukin-5 therapies in patients with severe asthma: global and indirect meta-analyses of randomized placebo-controlled trials. Clin Exp Allergy 47:129–138. https://doi.org/10.1111/cea.12853.
703. Cheung CC, Constantine M, Ahmadi A, Shiau C, Chen L. 2017. Eosinophilic myocarditis. Am J Med Sci 354:486–492. https://doi.org/10.1016/j.amjms.2017.04.002.
704. Gevaert P, Lang-Loidolt D, Lackner A, Stammberger H, Staudinger H, Van Zele T, Holtappels G, Tavernier J, van Cauwenberge P, Bachert C. 2006. Nasal IL-5 levels determine the response to anti-IL-5 treatment in patients with nasal polyps. J Allergy Clin Immunol 118:1133–1141. https://doi.org/10.1016/j.jaci.2006.05.031.
705. Altman MC, Lenington J, Bronson S, Ayars AG. 2017. Combination omalizumab and mepolizumab therapy for refractory allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol Pract 5:1137–1139. https://doi.org/10.1016/j.jaip.2017.01.013.
706. Bachert C, Sousa AR, Lund VJ, Scadding GK, Gevaert P, Nasser S, Durham SR, Cornet ME, Kariyawasam HH, Gilbert J, Austin D, Maxwell AC, Marshall RP, Fokkens WJ. 2017. Reduced need for surgery in severe nasal polyposis with mepolizumab: randomized trial. J Allergy Clin Immunol 140:1024–1031.e14. https://doi.org/10.1016/j.jaci.2017.05.044.
707. Ray A, Raundhal M, Oriss TB, Ray P, Wenzel SE. 2016. Current concepts of severe asthma. J Clin Invest 126:2394–2403. https://doi.org/10.1172/JCI84144.
708. Boulet LP, Chapman KR, Cote J, Kalra S, Bhagat R, Swystun VA, Laviolette M, Cleland LD, Deschesnes F, Su JQ, DeVault A, Fick RB, Jr, Cockcroft DW. 1997. Inhibitory effects of an anti-IgE antibody E25 on allergen-induced early asthmatic response. Am J Respir Crit Care Med 155:1835–1840. https://doi.org/10.1164/ajrccm.155.6.9196083.
709. Bousquet J, Wenzel S, Holgate S, Lumry W, Freeman P, Fox H. 2004. Predicting response to omalizumab, an anti-IgE antibody, in patients with allergic asthma. Chest 125:1378–1386. https://doi.org/10.1378/chest.125.4.1378.
710. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, van As A, Gupta N. 2001. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J Allergy Clin Immunol 108:184–190. https://doi.org/10.1067/mai.2001.117880.
711. Hanania NA, Alpan O, Hamilos DL, Condemi JJ, Reyes-Rivera I, Zhu J, Rosen KE, Eisner MD, Wong DA, Busse W. 2011. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. Ann Intern Med 154:573–582. https://doi.org/10.7326/0003-4819-154-9-201105030-00002.
712. Holgate ST, Chuchalin AG, Hebert J, Lotvall J, Persson GB, Chung KF, Bousquet J, Kerstjens HA, Fox H, Thirlwell J, Cioppa GD, Omalizumab 011 International Study Group. 2004. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. Clin Exp Allergy 34:632–638. https://doi.org/10.1111/j.1365-2222.2004.1916.x.
713. Pillai P, Chan YC, Wu SY, Ohm-Laursen L, Thomas C, Durham SR, Menzies-Gow A, Rajakulasingam RK, Ying S, Gould HJ, Corrigan CJ. 2016. Omalizumab reduces bronchial mucosal IgE and improves lung function in non-atopic asthma. Eur Respir J 48:1593–1601. https://doi.org/10.1183/13993003.01501-2015.
714. Shimoda T, Odajima H, Okamasa A, Kawase M, Komatsubara M, Mayer B, Yancey S, Ortega H. 2017. Efficacy and safety of mepolizumab in Japanese patients with severe eosinophilic asthma. Allergol Int 66:445–451. https://doi.org/10.1016/j.alit.2016.11.006.
715. Gleich GJ, Klion AD, Lee JJ, Weller PF. 2013. The consequences of not having eosinophils. Allergy 68:829–835. https://doi.org/10.1111/all.12169.
716. Kung TT, Stelts DM, Zurcher JA, Adams GK, Egan RW, Kreutner W, Watnick AS, Jones H, Chapman RW. 1995. Involvement of IL-5 in a murine model of allergic pulmonary inflammation: prophylactic and therapeutic effect of an anti-IL-5 antibody. Am J Respir Cell Mol Biol 13:360–365. https://doi.org/10.1165/ajrcmb.13.3.7654390.
717. Mauser PJ, Pitman AM, Fernandez X, Foran SK, Adams GK, Kreutner W, Egan RW, Chapman RW. 1995. Effects of an antibody to interleukin-5 in a monkey model of asthma. Am J Respir Crit Care Med 152:467–472. https://doi.org/10.1164/ajrccm.152.2.7633694.
718. Hart TK, Cook RM, Zia-Amirhosseini P, Minthorn E, Sellers TS, Maleeff BE, Eustis S, Schwartz LW, Tsui P, Appelbaum ER, Martin EC, Bugelski PJ, Herzyk DJ. 2001. Preclinical efficacy and safety of mepolizumab (SB-240563), a humanized monoclonal antibody to IL-5, in cynomolgus monkeys. J Allergy Clin Immunol 108:250–257. https://doi.org/10.1067/mai.2001.116576.
719. Kelly EA, Esnault S, Liu LY, Evans MD, Johansson MW, Mathur S, Mosher DF, Denlinger LC, Jarjour NN. 2017. Mepolizumab attenuates airway eosinophil numbers, but not their functional phenotype, in asthma. Am J Respir Crit Care Med 196:1385–1395. https://doi.org/10.1164/rccm.201611-2234OC.
720. Swartz JM, Dyer KD, Cheever AW, Ramalingam T, Pesnicak L, Domachowske JB, Lee JJ, Lee NA, Foster PS, Wynn TA, Rosenberg HF. 2006. Schistosoma mansoni infection in eosinophil lineage-ablated mice. Blood 108:2420–2427. https://doi.org/10.1182/blood-2006-04-015933.
721. O'Connell AE, Hess JA, Santiago GA, Nolan TJ, Lok JB, Lee JJ, Abraham D. 2011. Major basic protein from eosinophils and myeloperoxidase from neutrophils are required for protective immunity to Strongyloides stercoralis in mice. Infect Immun 79:2770–2778. https://doi.org/10.1128/IAI.00931-10.
722. Fabre V, Beiting DP, Bliss SK, Gebreselassie NG, Gagliardo LF, Lee NA, Lee JJ, Appleton JA. 2009. Eosinophil deficiency compromises parasite survival in chronic nematode infection. J Immunol 182:1577–1583. https://doi.org/10.4049/jimmunol.182.3.1577.
723. Roufosse FE, Kahn JE, Gleich GJ, Schwartz LB, Singh AD, Rosenwasser LJ, Denburg JA, Ring J, Rothenberg ME, Sheikh J, Haig AE, Mallett SA, Templeton DN, Ortega HG, Klion AD. 2013. Long-term safety of mepolizumab for the treatment of hypereosinophilic syndromes. J Allergy Clin Immunol 131:461–467.e1-5. https://doi.org/10.1016/j.jaci.2012.07.055.
724. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, Humbert M, Katz LE, Keene ON, Yancey SW, Chanez P. 2014. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med 371:1198–1207. https://doi.org/10.1056/NEJMoa1403290.
725. Lugogo N, Domingo C, Chanez P, Leigh R, Gilson MJ, Price RG, Yancey SW, Ortega HG. 2016. Long-term efficacy and safety of mepolizumab in patients with severe eosinophilic asthma: a multi-center, open-label, phase IIIb study. Clin Ther 38:2058–2070.e1. https://doi.org/10.1016/j.clinthera.2016.07.010.
726. Normansell R, Walker S, Milan SJ, Walters EH, Nair P. 2014. Omali-

zumab for asthma in adults and children. Cochrane Database Syst Rev 2014:CD003559. https://doi.org/10.1002/14651858.CD003559.
727. Arshad S, K Holgate ST. 2001. Anti-IgE therapy in asthma and allergy. Taylor and Francis, London, United Kingdom.
728. Skiepko R, Zietkowski Z, Skiepko U, Tomasiak-Lozowska MM, Bodzenta-Lukaszyk A. 2013. Echinococcus multilocularis infection in a patient treated with omalizumab. J Invest Allergol Clin Immunol 23:199–200.
729. Cruz AA, Lima F, Sarinho E, Ayre G, Martin C, Fox H, Cooper PJ. 2007. Safety of anti-immunoglobulin E therapy with omalizumab in allergic patients at risk of geohelminth infection. Clin Exp Allergy 37:197–207. https://doi.org/10.1111/j.1365-2222.2007.02650.x.
730. Cooper PJ, Ayre G, Martin C, Rizzo JA, Ponte EV, Cruz AA. 2008. Geohelminth infections: a review of the role of IgE and assessment of potential risks of anti-IgE treatment. Allergy 63:409–417. https://doi.org/10.1111/j.1398-9995.2007.01601.x.
731. Perisson C, Destruys L, Grenet D, Bassinet L, Derelle J, Sermet-Gaudelus I, Thumerelle C, Prevotat A, Rosner V, Clement A, Corvol H. 2017. Omalizumab treatment for allergic bronchopulmonary aspergillosis in young patients with cystic fibrosis. Respir Med 133:12–15. https://doi.org/10.1016/j.rmed.2017.11.007.
732. Janahi IA, Rehman A, Al-Naimi AR. 2017. Allergic bronchopulmonary aspergillosis in patients with cystic fibrosis. Ann Thorac Med 12:74–82. https://doi.org/10.4103/atm.ATM_231_16.
733. Li JX, Fan LC, Li MH, Cao WJ, Xu JF. 2017. Beneficial effects of Omalizumab therapy in allergic bronchopulmonary aspergillosis: a synthesis review of published literature. Respir Med 122:33–42. https://doi.org/10.1016/j.rmed.2016.11.019.
734. Beam KT, Coop CA. 2015. Steroid sparing effect of omalizumab in seropositive allergic bronchopulmonary aspergillosis. Allergy Rhinol (Providence) 6:143–145. https://doi.org/10.2500/ar.2015.6.0128.
735. Rets A, Gupta R, Haseeb MA. 2013. Determinants of reactivation of inapparent Strongyloides stercoralis infection in patients hospitalized for unrelated admitting diagnosis. Eur J Gastroenterol Hepatol 25:1279–1285. https://doi.org/10.1097/MEG.0b013e328364b578.
736. Keiser PB, Nutman TB. 2004. Strongyloides stercoralis in the immunocompromised population. Clin Microbiol Rev 17:208–217. https://doi.org/10.1128/CMR.17.1.208-217.2004.
737. Chordia P, Christopher S, Abraham OC, Muliyil J, Kang G, Ajjampur S. 2011. Risk factors for acquiring Strongyloides stercoralis infection among patients attending a tertiary hospital in south India. Indian J Med Microbiol 29:147–151. https://doi.org/10.4103/0255-0857.81797.
738. Buhl R, Soler M, Matz J, Townley R, O'Brien J, Noga O, Champain K, Fox H, Thirlwell J, Della Cioppa G. 2002. Omalizumab provides long-term control in patients with moderate-to-severe allergic asthma. Eur Respir J 20:73–78. https://doi.org/10.1183/09031936.02.00278102.
739. Lanier BQ, Corren J, Lumry W, Liu J, Fowler-Taylor A, Gupta N. 2003. Omalizumab is effective in the long-term control of severe allergic asthma. Ann Allergy Asthma Immunol 91:154–159. https://doi.org/10.1016/S1081-1206(10)62170-9.
740. Ayres JG, Higgins B, Chilvers ER, Ayre G, Blogg M, Fox H. 2004. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma. Allergy 59:701–708. https://doi.org/10.1111/j.1398-9995.2004.00533.x.
741. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, Gruchalla RS, Kattan M, Teach SJ, Pongracic JA, Chmiel JF, Steinbach SF, Calatroni A, Togias A, Thompson KM, Szefler SJ, Sorkness CA. 2011. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. N Engl J Med 364:1005–1015. https://doi.org/10.1056/NEJMoa1009705.
742. Casale TB, Condemi J, LaForce C, Nayak A, Rowe M, Watrous M, McAlary M, Fowler-Taylor A, Racine A, Gupta N, Fick R, Della Cioppa G. 2001. Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. JAMA 286:2956–2967. https://doi.org/10.1001/jama.286.23.2956.
743. Kuehr J, Brauburger J, Zielen S, Schauer U, Kamin W, Von Berg A, Leupold W, Bergmann K-C, Rolinck-Werninghaus C, Gräve M, Hultsch T, Wahn U. 2002. Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. J Allergy Clin Immunol 109:274–280. https://doi.org/10.1067/mai.2002.121949.
744. Lotz M. 1995. Interleukin-6: a comprehensive review. Cancer Treat Res 80:209–233. https://doi.org/10.1007/978-1-4613-1241-3_8.
745. Heinrich PC, Castell JV, Andus T. 1990. Interleukin-6 and the acute phase response. Biochem J 265:621–636. https://doi.org/10.1042/bj2650621.
746. Liu X, Teichtahl AJ, Wicks IP. 2015. Interleukin-6 in rheumatoid arthritis—from the laboratory to the bedside. Curr Pharm Des 21:2187–2197. https://doi.org/10.2174/1381612821666150310143332.
747. Nishimoto N. 2006. Interleukin-6 in rheumatoid arthritis. Curr Opin Rheumatol 18:277–281. https://doi.org/10.1097/01.bor.0000218949.19860.d1.
748. Hack CE, De Groot ER, Felt-Bersma RJ, Nuijens JH, Strack Van Schijndel RJ, Eerenberg-Belmer AJ, Thijs LG, Aarden LA. 1989. Increased plasma levels of interleukin-6 in sepsis. Blood 74:1704–1710. https://doi.org/10.1182/blood.V74.5.1704.1704.
749. Remick DG, Bolgos G, Copeland S, Siddiqui J. 2005. Role of interleukin-6 in mortality from and physiologic response to sepsis. Infect Immun 73:2751–2757. https://doi.org/10.1128/IAI.73.5.2751-2757.2005.
750. Hanberg JS, Rao VS, Ahmad T, Chunara Z, Mahoney D, Jackson K, Jacoby D, Chen M, Wilson FP, Tang WHW, Kakkar R, Testani JM. 2018. Inflammation and cardio-renal interactions in heart failure: a potential role for interleukin-6. Eur J Heart Fail 20:933–934. https://doi.org/10.1002/ejhf.963.
751. Raj DS. 2009. Role of interleukin-6 in the anemia of chronic disease. Semin Arthritis Rheum 38:382–388. https://doi.org/10.1016/j.semarthrit.2008.01.006.
752. Whiteley W, Jackson C, Lewis S, Lowe G, Rumley A, Sandercock P, Wardlaw J, Dennis M, Sudlow C. 2009. Inflammatory markers and poor outcome after stroke: a prospective cohort study and systematic review of interleukin-6. PLoS Med 6:e1000145. https://doi.org/10.1371/journal.pmed.1000145.
753. Wollert KC, Drexler H. 2001. The role of interleukin-6 in the failing heart. Heart Fail Rev 6:95–103. https://doi.org/10.1023/a:1011401825680.
754. Zhang B, Li XL, Zhao CR, Pan CL, Zhang Z. 2018. Interleukin-6 as a predictor of the risk of cardiovascular disease: a meta-analysis of prospective epidemiological studies. Immunol Invest 47:689–699. https://doi.org/10.1080/08820139.2018.1480034.
755. Marti Arjona L, Moreno Camacho A. 2017. Prognostic value of interleukin-6 for death in patients with sepsis. Med Clin (Barc) 149:507. https://doi.org/10.1016/j.medcle.2017.10.022.
756. Lippitz BE, Harris RA. 2016. Cytokine patterns in cancer patients: a review of the correlation between interleukin 6 and prognosis. Oncoimmunology 5:e1093722. https://doi.org/10.1080/2162402X.2015.1093722.
757. Cainzos-Achirica M, Enjuanes C, Greenland P, McEvoy JW, Cushman M, Dardari Z, Nasir K, Budoff MJ, Al-Mallah MH, Yeboah J, Miedema MD, Blumenthal RS, Comin-Colet J, Blaha MJ. 2018. The prognostic value of interleukin 6 in multiple chronic diseases and all-cause death: the Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis 278:217–225. https://doi.org/10.1016/j.atherosclerosis.2018.09.034.
758. Zhang W, He J, Zhang F, Huang C, Wu Y, Han Y, Zhang W, Zhao Y. 2013. Prognostic role of C-reactive protein and interleukin-6 in dialysis patients: a systematic review and meta-analysis. J Nephrol 26:243–253. https://doi.org/10.5301/jn.5000169.
759. Cai B, Cai J-P, Luo Y-l, Chen C, Zhang S. 2015. The specific roles of JAK/STAT signaling pathway in sepsis. Inflammation 38:1599–1608. https://doi.org/10.1007/s10753-015-0135-z.
760. McLornan DP, Khan AA, Harrison CN. 2015. Immunological consequences of JAK inhibition: friend or foe? Curr Hematol Malig Rep 10:370–379. https://doi.org/10.1007/s11899-015-0284-z.
761. Scheller J, Rose-John S. 2006. Interleukin-6 and its receptor: from bench to bedside. Med Microbiol Immunol 195:173–183. https://doi.org/10.1007/s00430-006-0019-9.
762. Nakagiri T, Inoue M, Minami M, Shintani Y, Okumura M. 2012. Immunology mini-review: the basics of T(H)17 and interleukin-6 in transplantation. Transplant Proc 44:1035–1040. https://doi.org/10.1016/j.transproceed.2011.12.032.
763. Scott LJ. 2017. Tocilizumab: a review in rheumatoid arthritis. Drugs 77:1865–1879. https://doi.org/10.1007/s40265-017-0829-7.
764. Genovese MC, McKay JD, Nasonov EL, Mysler EF, da Silva NA, Alecock E, Woodworth T, Gomez-Reino JJ. 2008. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum 58:2968–2980. https://doi.org/10.1002/art.23940.
765. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J,

Alecock E, Woodworth T, Alten R, OPTION Investigators. 2008. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet 371:987–997. https://doi.org/10.1016/S0140-6736(08)60453-5.
766. Singh JA, Beg S, Lopez-Olivo MA. 2011. Tocilizumab for rheumatoid arthritis: a Cochrane systematic review. J Rheumatol 38:10–20. https://doi.org/10.3899/jrheum.100717.
767. Lotan I, Charlson RW, Ryerson LZ, Levy M, Kister I. 2020. Effectiveness of subcutaneous tocilizumab in neuromyelitis optica spectrum disorders. Mult Scler Relat Disord 39:101920. https://doi.org/10.1016/j.msard.2019.101920.
768. Ito H, Takazoe M, Fukuda Y, Hibi T, Kusugami K, Andoh A, Matsumoto T, Yamamura T, Azuma J, Nishimoto N, Yoshizaki K, Shimoyama T, Kishimoto T. 2004. A pilot randomized trial of a human anti-interleukin-6 receptor monoclonal antibody in active Crohn's disease. Gastroenterology 126:989–996. https://doi.org/10.1053/j.gastro.2004.01.012.
769. Illei GG, Shirota Y, Yarboro CH, Daruwalla J, Tackey E, Takada K, Fleisher T, Balow JE, Lipsky PE. 2010. Tocilizumab in systemic lupus erythematosus: data on safety, preliminary efficacy, and impact on circulating plasma cells from an open-label phase I dosage-escalation study. Arthritis Rheum 62:542–552. https://doi.org/10.1002/art.27221.
770. Iwamoto M, Nara H, Hirata D, Minota S, Nishimoto N, Yoshizaki K. 2002. Humanized monoclonal anti-interleukin-6 receptor antibody for treatment of intractable adult-onset Still's disease. Arthritis Rheum 46:3388–3389. https://doi.org/10.1002/art.10620.
771. Brighton TA, Khot A, Harrison SJ, Ghez D, Weiss BM, Kirsch A, Magen H, Gironella M, Oriol A, Streetly M, Kranenburg B, Qin X, Bandekar R, Hu P, Guilfoyle M, Qi M, Nemat S, Goldschmidt H. 2019. Randomized, double-blind, placebo-controlled, multicenter study of siltuximab in high-risk smoldering multiple myeloma. Clin Cancer Res 25:3772–3775. https://doi.org/10.1158/1078-0432.CCR-18-3470.
772. Orlowski RZ, Gercheva L, Williams C, Sutherland H, Robak T, Masszi T, Goranova-Marinova V, Dimopoulos MA, Cavenagh JD, Spicka I, Maiolino A, Suvorov A, Blade J, Samoylova O, Puchalski TA, Reddy M, Bandekar R, van de Velde H, Xie H, Rossi JF. 2015. A phase 2, randomized, double-blind, placebo-controlled study of siltuximab (anti-IL-6 mAb) and bortezomib versus bortezomib alone in patients with relapsed or refractory multiple myeloma. Am J Hematol 90:42–49. https://doi.org/10.1002/ajh.23868.
773. Shah JJ, Feng L, Thomas SK, Berkova Z, Weber DM, Wang M, Qazilbash MH, Champlin RE, Mendoza TR, Cleeland C, Orlowski RZ. 2016. Siltuximab (CNTO 328) with lenalidomide, bortezomib and dexamethasone in newly-diagnosed, previously untreated multiple myeloma: an open-label phase I trial. Blood Cancer J 6:e396. https://doi.org/10.1038/bcj.2016.4.
774. Genovese MC, van Adelsberg J, Fan C, Graham NMH, van Hoogstraten H, Parrino J, Mangan EK, Spindler A, Huizinga TWJ, van der Heijde D, EXTEND Study Investigators. 2018. Two years of sarilumab in patients with rheumatoid arthritis and an inadequate response to MTX: safety, efficacy and radiographic outcomes. Rheumatology (Oxford) 57:1423–1431. https://doi.org/10.1093/rheumatology/key121.
775. McCarty D, Robinson A. 2018. Efficacy and safety of sarilumab in patients with active rheumatoid arthritis. Ther Adv Musculoskelet Dis 10:61–67. https://doi.org/10.1177/1759720X17752037.
776. Sarosiek S, Shah R, Munshi NC. 2016. Review of siltuximab in the treatment of multicentric Castleman's disease. Ther Adv Hematol 7:360–366. https://doi.org/10.1177/2040620716653745.
777. Campbell L, Chen C, Bhagat SS, Parker RA, Ostor AJ. 2011. Risk of adverse events including serious infections in rheumatoid arthritis patients treated with tocilizumab: a systematic literature review and meta-analysis of randomized controlled trials. Rheumatology (Oxford) 50:552–562. https://doi.org/10.1093/rheumatology/keq343.
778. Genovese MC, Rubbert-Roth A, Smolen JS, Kremer J, Khraishi M, Gomez-Reino J, Sebba A, Pilson R, Williams S, Van Vollenhoven R. 2013. Longterm safety and efficacy of tocilizumab in patients with rheumatoid arthritis: a cumulative analysis of up to 4.6 years of exposure. J Rheumatol 40:768–780. https://doi.org/10.3899/jrheum.120687.
779. Pawar A, Desai RJ, Solomon DH, Santiago Ortiz AJ, Gale S, Bao M, Sarsour K, Schneeweiss S, Kim SC. 2019. Risk of serious infections in tocilizumab versus other biologic drugs in patients with rheumatoid arthritis: a multidatabase cohort study. Ann Rheum Dis 78:456–464. https://doi.org/10.1136/annrheumdis-2018-214367.
780. Nagashima T, Minota S. 2010. Tocilizumab for rheumatoid arthritis with chronic hepatitis B virus infection without antiviral therapy. J Rheumatol 37:1066. https://doi.org/10.3899/jrheum.091220. (Reply, 37:1067. https://doi.org/10.3899/jrheum.091394.)
781. Nagashima T, Maruyama A, Kamata Y, Minota S. 2012. Unchanged serum viral load and liver function during tocilizumab treatment in a patient with rheumatoid arthritis and hepatitis C virus infection. Rheumatol Int 32:2231–2232. https://doi.org/10.1007/s00296-011-2060-2.
782. Ahn SS, Jung SM, Song JJ, Park YB, Park JY, Lee SW. 2018. Safety of tocilizumab in rheumatoid arthritis patients with resolved hepatitis B virus infection: data from real-world experience. Yonsei Med J 59:452–456. https://doi.org/10.3349/ymj.2018.59.3.452.
783. Koike T, Harigai M, Inokuma S, Ishiguro N, Ryu J, Takeuchi T, Takei S, Tanaka Y, Sano Y, Yaguramaki H, Yamanaka H. 2014. Effectiveness and safety of tocilizumab: postmarketing surveillance of 7901 patients with rheumatoid arthritis in Japan. J Rheumatol 41:15–23. https://doi.org/10.3899/jrheum.130466.
784. Ogata A, Mori M, Hashimoto S, Yano Y, Fujikawa T, Kawai M, Kuwahara Y, Hirano T, Arimitsu J, Hagihara K, Shima Y, Narazaki M, Yokota S, Kishimoto T, Kawase I, Tanaka T. 2010. Minimal influence of tocilizumab on IFN-gamma synthesis by tuberculosis antigens. Mod Rheumatol 20:130–133. https://doi.org/10.3109/s10165-009-0243-4.
785. Roux C, Breuil V, Albert C, Allam V, Grisot C, Chami H, Dasilva V, Euller-Ziegler L. 2011. Ophthalmic herpes zoster infection in patients with rheumatoid arthritis who were treated with tocilizumab. J Rheumatol 38:399–399. https://doi.org/10.3899/jrheum.100737.
786. Mimata Y, Akasaka T, Nakano R, Murata T, Kawashima M, Shimamura T. 2013. Ramsay Hunt syndrome associated with tocilizumab therapy in rheumatoid arthritis: a case report. Int J Rheum Dis 16:367–368. https://doi.org/10.1111/1756-185X.12081.
787. Mourgues C, Henquell C, Tatar Z, Pereira B, Nourisson C, Tournadre A, Soubrier M, Couderc M. 2016. Monitoring of Epstein-Barr virus (EBV)/cytomegalovirus (CMV)/varicella-zoster virus (VZV) load in patients receiving tocilizumab for rheumatoid arthritis. Joint Bone Spine 83:412–415. https://doi.org/10.1016/j.jbspin.2015.07.009.
788. Gaffen SL, Jain R, Garg AV, Cua DJ. 2014. The IL-23-IL-17 immune axis: from mechanisms to therapeutic testing. Nat Rev Immunol 14:585–600. https://doi.org/10.1038/nri3707.
789. Teng MW, Bowman EP, McElwee JJ, Smyth MJ, Casanova JL, Cooper AM, Cua DJ. 2015. IL-12 and IL-23 cytokines: from discovery to targeted therapies for immune-mediated inflammatory diseases. Nat Med 21:719–729. https://doi.org/10.1038/nm.3895.
790. Ma C, Jairath V, Khanna R, Feagan BG. 10 August 2018. Investigational drugs in phase I and phase II clinical trials targeting interleukin 23 (IL23) for the treatment of Crohn's disease. Expert Opin Invest Drugs https://doi.org/10.1080/13543784.2018.1506764.
791. Wechter T, Cline A, Feldman SR. 2018. Targeting p19 as a treatment option for psoriasis: an evidence-based review of guselkumab. Ther Clin Risk Manag 14:1489–1497. https://doi.org/10.2147/TCRM.S177127.
792. van Mens LJJ, van de Sande MGH, Baeten D. 2018. New treatment paradigms in spondyloarthritis. Curr Opin Rheumatol 30:79–86. https://doi.org/10.1097/BOR.0000000000000457.
793. Maarouf M, Clark AK, Lee DE, Shi VY. 2018. Targeted treatments for hidradenitis suppurativa: a review of the current literature and ongoing clinical trials. J Dermatolog Treat 29:441–449. https://doi.org/10.1080/09546634.2017.1395806.
794. Casseres RG, Kahn JS, Her MJ, Rosmarin D. 2018. Guselkumab in the treatment of hidradenitis suppurativa: a retrospective chart review. J Am Acad Dermatol 81:265–267. https://doi.org/10.1016/j.jaad.2018.12.017.
795. Nunes G, Patita M, Fernandes V. 2019. Refractory pyoderma gangrenosum in a patient with Crohn's Disease: complete response to ustekinumab. J Crohns Colitis 13:812–813. https://doi.org/10.1093/ecco-jcc/jjy200.
796. Abdollahi E, Tavasolian F, Momtazi-Borojeni AA, Samadi M, Rafatpanah H. 2016. Protective role of R381Q (rs11209026) polymorphism in IL-23R gene in immune-mediated diseases: a comprehensive review. J Immunotoxicol 13:286–300. https://doi.org/10.3109/1547691X.2015.1115448.
797. Pidasheva S, Trifari S, Phillips A, Hackney JA, Ma Y, Smith A, Sohn SJ, Spits H, Little RD, Behrens TW, Honigberg L, Ghilardi N, Clark HF. 2011.

Functional studies on the IBD susceptibility gene IL23R implicate reduced receptor function in the protective genetic variant R381Q. PLoS One 6:e25038. https://doi.org/10.1371/journal.pone.0025038.
798. Gordon KB, Duffin KC, Bissonnette R, Prinz JC, Wasfi Y, Li S, Shen YK, Szapary P, Randazzo B, Reich K. 2015. A Phase 2 trial of guselkumab versus adalimumab for plaque psoriasis. N Engl J Med 373:136–144. https://doi.org/10.1056/NEJMoa1501646.
799. Sofen H, Smith S, Matheson RT, Leonardi CL, Calderon C, Brodmerkel C, Li K, Campbell K, Marciniak SJ, Jr, Wasfi Y, Wang Y, Szapary P, Krueger JG. 2014. Guselkumab (an IL-23-specific mAb) demonstrates clinical and molecular response in patients with moderate-to-severe psoriasis. J Allergy Clin Immunol 133:1032–1040. https://doi.org/10.1016/j.jaci.2014.01.025.
800. Blauvelt A, Papp KA, Griffiths CE, Randazzo B, Wasfi Y, Shen YK, Li S, Kimball AB. 2017. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. J Am Acad Dermatol 76:405–417. https://doi.org/10.1016/j.jaad.2016.11.041.
801. Reich K, Armstrong AW, Foley P, Song M, Wasfi Y, Randazzo B, Li S, Shen YK, Gordon KB. 2017. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. J Am Acad Dermatol 76:418–431. https://doi.org/10.1016/j.jaad.2016.11.042.
802. Krueger JG, Ferris LK, Menter A, Wagner F, White A, Visvanathan S, Lalovic B, Aslanyan S, Wang EE, Hall D, Solinger A, Padula S, Scholl P. 2015. Anti-IL-23A mAb BI 655066 for treatment of moderate-to-severe psoriasis: safety, efficacy, pharmacokinetics, and biomarker results of a single-rising-dose, randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol 136:116–124.e7. https://doi.org/10.1016/j.jaci.2015.01.018.
803. Feagan BG, Sandborn WJ, D'Haens G, Panes J, Kaser A, Ferrante M, Louis E, Franchimont D, Dewit O, Seidler U, Kim KJ, Neurath MF, Schreiber S, Scholl P, Pamulapati C, Lalovic B, Visvanathan S, Padula SJ, Herichova I, Soaita A, Hall DB, Bocher WO. 2017. Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomised, double-blind, placebo-controlled phase 2 study. Lancet 389:1699–1709. https://doi.org/10.1016/S0140-6736(17)30570-6.
804. Gordon KB, Strober B, Lebwohl M, Augustin M, Blauvelt A, Poulin Y, Papp KA, Sofen H, Puig L, Foley P, Ohtsuki M, Flack M, Geng Z, Gu Y, Valdes JM, Thompson EHZ, Bachelez H. 2018. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. Lancet 392:650–661. https://doi.org/10.1016/S0140-6736(18)31713-6.
805. Feagan BG, Panes J, Ferrante M, Kaser A, D'Haens GR, Sandborn WJ, Louis E, Neurath MF, Franchimont D, Dewit O, Seidler U, Kim KJ, Selinger C, Padula SJ, Herichova I, Robinson AM, Wallace K, Zhao J, Minocha M, Othman AA, Soaita A, Visvanathan S, Hall DB, Bocher WO. 2018. Risankizumab in patients with moderate to severe Crohn's disease: an open-label extension study. Lancet Gastroenterol Hepatol 3:671–680. https://doi.org/10.1016/S2468-1253(18)30233-4.
806. Baeten D, Ostergaard M, Wei JC, Sieper J, Jarvinen P, Tam LS, Salvarani C, Kim TH, Solinger A, Datsenko Y, Pamulapati C, Visvanathan S, Hall DB, Aslanyan S, Scholl P, Padula SJ. 2018. Risankizumab, an IL-23 inhibitor, for ankylosing spondylitis: results of a randomised, double-blind, placebo-controlled, proof-of-concept, dose-finding phase 2 study. Ann Rheum Dis 77:1295–1302. https://doi.org/10.1136/annrheumdis-2018-213328.
807. Papp KA, Blauvelt A, Bukhalo M, Gooderham M, Krueger JG, Lacour JP, Menter A, Philipp S, Sofen H, Tyring S, Berner BR, Visvanathan S, Pamulapati C, Bennett N, Flack M, Scholl P, Padula SJ. 2017. Risankizumab versus ustekinumab for moderate-to-severe plaque psoriasis. N Engl J Med 376:1551–1560. https://doi.org/10.1056/NEJMoa1607017.
808. Reich K, Papp KA, Blauvelt A, Tyring SK, Sinclair R, Thaci D, Nograles K, Mehta A, Cichanowitz N, Li Q, Liu K, La Rosa C, Green S, Kimball AB. 2017. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. Lancet 390:276–288. https://doi.org/10.1016/S0140-6736(17)31279-5.
809. Fieschi C, Casanova JL. 2003. The role of interleukin-12 in human infectious diseases: only a faint signature. Eur J Immunol 33:1461–1464. https://doi.org/10.1002/eji.200324038.
810. de Jong R, Altare F, Haagen IA, Elferink DG, Boer T, van Breda Vriesman PJ, Kabel PJ, Draaisma JM, van Dissel JT, Kroon FP, Casanova JL, Ottenhoff TH. 1998. Severe mycobacterial and Salmonella infections in interleukin-12 receptor-deficient patients. Science 280:1435–1438. https://doi.org/10.1126/science.280.5368.1435.
811. Rosain J, Kong XF, Martinez-Barricarte R, Oleaga-Quintas C, Ramirez-Alejo N, Markle J, Okada S, Boisson-Dupuis S, Casanova JL, Bustamante J. 2019. Mendelian susceptibility to mycobacterial disease: 2014–2018 update. Immunol Cell Biol 97:360–367. https://doi.org/10.1111/imcb.12210.
812. Bustamante J, Boisson-Dupuis S, Abel L, Casanova JL. 2014. Mendelian susceptibility to mycobacterial disease: genetic, immunological, and clinical features of inborn errors of IFN-gamma immunity. Semin Immunol 26:454–470. https://doi.org/10.1016/j.smim.2014.09.008.
813. Okada S, Puel A, Casanova JL, Kobayashi M. 2016. Chronic mucocutaneous candidiasis disease associated with inborn errors of IL-17 immunity. Clin Trans Immunol 5:e114. https://doi.org/10.1038/cti.2016.71.
814. Hueber W, Sands BE, Lewitzky S, Vandemeulebroecke M, Reinisch W, Higgins PD, Wehkamp J, Feagan BG, Yao MD, Karczewski M, Karczewski J, Pezous N, Bek S, Bruin G, Mellgard B, Berger C, Londei M, Bertolino AP, Tougas G, Travis SP, Secukinumab in Crohn's Disease Study Group. 2012. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial. Gut 61:1693–1700. https://doi.org/10.1136/gutjnl-2011-301668.
815. Levy R, Okada S, Beziat V, Moriya K, Liu C, Chai LY, Migaud M, Hauck F, Al Ali A, Cyrus C, Vatte C, Patiroglu T, Unal E, Ferneiny M, Hyakuna N, Nepesov S, Oleastro M, Ikinciogullari A, Dogu F, Asano T, Ohara O, Yun L, Della Mina E, Bronnimann D, Itan Y, Gothe F, Bustamante J, Boisson-Dupuis S, Tahuil N, Aytekin C, Salhi A, Al Muhsen S, Kobayashi M, Toubiana J, Abel L, Li X, Camcioglu Y, Celmeli F, Klein C, AlKhater SA, Casanova JL, Puel A. 2016. Genetic, immunological, and clinical features of patients with bacterial and fungal infections due to inherited IL-17RA deficiency. Proc Natl Acad Sci U S A 113:E8277–E8285. https://doi.org/10.1073/pnas.1618300114.
816. Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, Li S, Dooley LT, Gordon KB. 2008. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 371:1665–1674. https://doi.org/10.1016/S0140-6736(08)60725-4.
817. Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, Guzzo C, Hsu MC, Wang Y, Li S, Dooley LT, Reich K. 2008. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet 371:1675–1684. https://doi.org/10.1016/S0140-6736(08)60726-6.
818. Griffiths CE, Strober BE, van de Kerkhof P, Ho V, Fidelus-Gort R, Yeilding N, Guzzo C, Xia Y, Zhou B, Li S, Dooley LT, Goldstein NH, Menter A. 2010. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med 362:118–128. https://doi.org/10.1056/NEJMoa0810652.
819. Igarashi A, Kato T, Kato M, Song M, Nakagawa H, Japanese Ustekinumab Study Group. 2012. Efficacy and safety of ustekinumab in Japanese patients with moderate-to-severe plaque-type psoriasis: long-term results from a phase 2/3 clinical trial. J Dermatol 39:242–252. https://doi.org/10.1111/j.1346-8138.2011.01347.x.
820. Krueger GG, Langley RG, Leonardi C, Yeilding N, Guzzo C, Wang Y, Dooley LT, Lebwohl M. 2007. A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. N Engl J Med 356:580–592. https://doi.org/10.1056/NEJMoa062382.
821. Tsai TF, Ho JC, Song M, Szapary P, Guzzo C, Shen YK, Li S, Kim KJ, Kim TY, Choi JH, Youn JI. 2011. Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: a phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL). J Dermatol Sci 63:154–163. https://doi.org/10.1016/j.jdermsci.2011.05.005.
822. Zhu X, Zheng M, Song M, Shen YK, Chan D, Szapary PO, Wang B. 2013.

Efficacy and safety of ustekinumab in Chinese patients with moderate to severe plaque-type psoriasis: results from a phase 3 clinical trial (LOTUS). J Drugs Dermatol 12:166–174.
823. Gottlieb A, Menter A, Mendelsohn A, Shen YK, Li S, Guzzo C, Fretzin S, Kunynetz R, Kavanaugh A. 2009. Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. Lancet 373:633–640. https://doi.org/10.1016/S0140-6736(09)60140-9.
824. McInnes IB, Kavanaugh A, Gottlieb AB, Puig L, Rahman P, Ritchlin C, Brodmerkel C, Li S, Wang Y, Mendelsohn AM, Doyle MK. 2013. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet 382:780–789. https://doi.org/10.1016/S0140-6736(13)60594-2.
825. Ritchlin C, Rahman P, Kavanaugh A, McInnes IB, Puig L, Li S, Wang Y, Shen YK, Doyle MK, Mendelsohn AM, Gottlieb AB, PSUMMIT 2 Study Group. 2014. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. Ann Rheum Dis 73:990–999. https://doi.org/10.1136/annrheumdis-2013-204655.
826. Kavanaugh A, Ritchlin C, Rahman P, Puig L, Gottlieb AB, Li S, Wang Y, Noonan L, Brodmerkel C, Song M, Mendelsohn AM, McInnes IB, PSUMMIT-1 and 2 Study Groups. 2014. Ustekinumab, an anti-IL-12/23 p40 monoclonal antibody, inhibits radiographic progression in patients with active psoriatic arthritis: results of an integrated analysis of radiographic data from the phase 3, multicentre, randomised, double-blind, placebo-controlled PSUMMIT-1 and PSUMMIT-2 trials. Ann Rheum Dis 73:1000–1006. https://doi.org/10.1136/annrheumdis-2013-204741.
827. Sandborn WJ, Gasink C, Gao LL, Blank MA, Johanns J, Guzzo C, Sands BE, Hanauer SB, Targan S, Rutgeerts P, Ghosh S, de Villiers WJ, Panaccione R, Greenberg G, Schreiber S, Lichtiger S, Feagan BG. 2012. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. N Engl J Med 367:1519–1528. https://doi.org/10.1056/NEJMoa1203572.
828. Khanna R, Preiss JC, MacDonald JK, Timmer A. 2015. Anti-IL-12/23p40 antibodies for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2015:CD007572. https://doi.org/10.1002/14651858.CD007572.
829. Khorrami S, Ginard D, Marín-Jiménez I, Chaparro M, Sierra M, Aguas M, Sicilia B, García-Sánchez V, Suarez C, Villoria A, Taxonera C, Velasco-Guardado A, Martínez-González J, Gisbert JP. 2016. Ustekinumab for the treatment of refractory Crohn's disease: the Spanish experience in a large multicentre open-label cohort. Inflamm Bowel Dis 22:1662–1669. https://doi.org/10.1097/MIB.0000000000000842.
830. Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, Blank MA, Johanns J, Gao LL, Miao Y, Adedokun OJ, Sands BE, Hanauer SB, Vermeire S, Targan S, Ghosh S, de Villiers WJ, Colombel JF, Tulassay Z, Seidler U, Salzberg BA, Desreumaux P, Lee SD, Loftus EV, Jr, Dieleman LA, Katz S, Rutgeerts P. 2016. Ustekinumab as induction and maintenance therapy for Crohn's disease. N Engl J Med 375:1946–1960. https://doi.org/10.1056/NEJMoa1602773.
831. Tsai TF, Ho V, Song M, Szapary P, Kato T, Wasfi Y, Li S, Shen YK, Leonardi C, PHOENIX 1, PHOENIX 2, ACCEPT, PEARL, and Japanese Ustekinumab Study Groups. 2012. The safety of ustekinumab treatment in patients with moderate-to-severe psoriasis and latent tuberculosis infection. Br J Dermatol 167:1145–1152. https://doi.org/10.1111/j.1365-2133.2012.11142.x.
832. Meng Y, Dongmei L, Yanbin P, Jinju F, Meile T, Binzhu L, Xiao H, Ping T, Jianmin L. 2014. Systematic review and meta-analysis of ustekinumab for moderate to severe psoriasis. Clin Exp Dermatol 39:696–707. https://doi.org/10.1111/ced.12390.
833. Gordon KB, Papp KA, Langley RG, Ho V, Kimball AB, Guzzo C, Yeilding N, Szapary PO, Fakharzadeh S, Li S, Hsu MC, Reich K. 2012. Long-term safety experience of ustekinumab in patients with moderate to severe psoriasis (part II of II): results from analyses of infections and malignancy from pooled phase II and III clinical trials. J Am Acad Dermatol 66:742–751. https://doi.org/10.1016/j.jaad.2011.06.041.
834. Lebwohl M, Leonardi C, Griffiths CE, Prinz JC, Szapary PO, Yeilding N, Guzzo C, Li S, Hsu MC, Strober B. 2012. Long-term safety experience of ustekinumab in patients with moderate-to-severe psoriasis (part I of II): results from analyses of general safety parameters from pooled Phase 2 and 3 clinical trials. J Am Acad Dermatol 66:731–741. https://doi.org/10.1016/j.jaad.2011.06.011.
835. Papp KA, Griffiths CE, Gordon K, Lebwohl M, Szapary PO, Wasfi Y, Chan D, Hsu MC, Ho V, Ghislain PD, Strober B, Reich K, PHOENIX 1, PHOENIX 2 and ACCEPT Investigators. 2013. Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. Br J Dermatol 168:844–854. https://doi.org/10.1111/bjd.12214.
836. Kalb RE, Fiorentino DF, Lebwohl MG, Toole J, Poulin Y, Cohen AD, Goyal K, Fakharzadeh S, Calabro S, Chevrier M, Langholff W, You Y, Leonardi CL. 2015. Risk of serious infection with biologic and systemic treatment of psoriasis: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). JAMA Dermatol 151:961–969. https://doi.org/10.1001/jamadermatol.2015.0718.
837. Chiu HY, Chen CH, Wu MS, Cheng YP, Tsai TF. 2013. The safety profile of ustekinumab in the treatment of patients with psoriasis and concurrent hepatitis B or C. Br J Dermatol 169:1295–1303. https://doi.org/10.1111/bjd.12461.
838. Ting SW, Chen YC, Huang YH. 2018. Risk of hepatitis B reactivation in patients with psoriasis on ustekinumab. Clin Drug Invest 38:873–880. https://doi.org/10.1007/s40261-018-0671-z.
839. Failla V, Nikkels AF. 2011. Ustekinumab and herpes zoster. Dermatology 222:119–122. https://doi.org/10.1159/000323736.
840. Umezawa Y, Fukuchi O, Ito T, Saeki H, Nakagawa H. 2014. Risk of herpes zoster in psoriatic patients undergoing biologic treatment. J Dermatol 41:168–170. https://doi.org/10.1111/1346-8138.12370.
841. Stollberger C, Finsterer J. 2017. Varicella zoster virus meningitis under ustekinumab because of plaque psoriasis. J Dermatol 44:703–705. https://doi.org/10.1111/1346-8138.13755.
842. Shalom G, Naldi L, Lebwohl M, Nikkels A, de Jong E, Fakharzadeh S, Goyal KG, Srivastava B, Langholff W, Galindo C, Cohen AD. 2019. Biological treatment for psoriasis and the risk of herpes zoster: results from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). J Dermatolog Treat 30:534–539. https://doi.org/10.1080/09546634.2018.1445193.
843. Foley P, Gordon K, Griffiths CEM, Wasfi Y, Randazzo B, Song M, Li S, Shen YK, Blauvelt A. 2018. Efficacy of guselkumab compared with adalimumab and placebo for psoriasis in specific body regions: a secondary analysis of 2 randomized clinical trials. JAMA Dermatol 154:676–683. https://doi.org/10.1001/jamadermatol.2018.0793.
844. Langley RG, Tsai TF, Flavin S, Song M, Randazzo B, Wasfi Y, Jiang J, Li S, Puig L. 2018. Efficacy and safety of guselkumab in patients with psoriasis who have an inadequate response to ustekinumab: results of the randomized, double-blind, phase III NAVIGATE trial. Br J Dermatol 178:114–123. https://doi.org/10.1111/bjd.15750.
845. Deodhar A, Gottlieb AB, Boehncke W-H, Dong B, Wang Y, Zhuang Y, Barchuk W, Xu XL, Hsia EC, Aelion J, Amarelo-Ramos J, Balsa A, Berghea F, Brzezicki J, Burnette M, Fretzin S, García-Carazo S, Gladstein G, Gomez-Reino J, Gooderham M, González-Fernández C, Gottlieb A, Gratacos J, Haaland D, Kamalova R, Leszczynski P, Martin-Mola E, Maslyansky A, Navarro F, Opris D, Papp K, Perlamutrov Y, Philipp S, Racewicz A, Rebrov A, Rell-Bakalarska M, Rosmarin D, Rubbert-Roth A, Shergy W, Shirinsky I, Sonin D, Stanislav M, Sukharev A, Temnikov V, Vinogradova I, Waytz P, Yakushevich V. 2018. Efficacy and safety of guselkumab in patients with active psoriatic arthritis: a randomised, double-blind, placebo-controlled, phase 2 study. Lancet 391:2213–2224. https://doi.org/10.1016/S0140-6736(18)30952-8.
846. Sano S, Kubo H, Morishima H, Goto R, Zheng R, Nakagawa H. 2018. Guselkumab, a human interleukin-23 monoclonal antibody in Japanese patients with generalized pustular psoriasis and erythrodermic psoriasis: efficacy and safety analyses of a 52-week, phase 3, multicenter, open-label study. J Dermatol 45:529–539. https://doi.org/10.1111/1346-8138.14294.
847. Blauvelt A, Reich K, Papp KA, Kimball AB, Gooderham M, Tyring SK, Sinclair R, Thaci D, Li Q, Cichanowitz N, Green S, La Rosa C. 2018. Safety of tildrakizumab for moderate-to-severe plaque psoriasis: pooled analysis of three randomized controlled trials. Br J Dermatol 179:615–622. https://doi.org/10.1111/bjd.16724.
848. Reich K, Warren RB, Iversen L, Puig L, Pau-Charles I, Igarashi A, Ohtsuki M, Falqués M, Harmut M, Rozzo S, Lebwohl MG, Cantrell W, Blauvelt A, Thaçi D. 2020. Long-term efficacy and safety of tildrakizumab for moderate-to-severe psoriasis: pooled analyses of two randomized

phase III clinical trials (reSURFACE 1 and reSURFACE 2) through 148 weeks. Br J Dermatol 182:605–617. https://doi.org/10.1111/bjd.18232.
849. Sanz-Bueno J, Vanaclocha F, García-Doval I, Torrado R, Carretero G, Daudén E, Patricia Ruiz-Genao D, Alsina-Gibert MM, Pérez-Zafrilla B, Pérez-Rial G, Rivera R, members of the BIOBADADERM Group. 2015. Risk of reactivation of hepatitis B virus infection in psoriasis patients treated with biologics: a retrospective analysis of 20 cases from the BIOBADADERM database. Actas Dermosifiliogr 106:477–482. https://doi.org/10.1016/j.adengl.2015.05.013.
850. Koskinas J, Tampaki M, Doumba PP, Rallis E. 2013. Hepatitis B virus reactivation during therapy with ustekinumab for psoriasis in a hepatitis B surface-antigen-negative anti-HBs-positive patient. Br J Dermatol 168:679–680. https://doi.org/10.1111/bjd.12120.
851. Navarro R, Vilarrasa E, Herranz P, Puig L, Bordas X, Carrascosa JM, Taberner R, Ferrán M, García-Bustinduy M, Romero-Maté A, Pedragosa R, García-Diez A, Daudén E. 2013. Safety and effectiveness of ustekinumab and antitumour necrosis factor therapy in patients with psoriasis and chronic viral hepatitis B or C: a retrospective, multicentre study in a clinical setting. Br J Dermatol 168:609–616. https://doi.org/10.1111/bjd.12045.
852. Toy D, Kugler D, Wolfson M, Vanden Bos T, Gurgel J, Derry J, Tocker J, Peschon J. 2006. Cutting edge: interleukin 17 signals through a heteromeric receptor complex. J Immunol 177:36–39. https://doi.org/10.4049/jimmunol.177.1.36.
853. Chang SH, Dong C. 2007. A novel heterodimeric cytokine consisting of IL-17 and IL-17F regulates inflammatory responses. Cell Res 17:435–440. https://doi.org/10.1038/cr.2007.35.
854. Dong C. 2006. Diversification of T-helper-cell lineages: finding the family root of IL-17-producing cells. Nat Rev Immunol 6:329–333. https://doi.org/10.1038/nri1807.
855. Mellett M, Atzei P, Horgan A, Hams E, Floss T, Wurst W, Fallon PG, Moynagh PN. 2012. Orphan receptor IL-17RD tunes IL-17A signalling and is required for neutrophilia. Nat Commun 3:1119. https://doi.org/10.1038/ncomms2127.
856. Kuwabara T, Ishikawa F, Kondo M, Kakiuchi T. 2017. The role of IL-17 and related cytokines in inflammatory autoimmune diseases. Mediators Inflamm 2017:3908061. https://doi.org/10.1155/2017/3908061.
857. Cua DJ, Tato CM. 2010. Innate IL-17-producing cells: the sentinels of the immune system. Nat Rev Immunol 10:479–489. https://doi.org/10.1038/nri2800.
858. Ye P, Rodriguez FH, Kanaly S, Stocking KL, Schurr J, Schwarzenberger P, Oliver P, Huang W, Zhang P, Zhang J, Shellito JE, Bagby GJ, Nelson S, Charrier K, Peschon JJ, Kolls JK. 2001. Requirement of interleukin 17 receptor signaling for lung CXC chemokine and granulocyte colony-stimulating factor expression, neutrophil recruitment, and host defense. J Exp Med 194:519–527. https://doi.org/10.1084/jem.194.4.519.
859. Kisand K, Boe Wolff AS, Podkrajsek KT, Tserel L, Link M, Kisand KV, Ersvaer E, Perheentupa J, Erichsen MM, Bratanic N, Meloni A, Cetani F, Perniola R, Ergun-Longmire B, Maclaren N, Krohn KJ, Pura M, Schalke B, Strobel P, Leite MI, Battelino T, Husebye ES, Peterson P, Willcox N, Meager A. 2010. Chronic mucocutaneous candidiasis in APECED or thymoma patients correlates with autoimmunity to Th17-associated cytokines. J Exp Med 207:299–308. https://doi.org/10.1084/jem.20091669.
860. Puel A, Doffinger R, Natividad A, Chrabieh M, Barcenas-Morales G, Picard C, Cobat A, Ouachee-Chardin M, Toulon A, Bustamante J, Al-Muhsen S, Al-Owain M, Arkwright PD, Costigan C, McConnell V, Cant AJ, Abinun M, Polak M, Bougneres PF, Kumararatne D, Marodi L, Nahum A, Roifman C, Blanche S, Fischer A, Bodemer C, Abel L, Lilic D, Casanova JL. 2010. Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I. J Exp Med 207:291–297. https://doi.org/10.1084/jem.20091983.
861. Puel A, Cypowyj S, Marodi L, Abel L, Picard C, Casanova JL. 2012. Inborn errors of human IL-17 immunity underlie chronic mucocutaneous candidiasis. Curr Opin Allergy Clin Immunol 12:616–622. https://doi.org/10.1097/ACI.0b013e328358cc0b.
862. Kniffin C. 2015. Interleukin 17 receptor C; IL17RC. Alternative titles; symbols: Interleukin 17 receptor-like protein; IL17RL. OMIM, Johns Hopkins University, Baltimore, MD. https://www.omim.org/entry/610925. Accessed 22 March 2019.
863. Hamosh A. 2011. Candidiasis, familial, 6; CANDF6. Alternative titles; symbols: Candidiasis, Familial Chronic Mucocutaneous, Autosomal Dominant, OMIM, Johns Hopkins University, Baltimore, MD. https://www.omim.org/entry/613956. Accessed 22 March 2019.
864. Kniffin C. 2015. Candidiasis, familial, 9; CANDF9. OMIM, Johns Hopkins University, Baltimore, MD. https://www.omim.org/entry/616445. Accessed 22 March 2019.
865. Kniffin C. 2000. Interleukin 17C; IL17C. OMIM. Johns Hopkins University, Baltimore, MD. https://www.omim.org/entry/604628. Accessed 22 March 2019.
866. Kniffin C. 2000. Interleukin 17 receptor A; IL17RA. Alternative titles; symbols: IL17R. OMIM, Johns Hopkins University, Baltimore, MD. https://www.omim.org/entry/605461. Accessed 22 March 2019.
867. Blauvelt A, Lebwohl MG, Bissonnette R. 2015. IL-23/IL-17A dysfunction phenotypes inform possible clinical effects from anti-IL-17A therapies. J Invest Dermatol 135:1946–1953. https://doi.org/10.1038/jid.2015.144.
868. Kammuller M, Tsai TF, Griffiths CE, Kapoor N, Kolattukudy PE, Brees D, Chibout SD, Safi J, Jr, Fox T. 2017. Inhibition of IL-17A by secukinumab shows no evidence of increased Mycobacterium tuberculosis infections. Clin Trans Immunol 6:e152. https://doi.org/10.1038/cti.2017.34.
869. Veldhoen M. 2017. Interleukin 17 is a chief orchestrator of immunity. Nat Immunol 18:612–621. https://doi.org/10.1038/ni.3742.
870. van Hamburg JP, Tas SW. 2018. Molecular mechanisms underpinning T helper 17 cell heterogeneity and functions in rheumatoid arthritis. J Autoimmun 87:69–81. https://doi.org/10.1016/j.jaut.2017.12.006.
871. Baraliakos X, Kivitz AJ, Deodhar AA, Braun J, Wei JC, Delicha EM, Talloczy Z, Porter B. 2018. Long-term effects of interleukin-17A inhibition with secukinumab in active ankylosing spondylitis: 3-year efficacy and safety results from an extension of the phase 3 MEASURE 1 trial. Clin Exp Rheumatol 36:50–55.
872. Baeten D, Sieper J, Braun J, Baraliakos X, Dougados M, Emery P, Deodhar A, Porter B, Martin R, Andersson M, Mpofu S, Richards HB. 2015. Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis. N Engl J Med 373:2534–2548. https://doi.org/10.1056/NEJMoa1505066.
873. van der Heijde D, Cheng-Chung Wei J, Dougados M, Mease P, Deodhar A, Maksymowych WP, Van den Bosch F, Sieper J, Tomita T, Landewé R, Zhao F, Krishnan E, Adams DH, Pangallo B, Carlier H, Churchill M, Flint K, Gladstein G, Greenwald M, Howell M, Ince A, Kaine J, Mehta D, Peters E, Querubin R, Reveille J, Roseff R, Diegel R, Thai C, Bessette L, Morin F, Rahman P, Barrera Rodriguez AA, Cons-Molina F, Duran Barragan S, Skinner C, Pacheco Tena C, Ramos Remus C, Rizo Rodriguez JC, Hong S-J, Lee Y-A, Ju JH, Kang SW, Kim T-H, Lee CK, Lee EB, Lee SH, Park M-C, Shin K, et al. 2018. Ixekizumab, an interleukin-17A antagonist in the treatment of ankylosing spondylitis or radiographic axial spondyloarthritis in patients previously untreated with biological disease-modifying anti-rheumatic drugs (COAST-V): 16 week results of a phase 3 randomised, double-blind, active-controlled and placebo-controlled trial. Lancet 392:2441–2451. https://doi.org/10.1016/S0140-6736(18)31946-9.
874. Blanco FJ, Moricke R, Dokoupilova E, Codding C, Neal J, Andersson M, Rohrer S, Richards H. 2017. Secukinumab in active rheumatoid arthritis: a phase III randomized, double-blind, active comparator- and placebo-controlled study. Arthritis Rheumatol 69:1144–1153. https://doi.org/10.1002/art.40070.
875. Kunwar S, Dahal K, Sharma S. 2016. Anti-IL-17 therapy in treatment of rheumatoid arthritis: a systematic literature review and meta-analysis of randomized controlled trials. Rheumatol Int 36:1065–1075. https://doi.org/10.1007/s00296-016-3480-9.
876. Dokoupilova E, Aelion J, Takeuchi T, Malavolta N, Sfikakis PP, Wang Y, Rohrer S, Richards HB. 2018. Secukinumab after anti-tumour necrosis factor-alpha therapy: a phase III study in active rheumatoid arthritis. Scand J Rheumatol 47:276–281. https://doi.org/10.1080/03009742.2017.1390605.
877. Leonardi C, Maari C, Philipp S, Goldblum O, Zhang L, Burkhardt N, Ball S, Mallbris L, Gonzalez P, Fernández-Peñas P, Puig L. 2018. Maintenance of skin clearance with ixekizumab treatment of psoriasis: three-year results from the UNCOVER-3 study. J Am Acad Dermatol 79:824–830.e2. https://doi.org/10.1016/j.jaad.2018.05.032.
878. Gottlieb AB, Strand V, Kishimoto M, Mease P, Thaci D, Birt J, Lee CH, Shuler CL, Lin CY, Gladman DD. 2018. Ixekizumab improves patient-reported outcomes up to 52 weeks in bDMARD-naive patients with active psoriatic arthritis (SPIRIT-P1). Rheumatology (Oxford) 57:1777–1788. https://doi.org/10.1093/rheumatology/key161.
879. Mease PJ, van der Heijde D, Ritchlin CT, Okada M, Cuchacovich RS,

Shuler CL, Lin CY, Braun DK, Lee CH, Gladman DD. 2017. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Ann Rheum Dis 76:79–87. https://doi.org/10.1136/annrheumdis-2016-209709.
880. Bissonnette R, Luger T, Thaci D, Toth D, Lacombe A, Xia S, Mazur R, Patekar M, Charef P, Milutinovic M, Leonardi C, Mrowietz U. 2018. Secukinumab demonstrates high sustained efficacy and a favourable safety profile in patients with moderate-to-severe psoriasis through 5 years of treatment (SCULPTURE Extension Study). J Eur Acad Dermatol Venereol 32:1507–1514. https://doi.org/10.1111/jdv.14878.
881. McInnes IB, Mease PJ, Ritchlin CT, Rahman P, Gottlieb AB, Kirkham B, Kajekar R, Delicha EM, Pricop L, Mpofu S. 2017. Secukinumab sustains improvement in signs and symptoms of psoriatic arthritis: 2 year results from the phase 3 FUTURE 2 study. Rheumatology (Oxford) 56:1993–2003. https://doi.org/10.1093/rheumatology/kex301.
882. Sticherling M, Mrowietz U, Augustin M, Thaci D, Melzer N, Hentschke C, Kneidl J, Sieder C, Reich K. 2017. Secukinumab is superior to fumaric acid esters in treating patients with moderate-to-severe plaque psoriasis who are naive to systemic treatments: results from the randomized controlled PRIME trial. Br J Dermatol 177:1024–1032. https://doi.org/10.1111/bjd.15707.
883. Wei JC, Baeten D, Sieper J, Deodhar A, Bhosekar V, Martin R, Porter B. 2017. Efficacy and safety of secukinumab in Asian patients with active ankylosing spondylitis: 52-week pooled results from two phase 3 studies. Int J Rheum Dis 20:589–596. https://doi.org/10.1111/1756-185X.13094.
884. Kavanaugh A, Mease PJ, Reimold AM, Tahir H, Rech J, Hall S, Geusens P, Wang Z, Pricop L, Mpofu S, FUTURE-1 Study Group. 2017. Secukinumab for long-term treatment of psoriatic arthritis: a two-year followup from a phase III, randomized, double-blind placebo-controlled study. Arthritis Care Res (Hoboken) 69:347–355. https://doi.org/10.1002/acr.23111.
885. Mease PJ, McInnes IB, Kirkham B, Kavanaugh A, Rahman P, van der Heijde D, Landewe R, Nash P, Pricop L, Yuan J, Richards HB, Mpofu S. 2015. Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. N Engl J Med 373:1329–1339. https://doi.org/10.1056/NEJMoa1412679.
886. McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P, van der Heijde D, Landewe R, Conaghan PG, Gottlieb AB, Richards H, Pricop L, Ligozio G, Patekar M, Mpofu S. 2015. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 386:1137–1146. https://doi.org/10.1016/S0140-6736(15)61134-5.
887. Lebwohl MG, Papp KA, Marangell LB, Koo J, Blauvelt A, Gooderham M, Wu JJ, Rastogi S, Harris S, Pillai R, Israel RJ. 2018. Psychiatric adverse events during treatment with brodalumab: analysis of psoriasis clinical trials. J Am Acad Dermatol 78:81–89.e5. https://doi.org/10.1016/j.jaad.2017.08.024.
888. Rusta-Sallehy S, Gooderham M, Papp K. 2018. Brodalumab: a review of safety. Skin Therapy Lett 23:1–3.
889. Danesh MJ, Kimball AB. 2016. Brodalumab and suicidal ideation in the context of a recent economic crisis in the United States. J Am Acad Dermatol 74:190–192. https://doi.org/10.1016/j.jaad.2015.08.057.
890. Zou W, Restifo NP. 2010. T(H)17 cells in tumour immunity and immunotherapy. Nat Rev Immunol 10:248–256. https://doi.org/10.1038/nri2742.
891. Simon T, Taleb S, Danchin N, Laurans L, Rousseau B, Cattan S, Montely JM, Dubourg O, Tedgui A, Kotti S, Mallat Z. 2013. Circulating levels of interleukin-17 and cardiovascular outcomes in patients with acute myocardial infarction. Eur Heart J 34:570–577. https://doi.org/10.1093/eurheartj/ehs263.
892. Egeberg A, Wu JJ, Korman N, Solomon JA, Goldblum O, Zhao F, Mallbris L. 2018. Ixekizumab treatment shows a neutral impact on cardiovascular parameters in patients with moderate-to-severe plaque psoriasis: results from UNCOVER-1, UNCOVER-2, and UNCOVER-3. J Am Acad Dermatol 79:104–109.e8. https://doi.org/10.1016/j.jaad.2018.02.074.
893. Paul C, Guenther L, Torii H, Sofen H, Burge R, Lin CY, Potts Bleakman A, Mallbris L, Poulin Y. 2018. Impact of ixekizumab on facial psoriasis and related quality of life measures in moderate-to-severe psoriasis patients: 12-week results from two phase III trials. J Eur Acad Dermatol Venereol 32:68–72. https://doi.org/10.1111/jdv.14581.
894. Zachariae C, Gordon K, Kimball AB, Lebwohl M, Blauvelt A, Leonardi C, Braun D, McKean-Matthews M, Burge R, Cameron G. 2018. Efficacy and safety of ixekizumab over 4 years of open-label treatment in a phase 2 study in chronic plaque psoriasis. J Am Acad Dermatol 79:294–301.e6. https://doi.org/10.1016/j.jaad.2018.03.047.
895. Kimball AB, Luger T, Gottlieb A, Puig L, Kaufmann R, Burge R, Lin CY, Yosipovitch G. 2018. Long-term impact of ixekizumab on psoriasis itch severity: results from a phase III clinical trial and long-term extension. Acta Derm Venereol 98:98–102. https://doi.org/10.2340/00015555-2801.
896. Saunte DM, Mrowietz U, Puig L, Zachariae C. 2017. Candida infections in patients with psoriasis and psoriatic arthritis treated with interleukin-17 inhibitors and their practical management. Br J Dermatol 177:47–62. https://doi.org/10.1111/bjd.15015.
897. Papini M, Natalini Y. 2018. Candida infections in psoriatic patients on anti-IL17 therapy: a case series. J Dermatolog Treat 29:3–4. https://doi.org/10.1080/09546634.2018.1530437.
898. van de Kerkhof PC, Griffiths CE, Reich K, Leonardi CL, Blauvelt A, Tsai TF, Gong Y, Huang J, Papavassilis C, Fox T. 2016. Secukinumab long-term safety experience: a pooled analysis of 10 phase II and III clinical studies in patients with moderate to severe plaque psoriasis. J Am Acad Dermatol 75:83–98.e4. https://doi.org/10.1016/j.jaad.2016.03.024.
899. Strober B, Leonardi C, Papp KA, Mrowietz U, Ohtsuki M, Bissonnette R, Ferris LK, Paul C, Lebwohl M, Braun DK, Mallbris L, Wilhelm S, Xu W, Ljungberg A, Acharya N, Reich K. 2017. Short- and long-term safety outcomes with ixekizumab from 7 clinical trials in psoriasis: etanercept comparisons and integrated data. J Am Acad Dermatol 76:432–440.e17. https://doi.org/10.1016/j.jaad.2016.09.026.
900. Targan SR, Feagan B, Vermeire S, Panaccione R, Melmed GY, Landers C, Li D, Russell C, Newmark R, Zhang N, Chon Y, Hsu YH, Lin SL, Klekotka P. 2016. A randomized, double-blind, placebo-controlled phase 2 study of brodalumab in patients with moderate-to-severe Crohn's disease. Am J Gastroenterol 111:1599–1607. https://doi.org/10.1038/ajg.2016.298.
901. Reich K, Leonardi C, Langley RG, Warren RB, Bachelez H, Romiti R, Ohtsuki M, Xu W, Acharya N, Solotkin K, Colombel JF, Hardin DS. 2017. Inflammatory bowel disease among patients with psoriasis treated with ixekizumab: a presentation of adjudicated data from an integrated database of 7 randomized controlled and uncontrolled trials. J Am Acad Dermatol 76:441–448.e2. https://doi.org/10.1016/j.jaad.2016.10.027.
902. Papp K, Menter A, Strober B, Kricorian G, Thompson EH, Milmont CE, Nirula A, Klekotka P. 2015. Efficacy and safety of brodalumab in subpopulations of patients with difficult-to-treat moderate-to-severe plaque psoriasis. J Am Acad Dermatol 72:436–439.e1. https://doi.org/10.1016/j.jaad.2014.10.026.
903. Lebwohl M, Strober B, Menter A, Gordon K, Weglowska J, Puig L, Papp K, Spelman L, Toth D, Kerdel F, Armstrong AW, Stingl G, Kimball AB, Bachelez H, Wu JJ, Crowley J, Langley RG, Blicharski T, Paul C, Lacour JP, Tyring S, Kircik L, Chimenti S, Callis Duffin K, Bagel J, Koo J, Aras G, Li J, Song W, Milmont CE, Shi Y, Erondu N, Klekotka P, Kotzin B, Nirula A. 2015. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. N Engl J Med 373:1318–1328. https://doi.org/10.1056/NEJMoa1503824.
904. Papp KA, Reich K, Paul C, Blauvelt A, Baran W, Bolduc C, Toth D, Langley RG, Cather J, Gottlieb AB, Thaci D, Krueger JG, Russell CB, Milmont CE, Li J, Klekotka PA, Kricorian G, Nirula A. 2016. A prospective phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. Br J Dermatol 175:273–286. https://doi.org/10.1111/bjd.14493.
905. Yamasaki K, Nakagawa H, Kubo Y, Ootaki K, Japanese Brodalumab Study Group. 2017. Efficacy and safety of brodalumab in patients with generalized pustular psoriasis and psoriatic erythroderma: results from a 52-week, open-label study. Br J Dermatol 176:741–751. https://doi.org/10.1111/bjd.14702.
906. Mease PJ, Genovese MC, Greenwald MW, Ritchlin CT, Beaulieu AD, Deodhar A, Newmark R, Feng J, Erondu N, Nirula A. 2014. Brodalumab, an anti-IL17RA monoclonal antibody, in psoriatic arthritis. N Engl J Med 370:2295–2306. https://doi.org/10.1056/NEJMoa1315231.
907. Papp KA, Leonardi C, Menter A, Ortonne JP, Krueger JG, Kricorian G, Aras G, Li J, Russell CB, Thompson EH, Baumgartner S. 2012. Broda-

lumab, an anti-interleukin-17-receptor antibody for psoriasis. N Engl J Med 366:1181–1189. https://doi.org/10.1056/NEJMoa1109017.
908. Hartmann JT, Haap M, Kopp HG, Lipp HP. 2009. Tyrosine kinase inhibitors—a review on pharmacology, metabolism and side effects. Curr Drug Metab 10:470–481. https://doi.org/10.2174/138920009788897975.
909. Drenberg CD, Baker SD, Sparreboom A. 2013. Integrating clinical pharmacology concepts in individualized therapy with tyrosine kinase inhibitors. Clin Pharmacol Ther 93:215–219. https://doi.org/10.1038/clpt.2012.247.
910. Pajares B, Torres E, Trigo JM, Saez MI, Ribelles N, Jimenez B, Alba E. 2012. Tyrosine kinase inhibitors and drug interactions: a review with practical recommendations. Clin Transl Oncol 14:94–101. https://doi.org/10.1007/s12094-012-0767-5.
911. Hodge JA, Kawabata TT, Krishnaswami S, Clark JD, Telliez JB, Dowty ME, Menon S, Lamba M, Zwillich S. 2016. The mechanism of action of tofacitinib—an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis. Clin Exp Rheumatol 34:318–328.
912. Maeshima K, Yamaoka K, Kubo S, Nakano K, Iwata S, Saito K, Ohishi M, Miyahara H, Tanaka S, Ishii K, Yoshimatsu H, Tanaka Y. 2012. The JAK inhibitor tofacitinib regulates synovitis through inhibition of interferon-gamma and interleukin-17 production by human CD4+ T cells. Arthritis Rheum 64:1790–1798. https://doi.org/10.1002/art.34329.
913. Kubo S, Yamaoka K, Kondo M, Yamagata K, Zhao J, Iwata S, Tanaka Y. 2014. The JAK inhibitor, tofacitinib, reduces the T cell stimulatory capacity of human monocyte-derived dendritic cells. Ann Rheum Dis 73:2192–2198. https://doi.org/10.1136/annrheumdis-2013-203756.
914. Boor PPC, de Ruiter PE, Asmawidjaja PS, Lubberts E, van der Laan LJW, Kwekkeboom J. 2017. JAK-inhibitor tofacitinib suppresses interferon alfa production by plasmacytoid dendritic cells and inhibits arthrogenic and antiviral effects of interferon alfa. Transl Res 188:67–79. https://doi.org/10.1016/j.trsl.2016.11.006.
915. Ghoreschi K, Jesson MI, Li X, Lee JL, Ghosh S, Alsup JW, Warner JD, Tanaka M, Steward-Tharp SM, Gadina M, Thomas CJ, Minnerly JC, Storer CE, LaBranche TP, Radi ZA, Dowty ME, Head RD, Meyer DM, Kishore N, O'Shea JJ. 2011. Modulation of innate and adaptive immune responses by tofacitinib (CP-690,550). J Immunol 186:4234–4243. https://doi.org/10.4049/jimmunol.1003668.
916. Anonymous. 2018. Xeljanz (tofacitinib). Prescribing information. Reference ID 4308396. Food and Drug Administration, Silver Spring, MD. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203214s021,208246s007lbl.pdf. Accessed August 2019.
917. European Medicines Agency. 2018. Xeljanz, INN—tofacitinib citrate. Product information. European Medicines Agency, Amsterdam, The Netherlands. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004214/WC500224911.pdf. Accessed August 2019.
918. Bachelez H, van de Kerkhof PC, Strohal R, Kubanov A, Valenzuela F, Lee JH, Yakusevich V, Chimenti S, Papacharalambous J, Proulx J, Gupta P, Tan H, Tawadrous M, Valdez H, Wolk R. 2015. Tofacitinib versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial. Lancet 386:552–561. https://doi.org/10.1016/S0140-6736(14)62113-9.
919. Merola JF, Elewski B, Tatulych S, Lan S, Tallman A, Kaur M. 2017. Efficacy of tofacitinib for the treatment of nail psoriasis: two 52-week, randomized, controlled phase 3 studies in patients with moderate-to-severe plaque psoriasis. J Am Acad Dermatol 77:79–87.e1. https://doi.org/10.1016/j.jaad.2017.01.053.
920. Keystone EC, Taylor PC, Drescher E, Schlichting DE, Beattie SD, Berclaz PY, Lee CH, Fidelus-Gort RK, Luchi ME, Rooney TP, Macias WL, Genovese MC. 2015. Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate. Ann Rheum Dis 74:333–340. https://doi.org/10.1136/annrheumdis-2014-206478.
921. Kubo S, Nakayamada S, Sakata K, Kitanaga Y, Ma X, Lee S, Ishii A, Yamagata K, Nakano K, Tanaka Y. 2018. Janus kinase inhibitor baricitinib modulates human innate and adaptive immune system. Front Immunol 9:1510. https://doi.org/10.3389/fimmu.2018.01510.
922. European Medicines Agency. 2018. Olumiant, INN—baricitinib. Product information. European Medicines Agency, Amsterdam, The Netherlands. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004085/WC500223723.pdf. Accessed August 2019.
923. Therapeutic Goods Administration. 2018. Australian PI—Olumiant (baricitinib). Therapeutic Goods Administration, Woden, Australia. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2018-PI-01225-1. Accessed August 2019.
924. Anonymous. 2018. Olumiant (baricitinib). Prescribing information. Reference ID 4271150. Food and Drug Administration, Silver Spring, MD. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/207924Orig1s000lbl.pdf. Accessed August 2019.
925. Wallace DJ, Furie RA, Tanaka Y, Kalunian KC, Mosca M, Petri MA, Dorner T, Cardiel MH, Bruce IN, Gomez E, Carmack T, DeLozier AM, Janes JM, Linnik MD, de Bono S, Silk ME, Hoffman RW. 2018. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet 392:222–231. https://doi.org/10.1016/S0140-6736(18)31363-1.
926. Sanchez GAM, Reinhardt A, Ramsey S, Wittkowski H, Hashkes PJ, Berkun Y, Schalm S, Murias S, Dare JA, Brown D, Stone DL, Gao L, Klausmeier T, Foell D, de Jesus AA, Chapelle DC, Kim H, Dill S, Colbert RA, Failla L, Kost B, O'Brien M, Reynolds JC, Folio LR, Calvo KR, Paul SM, Weir N, Brofferio A, Soldatos A, Biancotto A, Cowen EW, Digiovanna JJ, Gadina M, Lipton AJ, Hadigan C, Holland SM, Fontana J, Alawad AS, Brown RJ, Rother KI, Heller T, Brooks KM, Kumar P, Brooks SR, Waldman M, Singh HK, Nickeleit V, Silk M, Prakash A, Janes JM, et al. 2018. JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies. J Clin Invest 128:3041–3052. https://doi.org/10.1172/JCI98814.
927. Therapeutic Goods Administration. 2018. Australian product information—Jakavi (ruxolitinib). Therapeutic Goods Administration, Woden, Australia. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-01918-1&d=201809111016933. Accessed August 2019.
928. Anonymous. 2018. Jakafi (ruxolitinib). Prescribing information. Reference ID 4191667. Food and Drug Administration, Silver Spring, MD. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/202192s015lbl.pdf. Accessed August 2019.
929. European Medicines Agency. 2018. Jakavi, INN—ruxolitinib. Product information. European Medicines Agency, Amsterdam, The Netherlands. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002464/WC500133223.pdf. Accessed August 2019.
930. Verstovsek S, Mesa RA, Gotlib J, Levy RS, Gupta V, DiPersio JF, Catalano JV, Deininger M, Miller C, Silver RT, Talpaz M, Winton EF, Harvey JH, Jr, Arcasoy MO, Hexner E, Lyons RM, Paquette R, Raza A, Vaddi K, Erickson-Viitanen S, Koumenis IL, Sun W, Sandor V, Kantarjian HM. 2012. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med 366:799–807. https://doi.org/10.1056/NEJMoa1110557.
931. Means RT, Jr. 2008. JAK2 V617F mutation testing in polycythemia vera: use and impact in an academic practice. Am J Med Sci 336:327–329. https://doi.org/10.1097/MAJ.0b013e3181695687.
932. Genovese MC, Kalunian K, Gottenberg JE, Mozaffarian N, Bartok B, Matzkies F, Gao J, Guo Y, Tasset C, Sundy JS, de Vlam K, Walker D, Takeuchi T. 2019. Effect of filgotinib vs placebo on clinical response in patients with moderate to severe rheumatoid arthritis refractory to disease-modifying antirheumatic drug therapy: the FINCH 2 randomized clinical trial. JAMA 322:315–325. https://doi.org/10.1001/jama.2019.9055.
933. van der Heijde D, Baraliakos X, Gensler LS, Maksymowych WP, Tseluyko V, Nadashkevich O, Abi-Saab W, Tasset C, Meuleners L, Besuyen R, Hendrikx T, Mozaffarian N, Liu K, Greer JM, Deodhar A, Landewé R. 2018. Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active ankylosing spondylitis (TORTUGA): results from a randomised, placebo-controlled, phase 2 trial. Lancet 392:2378–2387. https://doi.org/10.1016/S0140-6736(18)32463-2.
934. Mease P, Coates LC, Helliwell PS, Stanislavchuk M, Rychlewska-Hanczewska A, Dudek A, Abi-Saab W, Tasset C, Meuleners L, Harrison P, Besuyen R, Van der Aa A, Mozaffarian N, Greer JM, Kunder R, Van den Bosch F, Gladman DD. 2018. Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active psoriatic arthritis (EQUATOR): results from a randomised, placebo-controlled, phase 2 trial. Lancet 392:2367–2377. https://doi.org/10.1016/S0140-6736(18)32483-8.
935. Labetoulle R, Paul S, Roblin X. 2018. Filgotinib for the treatment of Crohn's disease. Expert Opin Invest Drugs 27:295–300. https://doi.org/10.1080/13543784.2018.1442433.

936. Tanaka Y, McInnes IB, Taylor PC, Byers NL, Chen L, Bono S, Issa M, Macias WL, Rogai V, Rooney TP, Schlichting DE, Zuckerman SH, Emery P. 2018. Characterization and changes of lymphocyte subsets in baricitinib-treated patients with rheumatoid arthritis: an integrated analysis. Arthritis Rheumatol 70:1923–1932. https://doi.org/10.1002/art.40680.
937. Cohen S, Radominski SC, Gomez-Reino JJ, Wang L, Krishnaswami S, Wood SP, Soma K, Nduaka CI, Kwok K, Valdez H, Benda B, Riese R. 2014. Analysis of infections and all-cause mortality in phase II, phase III, and long-term extension studies of tofacitinib in patients with rheumatoid arthritis. Arthritis Rheumatol 66:2924–2937. https://doi.org/10.1002/art.38779.
938. Anonymous. 2018. Shingrix (zoster vaccine recombinant, adjuvanted). Prescribing information. Food and Drug Administration, Silver Spring, MD. https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM581605.pdf. Accessed September 2019.
939. Tran CT, Ducancelle A, Masson C, Lunel-Fabiani F. 2017. Herpes zoster: risk and prevention during immunomodulating therapy. Joint Bone Spine 84:21–27. https://doi.org/10.1016/j.jbspin.2016.04.001.
940. Winthrop KL, Wouters AG, Choy EH, Soma K, Hodge JA, Nduaka CI, Biswas P, Needle E, Passador S, Mojcik CF, Rigby WF. 2017. The safety and immunogenicity of live zoster vaccination in patients with rheumatoid arthritis before starting tofacitinib: a randomized phase II trial. Arthritis Rheumatol 69:1969–1977. https://doi.org/10.1002/art.40187.
941. Bharucha T, Ming D, Breuer J. 2017. A critical appraisal of 'Shingrix', a novel herpes zoster subunit vaccine (HZ/Su or GSK1437173A) for varicella zoster virus. Hum Vaccin Immunother 13:1789–1797. https://doi.org/10.1080/21645515.2017.1317410.
942. Atzeni F, Talotta R, Nucera V, Marino F, Gerratana E, Sangari D, Masala IF, Sarzi-Puttini P. 2018. Adverse events, clinical considerations and management recommendations in rheumatoid arthritis patients treated with JAK inhibitors. Expert Rev Clin Immunol 14:945–956. https://doi.org/10.1080/1744666x.2018.1504678.
943. Reinwald M, Silva JT, Mueller NJ, Fortun J, Garzoni C, de Fijter JW, Fernandez-Ruiz M, Grossi P, Aguado JM. 2018. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) consensus document on the safety of targeted and biological therapies: an infectious diseases perspective (intracellular signaling pathways: tyrosine kinase and mTOR inhibitors). Clin Microbiol Infect 24(Suppl 2):S53–S70. https://doi.org/10.1016/j.cmi.2018.02.009.
944. Dioverti MV, Abu Saleh OM, Tande AJ. 2018. Infectious complications in patients on treatment with ruxolitinib: case report and review of the literature. Infect Dis 50:381–387. https://doi.org/10.1080/23744235.2017.1390248.
945. Barf T, Covey T, Izumi R, van de Kar B, Gulrajani M, van Lith B, van Hoek M, de Zwart E, Mittag D, Demont D, Verkaik S, Krantz F, Pearson PG, Ulrich R, Kaptein A. 2017. Acalabrutinib (ACP-196): a covalent Bruton tyrosine kinase inhibitor with a differentiated selectivity and in vivo potency profile. J Pharmacol Exp Ther 363:240–252. https://doi.org/10.1124/jpet.117.242909.
946. Awan FT, Jurczak W. 2018. Use of acalabrutinib in patients with mantle cell lymphoma. Expert Rev Hematol 11:495–502. https://doi.org/10.1080/17474086.2018.1473030.
947. Byrd JC, Harrington B, O'Brien S, Jones JA, Schuh A, Devereux S, Chaves J, Wierda WG, Awan FT, Brown JR, Hillmen P, Stephens DM, Ghia P, Barrientos JC, Pagel JM, Woyach J, Johnson D, Huang J, Wang X, Kaptein A, Lannutti BJ, Covey T, Fardis M, McGreivy J, Hamdy A, Rothbaum W, Izumi R, Diacovo TG, Johnson AJ, Furman RR. 2016. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. N Engl J Med 374:323–332. https://doi.org/10.1056/NEJMoa1509981.
948. Anonymous. 2018. Imbruvica (ibrutinib). Prescribing information. Reference ID 4222705. Food and Drug Administration, Silver Spring, MD. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210563s000lbl.pdf. Accessed August 2019.
949. Therapeutic Goods Administration. 2018. Australian product information—Imbruvica (ibrutinib). Therapeutic Goods Administration, Woden, Australia. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2015-PI-01676-1&d=201808251016933. Accessed August 2019.
950. European Medicines Agency. 2018. Imbruvica, INN—ibrutinib. Product information. European Medicines Agency, Amsterdam, The Netherlands. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003791/WC500177775.pdf. Accessed August 2019.
951. Anonymous. 2018. Calquence (acalabrutinib). Prescribing information. Reference ID 4174611. Acalabrutinib Food and Drug Administration, Silver Spring, MD. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/210259s000lbl.pdf. Accessed August 2019.
952. Hilal T, Gea Banacloche JC, Leis JF. 2018. Chronic lymphocytic leukemia and infection risk in the era of targeted therapies: linking mechanisms with infections. Blood Rev 32:387–399. https://doi.org/10.1016/j.blre.2018.03.004.
953. Teh BW, Tam CS, Handunnetti S, Worth LJ, Slavin MA. 2018. Infections in patients with chronic lymphocytic leukaemia: mitigating risk in the era of targeted therapies. Blood Rev 32:499–507. https://doi.org/10.1016/j.blre.2018.04.007.
954. Jaglowski SM, Blazar BR. 2018. How ibrutinib, a B-cell malignancy drug, became an FDA-approved second-line therapy for steroid-resistant chronic GVHD. Blood Adv 2:2012–2019. https://doi.org/10.1182/bloodadvances.2018013060.
955. Varughese T, Taur Y, Cohen N, Palomba ML, Seo SK, Hohl TM, Redelman-Sidi G. 2018. Serious infections in patients receiving ibrutinib for treatment of lymphoid malignancies. Clin Infect Dis 67:687–692. https://doi.org/10.1093/cid/ciy175.
956. Tillman BF, Pauff JM, Satyanarayana G, Talbott M, Warner JL. 2018. Systematic review of infectious events with the Bruton tyrosine kinase inhibitor ibrutinib in the treatment of hematologic malignancies. Eur J Haematol 100:325–334. https://doi.org/10.1111/ejh.13020.
957. Chanan-Khan A, Cramer P, Demirkan F, Fraser G, Silva RS, Grosicki S, Pristupa A, Janssens A, Mayer J, Bartlett NL, Dilhuydy M-S, Pylypenko H, Loscertales J, Avigdor A, Rule S, Villa D, Samoilova O, Panagiotidis P, Goy A, Mato A, Pavlovsky MA, Karlsson C, Mahler M, Salman M, Sun S, Phelps C, Balasubramanian S, Howes A, Hallek M. 2016. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. Lancet Oncology 17:200–211. https://doi.org/10.1016/S1470-2045(15)00465-9.
958. Burger JA, Tedeschi A, Barr PM, Robak T, Owen C, Ghia P, Bairey O, Hillmen P, Bartlett NL, Li J, Simpson D, Grosicki S, Devereux S, McCarthy H, Coutre S, Quach H, Gaidano G, Maslyak Z, Stevens DA, Janssens A, Offner F, Mayer J, O'Dwyer M, Hellmann A, Schuh A, Siddiqi T, Polliack A, Tam CS, Suri D, Cheng M, Clow F, Styles L, James DF, Kipps TJ. 2015. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. N Engl J Med 373:2425–2437. https://doi.org/10.1056/NEJMoa1509388.
959. Jain P, Keating MJ, Wierda WG, Sivina M, Thompson PA, Ferrajoli A, Estrov Z, Kantarjian H, O'Brien S, Burger JA. 2017. Long-term follow-up of treatment with ibrutinib and rituximab in patients with high-risk chronic lymphocytic leukemia. Clin Cancer Res 23:2154–2158. https://doi.org/10.1158/1078-0432.CCR-16-1948.
960. Dimopoulos MA, Trotman J, Tedeschi A, Matous JV, Macdonald D, Tam C, Tournilhac O, Ma S, Oriol A, Heffner LT, Shustik C, Garcia-Sanz R, Cornell RF, de Larrea CF, Castillo JJ, Granell M, Kyrtsonis MC, Leblond V, Symeonidis A, Kastritis E, Singh P, Li J, Graef T, Bilotti E, Treon S, Buske C. 2017. Ibrutinib for patients with rituximab-refractory Waldenstrom's macroglobulinaemia (iNNOVATE): an open-label substudy of an international, multicentre, phase 3 trial. Lancet Oncol 18:241–250. https://doi.org/10.1016/S1470-2045(16)30632-5.
961. Noy A, de Vos S, Thieblemont C, Martin P, Flowers CR, Morschhauser F, Collins GP, Ma S, Coleman M, Peles S, Smith S, Barrientos JC, Smith A, Munneke B, Dimery I, Beaupre DM, Chen R. 2017. Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma. Blood 129:2224–2232. https://doi.org/10.1182/blood-2016-10-747345.
962. Lionakis MS, Dunleavy K, Roschewski M, Widemann BC, Butman JA, Schmitz R, Yang Y, Cole DE, Melani C, Higham CS, Desai JV, Ceribelli M, Chen L, Thomas CJ, Little RF, Gea-Banacloche J, Bhaumik S, Stetler-Stevenson M, Pittaluga S, Jaffe ES, Heiss J, Lucas N, Steinberg SM, Staudt LM, Wilson WH. 2017. Inhibition of B cell receptor signaling by ibrutinib in primary CNS lymphoma. Cancer Cell 31:833–843.e5. https://doi.org/10.1016/j.ccell.2017.04.012.
963. Arthurs B, Wunderle K, Hsu M, Kim S. 2017. Invasive aspergillosis related to ibrutinib therapy for chronic lymphocytic leukemia. Resp Med Case Rep 21:27–29. https://doi.org/10.1016/j.rmcr.2017.03.011.
964. Baron M, Zini JM, Challan Belval T, Vignon M, Denis B, Alanio A,

Malphettes M. 2017. Fungal infections in patients treated with ibrutinib: two unusual cases of invasive aspergillosis and cryptococcal meningoencephalitis. Leuk Lymphoma 58:2981–2982. https://doi.org/10.1080/10428194.2017.1320710.
965. Ruchlemer RB, Ami R, Lachish T. 2016. Ibrutinib for chronic lymphocytic leukemia. N Engl J Med 374:1593–1594. https://doi.org/10.1056/NEJMc1600328.
966. Chamilos G, Lionakis MS, Kontoyiannis DP. 2018. Call for action: invasive fungal infections associated with ibrutinib and other small molecule kinase inhibitors targeting immune signaling pathways. Clin Infect Dis 66:140–148. https://doi.org/10.1093/cid/cix687.
967. Ghez D, Calleja A, Protin C, Baron M, Ledoux MP, Damaj G, Dupont M, Dreyfus B, Ferrant E, Herbaux C, Laribi K, Le Calloch R, Malphettes M, Paul F, Souchet L, Truchan-Graczyk M, Delavigne K, Dartigeas C, Ysebaert L. 2018. Early-onset invasive aspergillosis and other fungal infections in patients treated with ibrutinib. Blood 131:1955–1959. https://doi.org/10.1182/blood-2017-11-818286.
968. Rogers KA, Luay M, Zhao Q, Wiczer T, Levine L, Zeinab EB, Blachly JS, Byrd JC, Guerrero T, Jones JA, Polina S, Sigmund A, Sullivan M, Awan FT, Woyach JA. 2017. Incidence and type of opportunistic infections during ibrutinib treatment at a single academic center. Blood 130:830. https://doi.org/10.1182/blood.V130.Suppl_1.830.830.
969. Okamoto K, Proia LA, Demarais PL. 2016. Disseminated cryptococcal disease in a patient with chronic lymphocytic leukemia on ibrutinib. Case Rep Infect Dis 2016:4642831. https://doi.org/10.1155/2016/4642831.
970. Sun K, Kasparian S, Iyer S, Pingali SR. 2018. Cryptococcal meningoencephalitis in patients with mantle cell lymphoma on ibrutinib. Ecancer 12:836. https://doi.org/10.3332/ecancer.2018.836.
971. Chan TSY, Au-Yeung R, Chim C-S, Wong SCY, Kwong Y-L. 2017. Disseminated fusarium infection after ibrutinib therapy in chronic lymphocytic leukaemia. Ann Hematol 96:871–872. https://doi.org/10.1007/s00277-017-2944-7.
972. de Jesus Ngoma P, Kabamba B, Dahlqvist G, Sempoux C, Lanthier N, Shindano T, Van Den Neste E, Horsmans Y. 2015. Occult HBV reactivation induced by ibrutinib treatment: a case report. Acta Gastroenterol Belg 78:424–426.
973. Herishanu Y, Katchman H, Polliack A. 2017. Severe hepatitis B virus reactivation related to ibrutinib monotherapy. Ann Hematol 96:689–690. https://doi.org/10.1007/s00277-016-2917-2.
974. Diamantopoulos PT, Psichogiou M, Pantazatou A, Zervakis K, Rougala N, Giannakopoulou N, Daikos G, Viniou N-A. 2017. Staphylococcus aureus meningitis in a patient with mantle cell lymphoma under treatment with ibrutinib. Ann Hematol 96:1049–1050. https://doi.org/10.1007/s00277-017-2964-3.
975. Wang S-Y, Ebert T, Jaekel N, Schubert S, Niederwieser D, Al-Ali HK. 2015. Miliary tuberculosis after initiation of ibrutinib in chronic lymphocytic leukemia. Ann Hematol 94:1419–1420. https://doi.org/10.1007/s00277-015-2385-0.
976. Stein MK, Karri S, Reynolds J, Owsley J, Wise A, Martin MG, Zare F. 2018. Cutaneous mucormycosis following a bullous pemphigoid flare in a chronic lymphocytic leukemia patient on ibrutinib. World J Oncol 9:62–65. https://doi.org/10.14740/wjon1099w.
977. Voshtina E, Huang H, Raj R, Atallah E. 2018. Amebic encephalitis in a patient with chronic lymphocytic leukemia on ibrutinib therapy. Case Rep Hematol 2018:6514604. https://doi.org/10.1155/2018/6514604.
978. Dousa KM, Babiker A, Van Aartsen D, Shah N, Bonomo RA, Johnson JL, Skalweit MJ. 2018. Ibrutinib therapy and Mycobacterium chelonae skin and soft tissue infection. Open Forum Infect Dis 5:ofy168. https://doi.org/10.1093/ofid/ofy168.
979. Giridhar KV, Shanafelt T, Tosh PK, Parikh SA, Call TG. 2017. Disseminated herpes zoster in chronic lymphocytic leukemia (CLL) patients treated with B-cell receptor pathway inhibitors. Leuk Lymphoma 58:1973–1976. https://doi.org/10.1080/10428194.2016.1267352.
980. Kreiniz N, Bejar J, Polliack A, Tadmor T. 2018. Severe pneumonia associated with ibrutinib monotherapy for CLL and lymphoma. Hematol Oncol 36:349–354. https://doi.org/10.1002/hon.2387.
981. Ahn IE, Jerussi T, Farooqui M, Tian X, Wiestner A, Gea-Banacloche J. 2016. Atypical Pneumocystis jirovecii pneumonia in previously untreated patients with CLL on single-agent ibrutinib. Blood 128:1940–1943. https://doi.org/10.1182/blood-2016-06-722991.
982. Lee R, Nayernama A, Jones SC, Wroblewski T, Waldron PE. 2017. Ibrutinib-associated Pneumocystis jirovecii pneumonia. Am J Hematol 92:E646–E648. https://doi.org/10.1002/ajh.24890.
983. de Weerdt I, Koopmans SM, Kater AP, van Gelder M. 2017. Incidence and management of toxicity associated with ibrutinib and idelalisib: a practical approach. Haematologica 102:1629–1639. https://doi.org/10.3324/haematol.2017.164103.
984. Wang M, Rule S, Zinzani PL, Goy A, Casasnovas O, Smith SD, Damaj G, Doorduijn J, Lamy T, Morschhauser F, Panizo C, Shah B, Davies A, Eek R, Dupuis J, Jacobsen E, Kater AP, Le Gouill S, Oberic L, Robak T, Covey T, Dua R, Hamdy A, Huang X, Izumi R, Patel P, Rothbaum W, Slatter JG, Jurczak W. 2018. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a Single-Arm, Multicentre, Phase 2 Trial. Lancet 391:659–667. https://doi.org/10.1016/S0140-6736(17)33108-2.
985. Byrd JC, Owen R, Brien SM, Brown JR, Hillmen P, Bitman B, Chernyukhin N, Hamdy A, Izumi R, Patel P, Schwartz-Sagi L, Tucker E, Fowler NH, Streetly MJ, Wiestner A, Rule S, Wang M. 2017. Pooled analysis of safety data from clinical trials evaluating acalabrutinib monotherapy in hematologic malignancies. Blood 130:4326.
986. Gribben JG, Bosch F, Cymbalista F, Geisler CH, Ghia P, Hillmen P, Moreno C, Stilgenbauer S. 2018. Optimising outcomes for patients with chronic lymphocytic leukaemia on ibrutinib therapy: European recommendations for clinical practice. Br J Haematol 180:666–679. https://doi.org/10.1111/bjh.15080.
987. Douglas AP, Trubiano JA, Barr I, Leung V, Slavin MA, Tam CS. 2017. Ibrutinib may impair serological responses to influenza vaccination. Haematologica 102:e397–e399. https://doi.org/10.3324/haematol.2017.164285.
988. Sun C, Gao J, Couzens L, Tian X, Farooqui MZ, Eichelberger MC, Wiestner A. 2016. Seasonal influenza vaccination in patients with chronic lymphocytic leukemia treated with ibrutinib. JAMA Oncol 2:1656–1657. https://doi.org/10.1001/jamaoncol.2016.2437.
989. Andrick B, Alwhaibi A, DeRemer DL, Quershi S, Khan R, Bryan LJ, Somanath PR, Pantin J. 2018. Lack of adequate pneumococcal vaccination response in chronic lymphocytic leukaemia patients receiving ibrutinib. Br J Haematol 182:712–714. https://doi.org/10.1111/bjh.14855.
990. Mensah FA, Blaize J-P, Bryan LJ. 2018. Spotlight on copanlisib and its potential in the treatment of relapsed/refractory follicular lymphoma: evidence to date. Onco Targets Ther 11:4817–4827. https://doi.org/10.2147/OTT.S142264.
991. Greenwell IB, Ip A, Cohen JB. 2017. PI3K inhibitors: understanding toxicity mechanisms and management. Oncology (Williston Park) 31:821–828.
992. Flinn IW, Kahl BS, Leonard JP, Furman RR, Brown JR, Byrd JC, Wagner-Johnston ND, Coutre SE, Benson DM, Peterman S, Cho Y, Webb HK, Johnson DM, Yu AS, Ulrich RG, Godfrey WR, Miller LL, Spurgeon SE. 2014. Idelalisib, a selective inhibitor of phosphatidylinositol 3-kinase-δ, as therapy for previously treated indolent non-Hodgkin lymphoma. Blood 123:3406–3413. https://doi.org/10.1182/blood-2013-11-538546.
993. Gopal AK, Kahl BS, de Vos S, Wagner-Johnston ND, Schuster SJ, Jurczak WJ, Flinn IW, Flowers CR, Martin P, Viardot A, Blum KA, Goy AH, Davies AJ, Zinzani PL, Dreyling M, Johnson D, Miller LL, Holes L, Li D, Dansey RD, Godfrey WR, Salles GA. 2014. PI3Kδ Inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med 370:1008–1018. https://doi.org/10.1056/NEJMoa1314583.
994. Anonymous. 2018. Zydelig (idelalisib). Prescribing information. Reference ID 4213201. Food and Drug Administration, Silver Spring, MD. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/205858s009lbl.pdf. Accessed August 2019.
995. European Medicines Agency. 2018. Zydelig, INN—idelalisib. Product information. European Medicines Agency, Amsterdam, The Netherlands. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003843/WC500175377.pdf. Accessed August 2019.
996. Therapeutic Goods Administration. 2018. Product information—Zydelig (idelalisib). Therapeutic Goods Administration, Woden, Australia. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2015-PI-01225-1&d=201809151016933. Accessed August 2019.
997. Martinelli S, Maffei R, Fiorcari S, Quadrelli C, Zucchini P, Benatti S, Potenza L, Luppi M, Marasca R. 2018. Idelalisib impairs T-cell-mediated immunity in chronic lymphocytic leukemia. Haematologica 103:e598–e601. https://doi.org/10.3324/haematol.2017.187070.
998. Liu N, Rowley BR, Bull CO, Schneider C, Haegebarth A, Schatz CA, Fracasso PR, Wilkie DP, Hentemann M, Wilhelm SM, Scott WJ, Mumberg D, Ziegelbauer K. 2013. BAY 80-6946 is a highly selective intra-

venous PI3K inhibitor with potent p110alpha and p110delta activities in tumor cell lines and xenograft models. Mol Cancer Ther 12:2319–2330. https://doi.org/10.1158/1535-7163.MCT-12-0993-T.
999. Anonymous. 2018. Aliqopa (copanlisib). Prescribing information. Reference ID 4152629. Food and Drug Administration, Silver Spring, MD. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209936s000lbl.pdf. Accessed August 2019.
1000. Furman RR, Sharman JP, Coutre SE, Cheson BD, Pagel JM, Hillmen P, Barrientos JC, Zelenetz AD, Kipps TJ, Flinn I, Ghia P, Eradat H, Ervin T, Lamanna N, Coiffier B, Pettitt AR, Ma S, Stilgenbauer S, Cramer P, Aiello M, Johnson DM, Miller LL, Li D, Jahn TM, Dansey RD, Hallek M, O'Brien SM. 2014. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Engl J Med 370:997–1007. https://doi.org/10.1056/NEJMoa1315226.
1001. Zelenetz AD, Barrientos JC, Brown JR, Coiffier B, Delgado J, Egyed M, Ghia P, Illes A, Jurczak W, Marlton P, Montillo M, Morschhauser F, Pristupa AS, Robak T, Sharman JP, Simpson D, Smolej L, Tausch E, Adewoye AH, Dreiling LK, Kim Y, Stilgenbauer S, Hillmen P. 2017. Idelalisib or placebo in combination with bendamustine and rituximab in patients with relapsed or refractory chronic lymphocytic leukaemia: interim results from a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Oncol 18:297–311. https://doi.org/10.1016/S1470-2045(16)30671-4.
1002. Jones JA, Robak T, Brown JR, Awan FT, Badoux X, Coutre S, Loscertales J, Taylor K, Vandenberghe E, Wach M, Wagner-Johnston N, Ysebaert L, Dreiling L, Dubowy R, Xing G, Flinn IW, Owen C. 2017. Efficacy and safety of idelalisib in combination with ofatumumab for previously treated chronic lymphocytic leukaemia: an open-label, randomised phase 3 trial. Lancet Haematol 4:e114–e126. https://doi.org/10.1016/S2352-3026(17)30019-4.
1003. Coutré SE, Barrientos JC, Brown JR, de Vos S, Furman RR, Keating MJ, Li D, O'Brien SM, Pagel JM, Poleski MH, Sharman JP, Yao N-S, Zelenetz AD. 2015. Management of adverse events associated with idelalisib treatment: expert panel opinion. Leuk Lymphoma 56:2779–2786. https://doi.org/10.3109/10428194.2015.1022770.
1004. Sehn LH, Hallek M, Jurczak W, Brown JR, Barr PM, Catalano J, Coutre SE, Furman RR, Lamanna N, Loïc Y, Zelenetz AD, Sharman JP, DeVos S, Adewoye AH, Kim Y, Flinn IW, Salles GA. 2016. A retrospective analysis of Pneumocystis jirovecii pneumonia infection in patients receiving idelalisib in clinical trials. Blood 128:3705–3705. https://doi.org/10.1182/blood.V128.22.3705.3705.
1005. Australian Government Department of Health. 2016. Idelalisib (zydelig) 100 mg and 150 mg tablets: monitoring communication—risk of serious adverse events for specific patient groups in clinical trials. https://www.tga.gov.au/monitoring-communication/idelalisib-zydelig-100-mg-and-150-mg-tablets. Accessed 16 July 2019.
1006. Australian Government Department of Health. 2017. Idelalisib (zydelig): safety advisory—change to indications and addition of warnings. https://www.tga.gov.au/alert/idelalisib-zydelig. Accessed 12 July 2019.
1007. Dreyling M, Morschhauser F, Bouabdallah K, Bron D, Cunningham D, Assouline SE, Verhoef G, Linton K, Thieblemont C, Vitolo U, Hiemeyer F, Giurescu M, Garcia-Vargas J, Gorbatchevsky I, Liu L, Koechert K, Pena C, Neves M, Childs BH, Zinzani PL. 2017. Phase II study of copanlisib, a PI3K inhibitor, in relapsed or refractory, indolent or aggressive lymphoma. Ann Oncol 28:2169–2178. https://doi.org/10.1093/annonc/mdx289.
1008. Dreyling M, Santoro A, Mollica L, Leppa S, Follows GA, Lenz G, Kim WS, Nagler A, Panayiotidis P, Demeter J, Ozcan M, Kosinova M, Bouabdallah K, Morschhauser F, Stevens DA, Trevarthen D, Giurescu M, Cupit L, Liu L, Kochert K, Seidel H, Pena C, Yin S, Hiemeyer F, Garcia-Vargas J, Childs BH, Zinzani PL. 2017. Phosphatidylinositol 3-kinase inhibition by copanlisib in relapsed or refractory indolent lymphoma. J Clin Oncol 35:3898–3905. https://doi.org/10.1200/JCO.2017.75.4648.
1009. Cuneo A, Barosi G, Danesi R, Fagiuoli S, Ghia P, Marzano A, Montillo M, Poletti V, Viale P, Zinzani PL. 2018. Management of adverse events associated with idelalisib treatment in chronic lymphocytic leukemia and follicular lymphoma: a multidisciplinary position paper. Hematol Oncol 37:3–14. https://doi.org/10.1002/hon.2540.
1010. Ozoya OO, Sokol L, Dalia S. 2016. Hepatitis B reactivation with novel agents in non-Hodgkin's lymphoma and prevention strategies. J Clin Transl Hepatol 4:143–150. https://doi.org/10.14218/JCTH.2016.00005.
1011. Anonymous. 2016. Straying from the target. Lancet Haematol 3:e205. https://doi.org/10.1016/S2352-3026(16)30025-4.
1012. O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, Cornelissen JJ, Fischer T, Hochhaus A, Hughes T, Lechner K, Nielsen JL, Rousselot P, Reiffers J, Saglio G, Shepherd J, Simonsson B, Gratwohl A, Goldman JM, Kantarjian H, Taylor K, Verhoef G, Bolton AE, Capdeville R, Druker BJ. 2003. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 348:994–1004. https://doi.org/10.1056/NEJMoa022457.
1013. Mughal A, Aslam HM, Khan AM, Saleem S, Umah R, Saleem M. 2013. Bcr-Abl tyrosine kinase inhibitors—current status. Infect Agents Cancer 8:23. https://doi.org/10.1186/1750-9378-8-23.
1014. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, Lydon NB, Kantarjian H, Capdeville R, Ohno-Jones S, Sawyers CL. 2001. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med 344:1031–1037. https://doi.org/10.1056/NEJM200104053441401.
1015. Faderl S, Talpaz M, Estrov Z, O'Brien S, Kurzrock R, Kantarjian HM. 1999. The biology of chronic myeloid leukemia. N Engl J Med 341:164–172. https://doi.org/10.1056/NEJM199907153410306.
1016. Anonymous. 2018. Gleevec (imatinib mesylate). Prescribing information. Reference ID 4309490. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021588s053lbl.pdf. Accessed September 2019.
1017. European Medicines Agency. 2018. Zydelig, INN—imatinib. Product information. European Medicines Agency, Amsterdam, The Netherlands. https://www.ema.europa.eu/documents/product-information/glivec-epar-product-information_en.pdf. Accessed September 2019.
1018. Therapeutic Goods Administration. 2018. Australian product information—Glivec (imatinib). Therapeutic Goods Administration, Woden, Australia. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-04296-3&d=201809271016933. Accessed September 2019.
1019. Anonymous. 2018. Sprycel (dasatinib). Prescribing information. Reference ID 4179887. Food and Drug Administration, Silver Spring, MD. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021986s020lbl.pdf. Accessed September 2019.
1020. Therapeutic Goods Administration. 2018. Australian product information—Sprycel (dasatinib). Therapeutic Goods Administration, Woden, Australia. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-02657-3. Accessed September 2019.
1021. European Medicines Agency. 2018. Sprycel, INN—dasatinib. Product information. European Medicines Agency, Amsterdam, The Netherlands. https://www.ema.europa.eu/documents/product-information/sprycel-epar-product-information_en.pdf. Accessed September 2019.
1022. Therapeutic Goods Administration. 2018. Australian product information—Tasigna (nilotinib). Therapeutic Goods Administration, Woden, Australia. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2009-PI-00292-3. Accessed September 2019.
1023. Anonymous. 2018. Tasigna (nilotinib). Prescribing information. Reference ID 4309495. Food and Drug Administration, Silver Spring, MD. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022068s029lbl.pdf. Accessed September 2019.
1024. European Medicines Agency. 2018. Tasigna, INN—nilotinib. Product information. European Medicines Agency, Amsterdam, The Netherlands. https://www.ema.europa.eu/documents/product-information/tasigna-epar-product-information_en.pdf. Accessed September 2019.
1025. Cortes JE, Kantarjian H, Shah NP, Bixby D, Mauro MJ, Flinn I, O'Hare T, Hu S, Narasimhan NI, Rivera VM, Clackson T, Turner CD, Haluska FG, Druker BJ, Deininger MW, Talpaz M. 2012. Ponatinib in refractory Philadelphia chromosome-positive leukemias. N Engl J Med 367:2075–2088. https://doi.org/10.1056/NEJMoa1205127.
1026. Cortes JE, Kantarjian HM, Brummendorf TH, Kim DW, Turkina AG, Shen ZX, Pasquini R, Khoury HJ, Arkin S, Volkert A, Besson N, Abbas R, Wang J, Leip E, Gambacorti-Passerini C. 2011. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. Blood 118:4567–4576. https://doi.org/10.1182/blood-2011-05-355594.
1027. European Medicines Agency. 2018. Bosulif, INN—bosutinib. Product information. European Medicines Agency, Amsterdam, The Netherlands. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002373/WC500141721.pdf. Accessed August 2019.
1028. Anonymous. 2018. Bosulif (bosutinib). Prescribing information. Reference ID 4197387. Food and Drug Administration, Silver Spring, MD.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/203341s009lbl.pdf. Accessed August 2019.
1029. Knoll BM, Seiter K. 2018. Infections in patients on BCR-ABL tyrosine kinase inhibitor therapy: cases and review of the literature. Infection 46:409–418. https://doi.org/10.1007/s15010-017-1105-1.
1030. Hantschel O, Rix U, Superti-Furga G. 2008. Target spectrum of the BCR-ABL inhibitors imatinib, nilotinib and dasatinib. Leuk Lymphoma 49:615–619. https://doi.org/10.1080/10428190801896103.
1031. Khoury HJ, Cortes JE, Kantarjian HM, Gambacorti-Passerini C, Baccarani M, Kim D-W, Zaritskey A, Countouriotis A, Besson N, Leip E, Kelly V, Brümmendorf TH. 2012. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. Blood 119:3403–3412. https://doi.org/10.1182/blood-2011-11-390120.
1032. Seggewiss R, Lore K, Greiner E, Magnusson MK, Price DA, Douek DC, Dunbar CE, Wiestner A. 2005. Imatinib inhibits T-cell receptor-mediated T-cell proliferation and activation in a dose-dependent manner. Blood 105:2473–2479. https://doi.org/10.1182/blood-2004-07-2527.
1033. Dietz AB, Souan L, Knutson GJ, Bulur PA, Litzow MR, Vuk-Pavlović S. 2004. Imatinib mesylate inhibits T-cell proliferation in vitro and delayed-type hypersensitivity in vivo. Blood 104:1094–1099. https://doi.org/10.1182/blood-2003-12-4266.
1034. Appel S, Boehmler AM, Grünebach F, Müller MR, Rupf A, Weck MM, Hartmann U, Reichardt VL, Kanz L, Brümmendorf TH, Brossart P. 2004. Imatinib mesylate affects the development and function of dendritic cells generated from CD34$^+$ peripheral blood progenitor cells. Blood 103:538–544. https://doi.org/10.1182/blood-2003-03-0975.
1035. Fei F, Yu Y, Schmitt A, Rojewski MT, Chen B, Greiner J, Gotz M, Guillaume P, Dohner H, Bunjes D, Schmitt M. 2008. Dasatinib exerts an immunosuppressive effect on CD8+ T cells specific for viral and leukemia antigens. Exp Hematol 36:1297–1308. https://doi.org/10.1016/j.exphem.2008.05.002.
1036. Chen J, Schmitt A, Chen B, Rojewski M, RuBeler V, Fei F, Yu Y, Yu X, Ringhoffer M, von Harsdorf S, Greiner J, Gbtzz M, Guillaume P, Dbhner H, Bunjes D, Schmitt M. 2008. Nilotinib hampers the proliferation and function of CD8+ T lymphocytes through inhibition of T cell receptor signalling. J Cell Mol Med 12:2107–2118. https://doi.org/10.1111/j.1582-4934.2008.00234.x.
1037. de Lavallade H, Khoder A, Hart M, Sarvaria A, Sekine T, Alsuliman A, Mielke S, Bazeos A, Stringaris K, Ali S, Milojkovic D, Foroni L, Chaidos A, Cooper N, Gabriel I, Apperley J, Belsey S, Flanagan RJ, Goldman J, Shpall EJ, Kelleher P, Marin D, Rezvani K. 2013. Tyrosine kinase inhibitors impair B-cell immune responses in CML through off-target inhibition of kinases important for cell signaling. Blood 122:227–238. https://doi.org/10.1182/blood-2012-11-465039.
1038. Fei F, Yu Y, Schmitt A, Rojewski MT, Chen B, Götz M, Döhner H, Bunjes D, Schmitt M. 2009. Dasatinib inhibits the proliferation and function of CD4+CD25+ regulatory T cells. Br J Haematol 144:195–205. https://doi.org/10.1111/j.1365-2141.2008.07433.x.
1039. Chen J, Schmitt A, Giannopoulos K, Chen B, Rojewski M, Dohner H, Bunjes D, Schmitt M. 2007. Imatinib impairs the proliferation and function of CD4+CD25+ regulatory T cells in a dose-dependent manner. Int J Oncol 31:1133–1139. https://doi.org/10.3892/ijo.31.5.1133.
1040. Rajala HLM, Missiry ME, Ruusila A, Koskenvesa P, Brummendorf TH, Gjertsen BT, Janssen J, Lotfi K, Markevarn B, Olsson-Stromberg U, Stenke L, Stentoft J, Richter J, Hjorth-Hansen H, Kreutzman A, Mustjoki S. 2017. Tyrosine kinase inhibitor therapy-induced changes in humoral immunity in patients with chronic myeloid leukemia. J Cancer Res Clin Oncol 143:1543–1554. https://doi.org/10.1007/s00432-017-2378-6.
1041. Schade AE, Schieven GL, Townsend R, Jankowska AM, Susulic V, Zhang R, Szpurka H, Maciejewski JP. 2008. Dasatinib, a small-molecule protein tyrosine kinase inhibitor, inhibits T-cell activation and proliferation. Blood 111:1366–1377. https://doi.org/10.1182/blood-2007-04-084814.
1042. Blake S, Hughes TP, Mayrhofer G, Lyons AB. 2008. The Src/ABL kinase inhibitor dasatinib (BMS-354825) inhibits function of normal human T-lymphocytes in vitro. Clin Immunol 127:330–339. https://doi.org/10.1016/j.clim.2008.02.006.
1043. Ikeda K, Shiga Y, Takahashi A, Kai T, Kimura H, Takeyama K, Noji H, Ogawa K, Nakamura A, Ohira H, Sato Y, Maruyama Y. 2006. Fatal hepatitis B virus reactivation in a chronic myeloid leukemia patient during imatinib mesylate treatment. Leuk Lymphoma 47:155–157. https://doi.org/10.1080/14639230500236818.
1044. Kang BW, Lee SJ, Moon JH, Kim SN, Chae YS, Kim JG, Hwang YJ, Sohn SK. 2009. Chronic myeloid leukemia patient manifesting fatal hepatitis B virus reactivation during treatment with imatinib rescued by liver transplantation: case report and literature review. Int J Hematol 90:383–387. https://doi.org/10.1007/s12185-009-0386-2.
1045. Lai GM, Yan SL, Chang CS, Tsai CY. 2013. Hepatitis B reactivation in chronic myeloid leukemia patients receiving tyrosine kinase inhibitor. World J Gastroenterol 19:1318–1321. https://doi.org/10.3748/wjg.v19.i8.1318.
1046. Lakhani S, Davidson L, Priebat DA, Sherker AH. 2008. Reactivation of chronic hepatitis B infection related to imatinib mesylate therapy. Hepatol Int 2:498–499. https://doi.org/10.1007/s12072-008-9099-5.
1047. Ando T, Kojima K, Isoda H, Eguchi Y, Honda T, Ishigami M, Kimura S. 2015. Reactivation of resolved infection with the hepatitis B virus immune escape mutant G145R during dasatinib treatment for chronic myeloid leukemia. Int J Hematol 102:379–382. https://doi.org/10.1007/s12185-015-1788-y.
1048. Thia TJ, Tan HH, Chuah TH, Chow WC, Lui HF. 2008. Imatinib mesylate-related fatal acute hepatic failure in a patient with chronic myeloid leukaemia and chronic hepatitis B infection. Singapore Med J 49:e86–e89.
1049. Chang C-S, Tsai C-Y, Yan S-L. 2017. Hepatitis B reactivation in patients receiving targeted therapies. Hematology 22:592–598. https://doi.org/10.1080/10245332.2017.1321882.
1050. Sanagawa A, Hotta Y, Kataoka T, Maeda Y, Kondo M, Kawade Y, Ogawa Y, Nishikawa R, Tohkin M, Kimura K. 2018. Hepatitis B infection reported with cancer chemotherapy: analyzing the US FDA Adverse Event Reporting System. Cancer Med 7:2269–2279. https://doi.org/10.1002/cam4.1429.
1051. Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT. 2015. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology 148:215–219. https://doi.org/10.1053/j.gastro.2014.10.039.
1052. Druker BJ, Guilhot F, O'Brien SG, Gathmann I, Kantarjian H, Gattermann N, Deininger MW, Silver RT, Goldman JM, Stone RM, Cervantes F, Hochhaus A, Powell BL, Gabrilove JL, Rousselot P, Reiffers J, Cornelissen JJ, Hughes T, Agis H, Fischer T, Verhoef G, Shepherd J, Saglio G, Gratwohl A, Nielsen JL, Radich JP, Simonsson B, Taylor K, Baccarani M, So C, Letvak L, Larson RA. 2006. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med 355:2408–2417. https://doi.org/10.1056/NEJMoa062867.
1053. Cortes JE, Baccarani M, Guilhot F, Druker BJ, Branford S, Kim D-W, Pane F, Pasquini R, Goldberg SL, Kalaycio M, Moiraghi B, Rowe JM, Tothova E, De Souza C, Rudoltz M, Yu R, Krahnke T, Kantarjian HM, Radich JP, Hughes TP. 2010. Phase III, randomized, open-label study of daily imatinib mesylate 400 mg versus 800 mg in patients with newly diagnosed, previously untreated chronic myeloid leukemia in chronic phase using molecular end points: tyrosine kinase inhibitor optimization and selectivity study. J Clin Oncol 28:424–430. https://doi.org/10.1200/JCO.2009.25.3724.
1054. Demetri GD, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ, Heinrich MC, Tuveson DA, Singer S, Janicek M, Fletcher JA, Silverman SG, Silberman SL, Capdeville R, Kiese B, Peng B, Dimitrijevic S, Druker BJ, Corless C, Fletcher CD, Joensuu H. 2002. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 347:472–480. https://doi.org/10.1056/NEJMoa020461.
1055. Blanke CD, Rankin C, Demetri GD, Ryan CW, von Mehren M, Benjamin RS, Raymond AK, Bramwell VH, Baker LH, Maki RG, Tanaka M, Hecht JR, Heinrich MC, Fletcher CD, Crowley JJ, Borden EC. 2008. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. J Clin Oncol 26:626–632. https://doi.org/10.1200/JCO.2007.13.4452.
1056. Heinrich MC, Joensuu H, Demetri GD, Corless CL, Apperley J, Fletcher JA, Soulieres D, Dirnhofer S, Harlow A, Town A, McKinley A, Supple SG, Seymour J, Di Scala L, van Oosterom A, Herrmann R, Nikolova Z, McArthur AG, Imatinib Target Exploration Consortium Study B2225. 2008. Phase II, open-label study evaluating the activity of imatinib in treating life-threatening malignancies known to be associated with

imatinib-sensitive tyrosine kinases. Clin Cancer Res 14:2717–2725. https://doi.org/10.1158/1078-0432.CCR-07-4575.
1057. Mattiuzzi GN, Cortes JE, Talpaz M, Reuben J, Rios MB, Shan J, Kontoyiannis D, Giles FJ, Raad I, Verstovsek S, Ferrajoli A, Kantarjian HM. 2003. Development of varicella-zoster virus infection in patients with chronic myelogenous leukemia treated with imatinib mesylate. Clin Cancer Res 98:1430–1480. https://doi.org/10.1002/cncr.11665.
1058. Breccia M, Girmenia C, Latagliata R, Loglisci G, Santopietro M, Federico V, Petrucci L, Serrao A, Salaroli A, Alimena G. 2011. Low incidence rate of opportunistic and viral infections during imatinib treatment in chronic myeloid leukemia patients in early and late chronic phase. Mediterr J Hematol Infect Dis 3:e2011021. https://doi.org/10.4084/mjhid.2011.021.
1059. Quixada A, Filho PA, Filho TP, Duarte FB, Moreira-Nunes CA, Lemes RP. 2016. Pancytopenia during tyrosine kinase inhibitor treatment—coexistence of chronic myeloid leukemia and visceral leishmaniasis: a case report. J Med Case Rep 10:207. https://doi.org/10.1186/s13256-016-0978-4.
1060. Anthony N, Shanks J, Terebelo H. 2010. Occurrences of opportunistic infections in chronic myelogenous leukemia patients treated with imatinib mesylate. Leuk Res 34:1250–1251. https://doi.org/10.1016/j.leukres.2010.05.019.
1061. Ferrand H, Tamburini J, Mouly S, Bouscary D, Bergmann JF. 2005. Listeria monocytogenes meningitis following imatinib mesylate-induced monocytopenia in a patient with chronic myeloid leukemia. Clin Infect Dis 41:1684–1685. https://doi.org/10.1086/498031.
1062. Daniels JMA, Vonk-Noordegraaf A, Janssen J, Postmus PE, van Altena R. 2009. Tuberculosis complicating imatinib treatment for chronic myeloid leukaemia. Eur Respir J 33:670–672. https://doi.org/10.1183/09031936.00025408.
1063. Senn L, Kovacsovics T, Tarr PE, Meylan P. 2009. Peritoneal tuberculosis after imatinib therapy. Arch Intern Med 169:312–316. https://doi.org/10.1001/archinternmed.2008.581.
1064. Takashima M, Igaki N, Matsuda T, Ohyama M, Kanda S, Tamada F, Goto T. 2005. Malignant gastrointestinal stromal tumor of the small intestine complicated with pulmonary tuberculosis during treatment with imatinib mesylate. Intern Med 44:114–119. https://doi.org/10.2169/internalmedicine.44.114.
1065. Shah NP, Kantarjian HM, Kim DW, Rea D, Dorlhiac-Llacer PE, Milone JH, Vela-Ojeda J, Silver RT, Khoury HJ, Charbonnier A, Khoroshko N, Paquette RL, Deininger M, Collins RH, Otero I, Hughes T, Bleickardt E, Strauss L, Francis S, Hochhaus A. 2008. Intermittent target inhibition with dasatinib 100 mg once daily preserves efficacy and improves tolerability in imatinib-resistant and -intolerant chronic-phase chronic myeloid leukemia. J Clin Oncol 26:3204–3212. https://doi.org/10.1200/JCO.2007.14.9260.
1066. Shah NP, Kim DW, Kantarjian H, Rousselot P, Llacer PE, Enrico A, Vela-Ojeda J, Silver RT, Khoury HJ, Muller MC, Lambert A, Matloub Y, Hochhaus A. 2010. Potent, transient inhibition of BCR-ABL with dasatinib 100 mg daily achieves rapid and durable cytogenetic responses and high transformation-free survival rates in chronic phase chronic myeloid leukemia patients with resistance, suboptimal response or intolerance to imatinib. Haematologica 95:232–240. https://doi.org/10.3324/haematol.2009.011452.
1067. Shah NP, Rousselot P, Schiffer C, Rea D, Cortes JE, Milone J, Mohamed H, Healey D, Kantarjian H, Hochhaus A, Saglio G. 2016. Dasatinib in imatinib-resistant or -intolerant chronic-phase, chronic myeloid leukemia patients: 7-year follow-up of study CA180-034. Am J Hematol 91:869–874. https://doi.org/10.1002/ajh.24423.
1068. Kantarjian H, Shah NP, Hochhaus A, Cortes J, Shah S, Ayala M, Moiraghi B, Shen Z, Mayer J, Pasquini R, Nakamae H, Huguet F, Boque C, Chuah C, Bleickardt E, Bradley-Garelik MB, Zhu C, Szatrowski T, Shapiro D, Baccarani M. 2010. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 362:2260–2270. https://doi.org/10.1056/NEJMoa1002315.
1069. Seiter K, Latremouille-Viau D, Guerin A, Ndife B, Habucky K, Tang DH, Pivneva I, Gagnon-Sanschagrin P, Joseph GJ. 2018. Burden of infections among chronic myeloid leukemia patients receiving dasatinib or nilotinib: a real-world retrospective healthcare claims study in the United States. Adv Ther 35:1671–1685. https://doi.org/10.1007/s12325-018-0772-3.
1070. Davalos F, Chaucer B, Zafar W, Salman S, Nfonoyim J. 2016. Dasatinib-induced CMV hepatitis in an immunocompetent patient: a rare complication of a common drug. Transl Oncol 9:248–250. https://doi.org/10.1016/j.tranon.2015.12.004.
1071. Prestes DP, Arbona E, Nevett-Fernandez A, Woolley AE, Ho VT, Koo S, Baden LR, Koreth J, Hammond SP, Issa NC, Marty FM. 2017. Dasatinib use and risk of cytomegalovirus reactivation after allogeneic hematopoietic-cell transplantation. Clin Infect Dis 65:510–513. https://doi.org/10.1093/cid/cix325.
1072. Yassin MA, Nashwan AJ, Soliman AT, Yousif A, Moustafa A, AlBattah A, Mohamed SF, Mudawi DS, Elkourashy S, Asaari DR, Gutierrez HL, Almusharaf M, Hussein RM, Moustafa AH, Derhoubi HE, Boukhris S, Kohla S, AlDewik N. 2015. Cytomegalovirus-induced hemorrhagic colitis in a patient with chronic myeloid leukemia (chronic phase) on dasatinib as an upfront therapy. Clin Med Insights Case Rep 8:77–81. https://doi.org/10.4137/CCRep.S25327.
1073. Choi JK, Cho SY, Choi SM, Kim GH, Lee SE, Lee S, Kim DW, Lee DG. 2018. Cytomegalovirus colitis during dasatinib treatment for patients with hematologic malignancy: case series and literature review. Infect Chemother 50:153–159. https://doi.org/10.3947/ic.2018.50.2.153.
1074. Saglio G, Kim D-W, Issaragrisil S, Le Coutre P, Etienne G, Lobo C, Pasquini R, Clark RE, Hochhaus A, Hughes TP, Gallagher N, Hoenekopp A, Dong M, Haque A, Larson RA, Kantarjian HM. 2010. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med 362:2251–2259. https://doi.org/10.1056/NEJMoa0912614.
1075. Larson RA, Hochhaus A, Hughes TP, Clark RE, Etienne G, Kim DW, Flinn IW, Kurokawa M, Moiraghi B, Yu R, Blakesley RE, Gallagher NJ, Saglio G, Kantarjian HM. 2012. Nilotinib vs imatinib in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: ENESTnd 3-year follow-up. Leukemia 26:2197–2203. https://doi.org/10.1038/leu.2012.134.
1076. Hochhaus A, Rosti G, Cross NCP, Steegmann JL, Le Coutre P, Ossenkoppele G, Petrov L, Masszi T, Hellmann A, Griskevicius L, Wiktor-Jedrzejczak W, Rea D, Coriu D, Brummendorf TH, Porkka K, Saglio G, Gastl G, Muller MC, Schuld P, Di Matteo P, Pellegrino A, Dezzani L, Mahon FX, Baccarani M, Giles FJ. 2016. Frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: results from the European ENEST1st study. Leukemia 30:57–64. https://doi.org/10.1038/leu.2015.270.
1077. Nicolini FE, Turkina A, Shen Z-X, Gallagher N, Jootar S, Powell BL, De Souza C, Zheng M, Szczudlo T, Le Coutre P. 2012. Expanding Nilotinib Access in Clinical Trials (ENACT). Cancer 118:118–126. https://doi.org/10.1002/cncr.26249.
1078. Le Coutre PD, Giles FJ, Hochhaus A, Apperley JF, Ossenkoppele GJ, Blakesley R, Shou Y, Gallagher NJ, Baccarani M, Cortes J, Kantarjian HM. 2012. Nilotinib in patients with Ph+ chronic myeloid leukemia in accelerated phase following imatinib resistance or intolerance: 24-month follow-up results. Leukemia 26:1189–1194. https://doi.org/10.1038/leu.2011.323.
1079. Al-Ameri AM, Cortes JE, Kantarjian H, Burton E, Quintas-Cardama A, Jabbour E, Badoux X, Brien S, Mattiuzzi G. 2010. Infectious events in patients with chronic myeloid leukemia treated with nilotinib as a front line therapy and after imatinib failure. Blood 116:1233. https://doi.org/10.1182/blood.V116.21.1233.1233.
1080. Go SI, Lee WS, Lee GW, Kang JH, Kang MH, Lee JH, Kim HG. 2013. Nilotinib-induced interstitial lung disease. Int J Hematol 98:361–365. https://doi.org/10.1007/s12185-013-1398-5.
1081. Cortes JE, Kim DW, Pinilla-Ibarz J, Le Coutre P, Paquette R, Chuah C, Nicolini FE, Apperley JF, Khoury HJ, Talpaz M, DiPersio J, DeAngelo DJ, Abruzzese E, Rea D, Baccarani M, Muller MC, Gambacorti-Passerini C, Wong S, Lustgarten S, Rivera VM, Clackson T, Turner CD, Haluska FG, Guilhot F, Deininger MW, Hochhaus A, Hughes T, Goldman JM, Shah NP, Kantarjian H. 2013. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med 369:1783–1796. https://doi.org/10.1056/NEJMoa1306494.
1082. Jain P, Kantarjian H, Jabbour E, Gonzalez GN, Borthakur G, Pemmaraju N, Daver N, Gachimova E, Ferrajoli A, Kornblau S, Ravandi F, O'Brien S, Cortes J. 2015. Ponatinib as first-line treatment for patients with chronic myeloid leukaemia in chronic phase: a phase 2 study. Lancet Haematology 2:e376–e383. https://doi.org/10.1016/S2352-3026(15)00127-1.
1083. Lipton JH, Chuah C, Guerci-Bresler A, Rosti G, Simpson D, Assouline S, Etienne G, Nicolini FE, Le Coutre P, Clark RE, Stenke L, Andorsky D, Oehler V, Lustgarten S, Rivera VM, Clackson T, Haluska FG, Baccarani M, Cortes JE, Guilhot F, Hochhaus A, Hughes T, Kantarjian HM, Shah NP, Talpaz M, Deininger MW. 2016. Ponatinib versus imatinib for newly diagnosed chronic myeloid leukaemia: an international, ran-

domised, open-label, phase 3 trial. Lancet Oncol 17:612–621. https://doi.org/10.1016/S1470-2045(16)00080-2.
1084. Cortes JE, Khoury HJ, Kantarjian HM, Lipton JH, Kim DW, Schafhausen P, Matczak E, Leip E, Noonan K, Brummendorf TH, Gambacorti-Passerini C. 2016. Long-term bosutinib for chronic phase chronic myeloid leukemia after failure of imatinib plus dasatinib and/or nilotinib. Am J Hematol 91:1206–1214. https://doi.org/10.1002/ajh.24536.
1085. Cortes JE, Kim DW, Kantarjian HM, Brummendorf TH, Dyagil I, Griskevicius L, Malhotra H, Powell C, Gogat K, Countouriotis AM, Gambacorti-Passerini C. 2012. Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: results from the BELA trial. J Clin Oncol 30:3486–3492. https://doi.org/10.1200/JCO.2011.38.7522.
1086. Brummendorf TH, Cortes JE, de Souza CA, Guilhot F, Duvillie L, Pavlov D, Gogat K, Countouriotis AM, Gambacorti-Passerini C. 2015. Bosutinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukaemia: results from the 24-month follow-up of the BELA trial. Br J Haematol 168:69–81. https://doi.org/10.1111/bjh.13108.
1087. Gambacorti-Passerini C, Cortes JE, Lipton JH, Dmoszynska A, Wong RS, Rossiev V, Pavlov D, Gogat Marchant K, Duvillié L, Khattry N, Kantarjian HM, Brümmendorf TH. 2014. Safety of bosutinib versus imatinib in the phase 3 BELA trial in newly diagnosed chronic phase chronic myeloid leukemia. Am J Hematol 89:947–953. https://doi.org/10.1002/ajh.23788.
1088. European Medicines Agency. 2016. PRAC recommendations on signals. Adopted at the PRAC meeting of 8–11 February 2016. European Medicines Agency, Amsterdam, The Netherlands. http://www.ema.europa.eu/docs/en_GB/document_library/PRAC_recommendation_on_signal/2016/02/WC500202306.pdf. Accessed 23 July 2019.
1089. European Association for the Study of the Liver. 2017. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol 67:370–398. https://doi.org/10.1016/j.jhep.2012.09.013.
1090. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS, Jr, Bzowej NH, Wong JB. 2018. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 67:1560–1599. https://doi.org/10.1002/hep.29800.
1091. Weinblatt ME, Kavanaugh A, Genovese MC, Musser TK, Grossbard EB, Magilavy DB. 2010. An oral spleen tyrosine kinase (Syk) inhibitor for rheumatoid arthritis. N Engl J Med 363:1303–1312. https://doi.org/10.1056/NEJMoa1000500.
1092. Kunwar S, Devkota AR, Ghimire DK. 2016. Fostamatinib, an oral spleen tyrosine kinase inhibitor, in the treatment of rheumatoid arthritis: a meta-analysis of randomized controlled trials. Rheumatol Int 36:1077–1087. https://doi.org/10.1007/s00296-016-3482-7.
1093. Braselmann S, Taylor V, Zhao H, Wang S, Sylvain C, Baluom M, Qu K, Herlaar E, Lau A, Young C, Wong BR, Lovell S, Sun T, Park G, Argade A, Jurcevic S, Pine P, Singh R, Grossbard EB, Payan DG, Masuda ES. 2006. R406, an orally available spleen tyrosine kinase inhibitor blocks Fc receptor signaling and reduces immune complex-mediated inflammation. J Pharmacol Exp Ther 319:998–1008. https://doi.org/10.1124/jpet.106.109058.
1094. Podolanczuk A, Lazarus AH, Crow AR, Grossbard E, Bussel JB. 2009. Of mice and men: an open-label pilot study for treatment of immune thrombocytopenic purpura by an inhibitor of Syk. Blood 113:3154–3160. https://doi.org/10.1182/blood-2008-07-166439.
1095. Anonymous. 2018. Tavalisse (fostamatinib disodium hexahydrate). Reference ID 4249943. Prescribing information. Food and Drug Administration, Silver Spring, MD. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209299lbl.pdf. Accessed August 2019.
1096. Platt AM, Benson RA, McQueenie R, Butcher JP, Braddock M, Brewer JM, McInnes IB, Garside P. 2015. The active metabolite of spleen tyrosine kinase inhibitor fostamatinib abrogates the CD4(+) T cell-priming capacity of dendritic cells. Rheumatology (Oxford) 54:169–177. https://doi.org/10.1093/rheumatology/keu273.
1097. Weinblatt ME, Kavanaugh A, Burgos-Vargas R, Dikranian AH, Medrano-Ramirez G, Morales-Torres JL, Murphy FT, Musser TK, Straniero N, Vicente-Gonzales AV, Grossbard E. 2008. Treatment of rheumatoid arthritis with a Syk kinase inhibitor: a twelve-week, randomized, placebo-controlled trial. Arthritis Rheum 58:3309–3318. https://doi.org/10.1002/art.23992.
1098. Weinblatt ME, Genovese MC, Ho M, Hollis S, Rosiak-Jedrychowicz K, Kavanaugh A, Millson DS, Leon G, Wang M, van der Heijde D. 2014. Effects of fostamatinib, an oral spleen tyrosine kinase inhibitor, in rheumatoid arthritis patients with an inadequate response to methotrexate: results from a phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheumatol 66:3255–3264. https://doi.org/10.1002/art.38851.
1099. Genovese MC, van der Heijde DM, Keystone EC, Spindler AJ, Benhamou C, Kavanaugh A, Fudman E, Lampl K, O'Brien C, Duffield EL, Poiley J, Weinblatt ME. 2014. A phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of 2 dosing regimens of fostamatinib in patients with rheumatoid arthritis with an inadequate response to a tumor necrosis factor-alpha antagonist. J Rheumatol 41:2120–2128. https://doi.org/10.3899/jrheum.140238.
1100. Bussel J, Arnold DM, Grossbard E, Mayer J, Treliński J, Homenda W, Hellmann A, Windyga J, Sivcheva L, Khalafallah AA, Zaja F, Cooper N, Markovtsov V, Zayed H, Duliege A-M. 2018. Fostamatinib for the treatment of adult persistent and chronic immune thrombocytopenia: results of two phase 3, randomized, placebo-controlled trials. Am J Hematol 93:921–930. https://doi.org/10.1002/ajh.25125.
1101. Taylor PC, Genovese MC, Greenwood M, Ho M, Nasonov E, Oemar B, Stoilov R, Vencovsky J, Weinblatt M. 2015. OSKIRA-4: a phase IIb randomised, placebo-controlled study of the efficacy and safety of fostamatinib monotherapy. Ann Rheum Dis 74:2123–2129. https://doi.org/10.1136/annrheumdis-2014-205361.
1102. Camidge DR, Bang Y-J, Kwak EL, Iafrate AJ, Varella-Garcia M, Fox SB, Riely GJ, Solomon B, Ou S-H, Kim D-W, Salgia R, Fidias P, Engelman JA, Gandhi L, Jänne PA, Costa DB, Shapiro GI, LoRusso P, Ruffner K, Stephenson P, Tang Y, Wilner K, Clark JW, Shaw AT. 2012. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol 13:1011–1019. https://doi.org/10.1016/S1470-2045(12)70344-3.
1103. Weickhardt AJ, Camidge DR. 2011. The therapeutic potential of anaplastic lymphoma kinase inhibitors in lung cancer: rationale and clinical evidence. Clin Invest 1:1119–1126. https://doi.org/10.4155/cli.11.92.
1104. Solomon B, Varella-Garcia M, Camidge DR. 2009. ALK gene rearrangements: a new therapeutic target in a molecularly defined subset of non-small cell lung cancer. J Thorac Oncol 4:1450–1454. https://doi.org/10.1097/JTO.0b013e3181c4dedb.
1105. European Medicines Agency. 2018. Xalkori, INN—crizotinib. Product information. European Medicines Agency, Amsterdam, The Netherlands. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002489/WC500134759.pdf. Accessed August 2019.
1106. Anonymous. 2018. Xalkori (crizotinib). Prescribing information. Reference ID 4216933. Food and Drug Administration, Silver Spring, MD. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/202570s023lbl.pdf. Accessed August 2019.
1107. Therapeutic Goods Administration. 2018. Australian product information—Xalkori (crizotinib). Therapeutic Goods Administration, Woden, Australia. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-02261-1. Accessed August 2019.
1108. European Medicines Agency. 2018. Zykadia, INN—ceritinib. Product information. European Medicines Agency, Amsterdam, The Netherlands. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003819/WC500187504.pdf. Accessed August 2019.
1109. Anonymous. 2018. Zykadia (ceritinib). Prescribing information. Reference ID 3497722. Food and Drug Administration, Silver Spring, MD. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205755s000lbl.pdf. Accessed August 2019.
1110. Therapeutic Goods Administration. 2018. Australian product information—Zykadia (ceritinib). Therapeutic Goods Administration, Woden, Australia. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2016-PI-01610-1. Accessed August 2019.
1111. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, Ou SI, Perol M, Dziadziuszko R, Rosell R, Zeaiter A, Mitry E, Golding S, Balas B, Noe J, Morcos PN, Mok T. 2017. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. N Engl J Med 377:829–838. https://doi.org/10.1056/NEJMoa1704795.
1112. European Medicines Agency. 2018. Alecensa, INN—alectinib. Product information. European Medicines Agency, Amsterdam, The Netherlands. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004164/WC500225707.pdf. Accessed August 2019.

1113. Anonymous. 2017. Alecensa (alectinib). Prescribing information. Reference ID 4177381. Food and Drug Administration, Silver Spring, MD. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208434s003lbl.pdf. Accessed August 2019.
1114. Therapeutic Goods Administration. 2018. Australian product information—Alecensa (alectinib). Therapeutic Goods Administration, Woden, Australia. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2017-PI-01495-1&d=201809061016933. Accessed August 2019.
1115. Shaw AT, Kim D-W, Nakagawa K, Seto T, Crinó L, Ahn M-J, De Pas T, Besse B, Solomon BJ, Blackhall F, Wu Y-L, Thomas M, O'Byrne KJ, Moro-Sibilot D, Camidge DR, Mok T, Hirsh V, Riely GJ, Iyer S, Tassell V, Polli A, Wilner KD, Jänne PA. 2013. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 368:2385–2394. https://doi.org/10.1056/NEJMoa1214886.
1116. Gettinger SN, Bazhenova LA, Langer CJ, Salgia R, Gold KA, Rosell R, Shaw AT, Weiss GJ, Tugnait M, Narasimhan NI, Dorer DJ, Kerstein D, Rivera VM, Clackson T, Haluska FG, Camidge DR. 2016. Activity and safety of brigatinib in ALK-rearranged non-small-cell lung cancer and other malignancies: a single-arm, open-label, phase 1/2 trial. Lancet Oncol 17:1683–1696. https://doi.org/10.1016/S1470-2045(16)30392-8.
1117. Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, Felip E, Cappuzzo F, Paolini J, Usari T, Iyer S, Reisman A, Wilner KD, Tursi J, Blackhall F, PROFILE 1014 Investigators. 2014. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 371:2167–2177. https://doi.org/10.1056/NEJMoa1408440.
1118. Kim DW, Mehra R, Tan DS, Felip E, Chow LQ, Camidge DR, Vansteenkiste J, Sharma S, De Pas T, Riely GJ, Solomon BJ, Wolf J, Thomas M, Schuler M, Liu G, Santoro A, Sutradhar S, Li S, Szczudlo T, Yovine A, Shaw AT. 2016. Activity and safety of ceritinib in patients with ALK-rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial. Lancet Oncol 17:452–463. https://doi.org/10.1016/S1470-2045(15)00614-2.
1119. Ikeda S, Yoshioka H, Arita M, Sakai T, Sone N, Nishiyama A, Niwa T, Hotta M, Tanaka T, Ishida T. 2015. Interstitial lung disease induced by alectinib (CH5424802/RO5424802). Jpn J Clin Oncol 45:221–224. https://doi.org/10.1093/jjco/hyu183.
1120. Yamamoto Y, Okamoto I, Otsubo K, Iwama E, Hamada N, Harada T, Takayama K, Nakanishi Y. 2015. Severe acute interstitial lung disease in a patient with anaplastic lymphoma kinase rearrangement-positive non-small cell lung cancer treated with alectinib. Invest New Drugs 33:1148–1150. https://doi.org/10.1007/s10637-015-0284-9.
1121. Yoneshima Y, Okamoto I, Arimura-Omori M, Kimura S, Hidaka-Fujimoto N, Iwama E, Harada T, Takayama K, Nakanishi Y. 2015. Infected complex renal cysts during crizotinib therapy in a patient with non-small cell lung cancer positive for ALK rearrangement. Invest New Drugs 33:510–512. https://doi.org/10.1007/s10637-014-0195-1.
1122. Shaw AT, Ou SH, Bang YJ, Camidge DR, Solomon BJ, Salgia R, Riely GJ, Varella-Garcia M, Shapiro GI, Costa DB, Doebele RC, Le LP, Zheng Z, Tan W, Stephenson P, Shreeve SM, Tye LM, Christensen JG, Wilner KD, Clark JW, Iafrate AJ. 2014. Crizotinib in ROS1-rearranged non-small-cell lung cancer. N Engl J Med 371:1963–1971. https://doi.org/10.1056/NEJMoa1406766.
1123. Soria J-C, Tan DSW, Chiari R, Wu Y-L, Paz-Ares L, Wolf J, Geater SL, Orlov S, Cortinovis D, Yu C-J, Hochmair M, Cortot AB, Tsai C-M, Moro-Sibilot D, Campelo RG, McCulloch T, Sen P, Dugan M, Pantano S, Branle F, Massacesi C, de Castro G. 2017. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label phase 3 study. Lancet 389:917–929. https://doi.org/10.1016/S0140-6736(17)30123-X.
1124. Shaw AT, Kim TM, Crino L, Gridelli C, Kiura K, Liu G, Novello S, Bearz A, Gautschi O, Mok T, Nishio M, Scagliotti G, Spigel DR, Deudon S, Zheng C, Pantano S, Urban P, Massacesi C, Viraswami-Appanna K, Felip E. 2017. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 18:874–886. https://doi.org/10.1016/S1470-2045(17)30339-X.
1125. Hida T, Nokihara H, Kondo M, Kim YH, Azuma K, Seto T, Takiguchi Y, Nishio M, Yoshioka H, Imamura F, Hotta K, Watanabe S, Goto K, Satouchi M, Kozuki T, Shukuya T, Nakagawa K, Mitsudomi T, Yamamoto N, Asakawa T, Asabe R, Tanaka T, Tamura T. 2017. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. Lancet 390:29–39. https://doi.org/10.1016/S0140-6736(17)30565-2.
1126. Spigel DR, Reynolds C, Waterhouse D, Garon EB, Chandler J, Babu S, Thurmes P, Spira A, Jotte R, Zhu J, Lin WH, Blumenschein G, Jr. 2018. Phase 1/2 study of the safety and tolerability of nivolumab plus crizotinib for the first-line treatment of anaplastic lymphoma kinase translocation-positive advanced non-small cell lung cancer (CheckMate 370). J Thorac Oncol 13:682–688. https://doi.org/10.1016/j.jtho.2018.02.022.
1127. Millard M, Odde S, Neamati N. 2011. Integrin targeted therapeutics. Theranostics 1:154–188. https://doi.org/10.7150/thno/v01p0154.
1128. Hynes RO. 2002. A reevaluation of integrins as regulators of angiogenesis. Nat Med 8:918–921. https://doi.org/10.1038/nm0902-918.
1129. Siebers MC, ter Brugge PJ, Walboomers XF, Jansen JA. 2005. Integrins as linker proteins between osteoblasts and bone replacing materials. A critical review. Biomaterials 26:137–146. https://doi.org/10.1016/j.biomaterials.2004.02.021.
1130. Hynes RO. 2002. Integrins: bidirectional, allosteric signaling machines. Cell 110:673–687. https://doi.org/10.1016/S0092-8674(02)00971-6.
1131. Tuckwell DS, Weston SA, Humphries MJ. 1993. Integrins: a review of their structure and mechanisms of ligand binding. Symp Soc Exp Biol 47:107–136.
1132. Pucci E, Giuliani G, Solari A, Simi S, Minozzi SD, Pietrantonj C, Galea I. 2011. Natalizumab for relapsing remitting multiple sclerosis. Cochrane Database Syst Rev 2011:CD007621. https://doi.org/10.1002/14651858.CD007621.pub2.
1133. Goodin DS, Cohen BA, O'Connor P, Kappos L, Stevens JC, Therapeutics, Technology Assessment Subcommittee of the American Academy of Neurology. 2008. Assessment: the use of natalizumab (Tysabri) for the treatment of multiple sclerosis (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 71:766–773. https://doi.org/10.1212/01.wnl.0000320512.21919.d2.
1134. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, Van Assche G, Axler J, Kim HJ, Danese S, Fox I, Milch C, Sankoh S, Wyant T, Xu J, Parikh A, GEMINI 1 Study Group. 2013. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 369:699–710. https://doi.org/10.1056/NEJMoa1215734.
1135. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, Lukas M, Fedorak RN, Lee S, Bressler B, Fox I, Rosario M, Sankoh S, Xu J, Stephens K, Milch C, Parikh A, GEMINI 2 Study Group. 2013. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med 369:711–721. https://doi.org/10.1056/NEJMoa1215739.
1136. Coltoff A, Lancman G, Kim S, Steinberg A. 2018. Vedolizumab for treatment of steroid-refractory lower gastrointestinal acute graft-versus-host disease. Bone Marrow Transplant 53:900–904. https://doi.org/10.1038/s41409-018-0094-8.
1137. Floisand Y, Lazarevic VL, Maertens J, Mattsson J, Shah NN, Zachee P, Taylor A, Akbari M, Quadri S, Parfionovas A, Chen YB. 2019. Safety and effectiveness of vedolizumab in patients with steroid-refractory gastrointestinal acute graft-versus-host disease: a retrospective record review. Biol Blood Marrow Transplant 25:720–727. https://doi.org/10.1016/j.bbmt.2018.11.013.
1138. Tang MT, Keir ME, Erickson R, Stefanich EG, Fuh FK, Ramirez-Montagut T, McBride JM, Danilenko DM. 2018. Review article: nonclinical and clinical pharmacology, pharmacokinetics and pharmacodynamics of etrolizumab, an anti-beta7 integrin therapy for inflammatory bowel disease. Aliment Pharmacol Ther 47:1440–1452. https://doi.org/10.1111/apt.14631.
1139. Frampton JE, Plosker GL. 2009. Efalizumab: a review of its use in the management of chronic moderate-to-severe plaque psoriasis. Am J Clin Dermatol 10:51–72. https://doi.org/10.2165/0128071-200910010-00009.
1140. Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Vergel YB, Misso K, Light K, Chalmers R, Sculpher M, Riemsma R. 2006. Etanercept and efalizumab for the treatment of psoriasis: a systematic review. Health Technol Assess 10:1–233. https://doi.org/10.3310/hta10460.
1141. Kothary N, Diak IL, Brinker A, Bezabeh S, Avigan M, Dal Pan G. 2011. Progressive multifocal leukoencephalopathy associated with efalizumab use in psoriasis patients. J Am Acad Dermatol 65:546–551. https://doi.org/10.1016/j.jaad.2010.05.033.
1142. Talamonti M, Spallone G, Di Stefani A, Costanzo A, Chimenti S. 2011. Efalizumab. Expert Opin Drug Saf 10:239–251. https://doi.org/10.1517/14740338.2011.524925.
1143. Chaisson RE, Griffin DE. 1990. Progressive multifocal leukoencepha-

lopathy in AIDS. JAMA 264:79–82. https://doi.org/10.1001/jama.1990.03450010083036.
1144. Langer-Gould A, Atlas SW, Green AJ, Bollen AW, Pelletier D. 2005. Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. N Engl J Med 353:375–381. https://doi.org/10.1056/NEJMoa051847.
1145. Kleinschmidt-DeMasters BK, Tyler KL. 2005. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. N Engl J Med 353:369–374. https://doi.org/10.1056/NEJMoa051782.
1146. Van Assche G, Van Ranst M, Sciot R, Dubois B, Vermeire S, Noman M, Verbeeck J, Geboes K, Robberecht W, Rutgeerts P. 2005. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. N Engl J Med 353:362–368. https://doi.org/10.1056/NEJMoa051586.
1147. Ho PR, Koendgen H, Campbell N, Haddock B, Richman S, Chang I. 2017. Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: a retrospective analysis of data from four clinical studies. Lancet Neurol 16:925–933. https://doi.org/10.1016/S1474-4422(17)30282-X.
1148. Schwab N, Schneider-Hohendorf T, Melzer N, Cutter G, Wiendl H. 2017. Natalizumab-associated PML: challenges with incidence, resulting risk, and risk stratification. Neurology 88:1197–1205. https://doi.org/10.1212/WNL.0000000000003739.
1149. Bozic C, Subramanyam M, Richman S, Plavina T, Zhang A, Ticho B. 2014. Anti-JC virus (JCV) antibody prevalence in the JCV Epidemiology in MS (JEMS) trial. Eur J Neurol 21:299–304. https://doi.org/10.1111/ene.12304.
1150. Major EO, Yousry TA, Clifford DB. 2018. Pathogenesis of progressive multifocal leukoencephalopathy and risks associated with treatments for multiple sclerosis: a decade of lessons learned. Lancet Neurol 17:467–480. https://doi.org/10.1016/S1474-4422(18)30040-1.
1151. Brew BJ, Davies NW, Cinque P, Clifford DB, Nath A. 2010. Progressive multifocal leukoencephalopathy and other forms of JC virus disease. Nat Rev Neurol 6:667–679. https://doi.org/10.1038/nrneurol.2010.164.
1152. Avsenik J, Horvat Ledinek A, Šurlan Popovič K. 2017. Progressive multifocal leukoencephalopathy-immune reconstitution inflammatory syndrome (PML-IRIS) in liver transplant recipient. Mult Scler Relat Disord 17:135–137. https://doi.org/10.1016/j.msard.2017.07.018.
1153. Krey L, Raab P, Sherzay R, Berding G, Stoll M, Stangel M, Wegner F. 2019. Severe progressive multifocal leukoencephalopathy (PML) and spontaneous immune reconstitution inflammatory syndrome (IRIS) in an immunocompetent patient. Front Immunol 10:1188. https://doi.org/10.3389/fimmu.2019.01188.
1154. Marousi S, Travasarou M, Karageorgiou CE, Gheuens S, Koralnik IJ. 2012. Simultaneous PML-IRIS after discontinuation of natalizumab in a patient with MS. Neurology 79:2160. https://doi.org/10.1212/01.wnl.0000423208.11698.16.
1155. Foley J, Carillo-Infante C, Wenten M, Lavallee N, Smith J, Evans K, Haddock B, Steiner D, Ho P-R, Lee L, Vermersch P, Hutchinson M, Pozzilli C, Bloomgren G. 2016. Long-term safety of natalizumab treatment in multiple sclerosis (MS) in clinical practice: results from the tysabri global observational program in safety (TYGRIS), abstr P1229. ECTRIMS 2016 Congr, London, United Kingdom, 14 to 17 September 2016.
1156. Luthra P, Peyrin-Biroulet L, Ford AC. 2015. Systematic review and meta-analysis: opportunistic infections and malignancies during treatment with anti-integrin antibodies in inflammatory bowel disease. Aliment Pharmacol Ther 41:1227–1236. https://doi.org/10.1111/apt.13215.
1157. Cooper MD, Herrin BR. 2010. How did our complex immune system evolve? Nat Rev Immunol 10:2–3. https://doi.org/10.1038/nri2686.
1158. Valdes AM, Walter J, Segal E, Spector TD. 2018. Role of the gut microbiota in nutrition and health. BMJ 361:k2179. https://doi.org/10.1136/bmj.k2179.
1159. Pardoll DM. 2012. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 12:252–264. https://doi.org/10.1038/nrc3239.
1160. Wei SC, Duffy CR, Allison JP. 2018. Fundamental mechanisms of immune checkpoint blockade therapy. Cancer Discov 8:1069–1086. https://doi.org/10.1158/2159-8290.CD-18-0367.
1161. Juliá EP, Amante A, Pampena MB, Mordoh J, Levy EM. 2018. Avelumab, an IgG1 anti-PD-L1 immune checkpoint inhibitor, triggers NK cell-mediated cytotoxicity and cytokine production against triple negative breast cancer cells. Front Immunol 9:2140–2140. https://doi.org/10.3389/fimmu.2018.02140.
1162. Beers SA, Glennie MJ, White AL. 2016. Influence of immunoglobulin isotype on therapeutic antibody function. Blood 127:1097–1101. https://doi.org/10.1182/blood-2015-09-625343.
1163. He M, Chai Y, Qi J, Zhang CWH, Tong Z, Shi Y, Yan J, Tan S, Gao GF. 2017. Remarkably similar CTLA-4 binding properties of therapeutic ipilimumab and tremelimumab antibodies. Oncotarget 8:67129–67139. https://doi.org/10.18632/oncotarget.18004.
1164. Fujita K, Kanai O, Kim YH, Yoshida H, Mio T, Hirai T. 2017. Emerging concern of infectious diseases in lung cancer patients receiving immune checkpoint inhibitor therapy. Eur Respir J 50:OA1478. https://doi.org/10.1183/1393003.congress-2017.OA1478.
1165. Del Castillo M, Romero FA, Argüello E, Kyi C, Postow MA, Redelman-Sidi G. 2016. The spectrum of serious infections among patients receiving immune checkpoint blockade for the treatment of melanoma. Clin Infect Dis 63:1490–1493. https://doi.org/10.1093/cid/ciw539.
1166. Su Q, Zhu EC, Wu J-B, Li T, Hou Y-L, Wang D-Y, Gao Z-H. 2019. Risk of pneumonitis and pneumonia associated with immune checkpoint inhibitors for solid tumors: a systematic review and meta-analysis. Front Immunol 10:108. https://doi.org/10.3389/fimmu.2019.00108.
1167. Khunger M, Rakshit S, Pasupuleti V, Hernandez AV, Mazzone P, Stevenson J, Pennell NA, Velcheti V. 2017. Incidence of pneumonitis with use of programmed death 1 and programmed death-ligand 1 inhibitors in non-small cell lung cancer: a systematic review and meta-analysis of trials. Chest 152:271–281. https://doi.org/10.1016/j.chest.2017.04.177.
1168. Komoda K, Ross JA, Margolin K, Pal S, Dickter J, Ito J, Salgia R, Dadwal S. 2018. Infectious disease complications with use of checkpoint inhibitors in solid organ malignancies. Open Forum Infect Dis 5:S484. https://doi.org/10.1093/ofid/ofy210.1384.
1169. Man J, Ritchie G, Links M, Lord S, Lee CK. 2018. Treatment-related toxicities of immune checkpoint inhibitors in advanced cancers: a meta-analysis. Asia-Pac J Clin Oncol 14:141–152. https://doi.org/10.1111/ajco.12838.
1170. Sun Y, Lee SK, Oo TH, Rojas-Hernandez CM. 2018. Management of immune-mediated cytopenias in the era of cancer immunotherapy: a report of 4 cases. J Immunother 41:32–34. https://doi.org/10.1097/CJI.0000000000000194.
1171. Saharia KK, Petrovas C, Ferrando-Martinez S, Leal M, Luque R, Ive P, Luetkemeyer A, Havlir D, Koup RA. 2016. Tuberculosis therapy modifies the cytokine profile, maturation state, and expression of inhibitory molecules on Mycobacterium tuberculosis-specific CD4+ T-cells. PLoS One 11:e0158262. https://doi.org/10.1371/journal.pone.0158262.
1172. Day CL, Abrahams DA, Bunjun R, Stone L, de Kock M, Walzl G, Wilkinson RJ, Burgers WA, Hanekom WA. 2018. PD-1 expression on Mycobacterium tuberculosis-specific CD4 T cells is associated with bacterial load in human tuberculosis. Front Immunol 9:1995. https://doi.org/10.3389/fimmu.2018.01995.
1173. Fujita K, Terashima T, Mio T. 2016. Anti-PD1 antibody treatment and the development of acute pulmonary tuberculosis. J Thorac Oncol 11:2238–2240. https://doi.org/10.1016/j.jtho.2016.07.006.
1174. Elkington PT, Bateman AC, Thomas GJ, Ottensmeier CH. 2018. Implications of tuberculosis reactivation after immune checkpoint inhibition. Am J Respir Crit Care Med 198:1451–1453. https://doi.org/10.1164/rccm.201807-1250LE.
1175. He W, Zhang X, Li W, Kong C, Wang Y, Zhu L, Xu R, Deng G, Zhang P. 2018. Activated pulmonary tuberculosis in a patient with melanoma during PD-1 inhibition: a case report. Onco Targets Ther 11:7423–7427. https://doi.org/10.2147/OTT.S178246.
1176. Chu Y-C, Fang K-C, Chen H-C, Yeh Y-C, Tseng C-E, Chou T-Y, Lai C-L. 2017. Pericardial tamponade caused by a hypersensitivity response to tuberculosis reactivation after anti-PD-1 treatment in a patient with advanced pulmonary adenocarcinoma. J Thoracic Oncology 12:e111–e114. https://doi.org/10.1016/j.jtho.2017.03.012.
1177. Picchi H, Mateus C, Chouaid C, Besse B, Marabelle A, Michot JM, Champiat S, Voisin AL, Lambotte O. 2018. Infectious complications associated with the use of immune checkpoint inhibitors in oncology: reactivation of tuberculosis after anti PD-1 treatment. Clin Microbiol Infect 24:216–218. https://doi.org/10.1016/j.cmi.2017.12.003.
1178. Barber DL, Sakai S, Kudchadkar RR, Fling SP, Day TA, Vergara JA, Ashkin D, Cheng JH, Lundgren LM, Raabe VN, Kraft CS, Nieva JJ, Cheever MA, Nghiem PT, Sharon E. 2019. Tuberculosis following PD-1

blockade for cancer immunotherapy. Sci Transl Med 11:eaat2702. https://doi.org/10.1126/scitranslmed.aat2702.
1179. Dobler CC, Cheung K, Nguyen J, Martin A. 2017. Risk of tuberculosis in patients with solid cancers and haematological malignancies: a systematic review and meta-analysis. Eur Respir J 50:1700157. https://doi.org/10.1183/13993003.00157-2017.
1180. Cheng MP, Chakra CNA, Yansouni CP, Cnossen S, Shrier I, Menzies D, Greenaway C. 2017. Risk of active tuberculosis in patients with cancer: a systematic review and metaanalysis. Clin Infect Dis 64:635–644. https://doi.org/10.1093/cid/ciw838.
1181. Hoang TN, Paiardini M. 2019. Role of cytokine agonists and immune checkpoint inhibitors toward HIV remission. Curr Opin HIV AIDS 14:121–128. https://doi.org/10.1097/COH.0000000000000528.
1182. Husnain M, Park W, Ramos JC, Johnson TE, Chan J, Dasari A, Mudad R, Hosein PJ. 2018. Complete response to ipilimumab and nivolumab therapy in a patient with extensive extrapulmonary high-grade small cell carcinoma of the pancreas and HIV infection. J Immunother Cancer 6:66. https://doi.org/10.1186/s40425-018-0379-x.
1183. Wang J, Jebbawi F, Bellanger A-P, Beldi G, Millon L, Gottstein B. 2018. Immunotherapy of alveolar echinococcosis via PD-1/PD-L1 immune checkpoint blockade in mice. Parasite Immunol 40:e12596. https://doi.org/10.1111/pim.12596.
1184. Roussey JA, Viglianti SP, Teitz-Tennenbaum S, Olszewski MA, Osterholzer JJ. 2017. Anti-PD-1 antibody treatment promotes clearance of persistent cryptococcal lung infection in mice. J Immunol 199:3535–3546. https://doi.org/10.4049/jimmunol.1700840.
1185. Patil NK, Guo Y, Luan L, Sherwood ER. 2017. Targeting immune cell checkpoints during sepsis. Int J Mol Sci 18:2413. https://doi.org/10.3390/ijms18112413.
1186. Hotchkiss RS, Colston E, Yende S, Angus DC, Moldawer LL, Crouser ED, Martin GS, Coopersmith CM, Brakenridge S, Mayr FB, Park PK, Ye J, Catlett IM, Girgis IG, Grasela DM. 2019. Immune checkpoint inhibition in sepsis: a phase 1b randomized, placebo-controlled, single ascending dose study of antiprogrammed cell death-ligand 1 antibody (BMS-936559). Crit Care Med 47:632–642. https://doi.org/10.1097/CCM.0000000000003685.
1187. Darcy CJ, Minigo G, Piera KA, Davis JS, McNeil YR, Chen Y, Volkheimer AD, Weinberg JB, Anstey NM, Woodberry T. 2014. Neutrophils with myeloid derived suppressor function deplete arginine and constrain T cell function in septic shock patients. Crit Care 18:R163. https://doi.org/10.1186/cc14003.
1188. Mengos AE, Gastineau DA, Gustafson MP. 2019. The CD14(+)HLA-DR(lo/neg) monocyte: an immunosuppressive phenotype that restrains responses to cancer immunotherapy. Front Immunol 10:1147–1147. https://doi.org/10.3389/fimmu.2019.01147.
1189. Zitvogel L, Ma Y, Raoult D, Kroemer G, Gajewski TF. 2018. The microbiome in cancer immunotherapy: diagnostic tools and therapeutic strategies. Science 359:1366–1370. https://doi.org/10.1126/science.aar6918.
1190. Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillère R, Fluckiger A, Messaoudene M, Rauber C, Roberti MP, Fidelle M, Flament C, Poirier-Colame V, Opolon P, Klein C, Iribarren K, Mondragón L, Jacquelot N, Qu B, Ferrere G, Clémenson C, Mezquita L, Masip JR, Naltet C, Brosseau S, Kaderbhai C, Richard C, Rizvi H, Levenez F, Galleron N, Quinquis B, Pons N, Ryffel B, Minard-Colin V, Gonin P, Soria J-C, Deutsch E, Loriot Y, Ghiringhelli F, Zalcman G, Goldwasser F, Escudier B, Hellmann MD, Eggermont A, Raoult D, Albiges L, Kroemer G, Zitvogel L. 2018. Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors. Science 359:91–97. https://doi.org/10.1126/science.aan3706.
1191. Derosa L, Hellmann MD, Spaziano M, Halpenny D, Fidelle M, Rizvi H, Long N, Plodkowski AJ, Arbour KC, Chaft JE, Rouche JA, Zitvogel L, Zalcman G, Albiges L, Escudier B, Routy B. 2018. Negative association of antibiotics on clinical activity of immune checkpoint inhibitors in patients with advanced renal cell and non-small-cell lung cancer. Ann Oncol 29:1437–1444. https://doi.org/10.1093/annonc/mdy103.
1192. Huemer F, Rinnerthaler G, Westphal T, Hackl H, Hutarew G, Gampenrieder SP, Weiss L, Greil R. 2018. Impact of antibiotic treatment on immune-checkpoint blockade efficacy in advanced non-squamous non-small cell lung cancer. Oncotarget 9:16512–16520. https://doi.org/10.18632/oncotarget.24751.
1193. Zhao S, Gao G, Li W, Li X, Zhao C, Jiang T, Jia Y, He Y, Li A, Su C, Ren S, Chen X, Zhou C. 2019. Antibiotics are associated with attenuated efficacy of anti-PD-1/PD-L1 therapies in Chinese patients with advanced non-small cell lung cancer. Lung Cancer 130:10–17. https://doi.org/10.1016/j.lungcan.2019.01.017.
1194. Elkrief A, El Raichani L, Richard C, Messaoudene M, Belkaid W, Malo J, Belanger K, Miller W, Jamal R, Letarte N, Wong P, Routy B. 2019. Antibiotics are associated with decreased progression-free survival of advanced melanoma patients treated with immune checkpoint inhibitors. Oncoimmunology 8:e1568812. https://doi.org/10.1080/2162402X.2019.1568812.
1195. Ahmed J, Kumar A, Parikh K, Anwar A, Knoll BM, Puccio C, Chun H, Fanucchi M, Lim SH. 2018. Use of broad-spectrum antibiotics impacts outcome in patients treated with immune checkpoint inhibitors. Oncoimmunology 7:e1507670. https://doi.org/10.1080/2162402X.2018.1507670.
1196. Frank MM. 1989. Complement: a brief review. J Allergy Clin Immunol 84:411–420. https://doi.org/10.1016/0091-6749(89)90350-3.
1197. Mizuno M. 2006. A review of current knowledge of the complement system and the therapeutic opportunities in inflammatory arthritis. Curr Med Chem 13:1707–1717. https://doi.org/10.2174/092986706777441959.
1198. Beatty D. 1987. Meningococcal infection and complement deficiency. Pediatr Infect Dis J 6:871–872. https://doi.org/10.1097/00006454-198709000-00021.
1199. Ellison RT, III, Curd JG, Kohler PF, Reller LB, Judson FN. 1987. Underlying complement deficiency in patients with disseminated gonococcal infection. Sex Transm Dis 14:201–204. https://doi.org/10.1097/00007435-198710000-00004.
1200. Leggiadro RJ. 2003. Systemic meningococcal infection and complement deficiency. Pediatr Infect Dis J 22:760–761. https://doi.org/10.1097/01.inf.0000081587.96151.77.
1201. Ross SC, Densen P. 1984. Complement deficiency states and infection: epidemiology, pathogenesis and consequences of neisserial and other infections in an immune deficiency. Medicine (Baltimore) 63:243–273. https://doi.org/10.1097/00005792-198409000-00001.
1202. McKeage K. 2011. Eculizumab: a review of its use in paroxysmal nocturnal haemoglobinuria. Drugs 71:2327–2345. https://doi.org/10.2165/11208300-000000000-00000.
1203. Rathbone J, Kaltenthaler E, Richards A, Tappenden P, Bessey A, Cantrell A. 2013. A systematic review of eculizumab for atypical haemolytic uraemic syndrome (aHUS). BMJ Open 3:e003573. https://doi.org/10.1136/bmjopen-2013-003573.
1204. Tran D, Boucher A, Collette S, Payette A, Royal V, Senecal L. 2016. Eculizumab for the treatment of severe antibody-mediated rejection: a case report and review of the literature. Case Rep Transplant 2016:9874261. https://doi.org/10.1155/2016/9874261.
1205. Geethakumari PR, Mille P, Gulati R, Nagalla S. 2017. Complement inhibition with eculizumab for thrombotic microangiopathy rescues a living-donor kidney transplant in a patient with antiphospholipid antibody syndrome. Transfus Apher Sci 56:400–403. https://doi.org/10.1016/j.transci.2017.02.007.
1206. Kocak B, Arpali E, Demiralp E, Yelken B, Karatas C, Gorcin S, Gorgulu N, Uzunalan M, Turkmen A, Kalayoglu M. 2013. Eculizumab for salvage treatment of refractory antibody-mediated rejection in kidney transplant patients: case reports. Transplant Proc 45:1022–1025. https://doi.org/10.1016/j.transproceed.2013.02.062.
1207. Kulkarni S, Kirkiles-Smith NC, Deng YH, Formica RN, Moeckel G, Broecker V, Bow L, Tomlin R, Pober JS. 2017. Eculizumab therapy for chronic antibody-mediated injury in kidney transplant recipients: a pilot randomized controlled trial. Am J Transplant 17:682–691. https://doi.org/10.1111/ajt.14001.
1208. Yelken B, Arpali E, Gorcin S, Kocak B, Karatas C, Demiralp E, Turkmen A. 2015. Eculizumab for treatment of refractory antibody-mediated rejection in kidney transplant patients: a single-center experience. Transplant Proc 47:1754–1759. https://doi.org/10.1016/j.transproceed.2015.06.029.
1209. Iqbal Z, Wood K, Carter V, Goodship TH, Brown AL, Sheerin NS. 2015. Thrombotic microangiopathy as a cause of chronic kidney transplant dysfunction: case report demonstrating successful treatment with eculizumab. Transplant Proc 47:2258–2261. https://doi.org/10.1016/j.transproceed.2015.08.004.
1210. Kaabak M, Babenko N, Shapiro R, Zokoyev A, Dymova O, Kim E. 2018. A prospective randomized, controlled trial of eculizumab to prevent ischemia-reperfusion injury in pediatric kidney transplantation. Pediatr Transplant 22:13129. https://doi.org/10.1111/petr.13129.
1211. Kulasekararaj AG, Hill A, Rottinghaus ST, Langemeijer S, Wells R,

Gonzalez-Fernandez FA, Gaya A, Lee JW, Gutierrez EO, Piatek CI, Szer J, Risitano A, Nakao S, Bachman E, Shafner L, Damokosh AI, Ortiz S, Röth A, Peffault de Latour R. 2019. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. Blood 133:540–549. https://doi.org/10.1182/blood-2018-09-876805.

1212. Lee JW, Sicre de Fontbrune F, Wong Lee Lee L, Pessoa V, Gualandro S, Fureder W, Ptushkin V, Rottinghaus ST, Volles L, Shafner L, Aguzzi R, Pradhan R, Schrezenmeier H, Hill A. 2019. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. Blood 133:530–539. https://doi.org/10.1182/blood-2018-09-876136.
1213. Rohrer B, Long Q, Coughlin B, Renner B, Huang Y, Kunchithapautham K, Ferreira VP, Pangburn MK, Gilkeson GS, Thurman JM, Tomlinson S, Holers VM. 2010. A targeted inhibitor of the complement alternative pathway reduces RPE injury and angiogenesis in models of age-related macular degeneration. Adv Exp Med Biol 703:137–149. https://doi.org/10.1007/978-1-4419-5635-4_10.
1214. Rohrer B, Long Q, Coughlin B, Wilson RB, Huang Y, Qiao F, Tang PH, Kunchithapautham K, Gilkeson GS, Tomlinson S. 2009. A targeted inhibitor of the alternative complement pathway reduces angiogenesis in a mouse model of age-related macular degeneration. Invest Ophthalmol Vis Sci 50:3056–3064. https://doi.org/10.1167/iovs.08-2222.
1215. Gleesing J, Chiwane S, Rongkavilit C. 2012. Gonococcal septic shock associated with eculizumab treatment. Pediatr Infect Dis J 31:543. https://doi.org/10.1097/INF.0b013e3182503849.
1216. Khandelwal A, Wright JK, Pavenski K, Taggart LR. 2017. Risks of novel therapeutics: gonococcemia in an immune-suppressed patient receiving eculizumab. CMAJ 189:E1558–E1560. https://doi.org/10.1503/cmaj.170508.
1217. Reher D, Fuhrmann V, Kluge S, Nierhaus A. 2018. A rare case of septic shock due to Neisseria meningitidis serogroup B infection despite prior vaccination in a young adult with paroxysmal nocturnal haemoglobinuria receiving eculizumab. Vaccine 36:2507–2509. https://doi.org/10.1016/j.vaccine.2018.03.087.
1218. Walsh TL, Bean HR, Kaplan RB. 2018. Neisseria cinerea bacteremia in a patient receiving eculizumab: a case report. Infection 46:271–274. https://doi.org/10.1007/s15010-017-1090-4.
1219. Crew PE, McNamara L, Waldron PE, McCulley L, Jones SC, Bersoff-Matcha SJ. 2019. Unusual Neisseria species as a cause of infection in patients taking eculizumab. J Infect 78:113–118. https://doi.org/10.1016/j.jinf.2018.10.015.
1220. Crew PE, Abara WE, McCulley L, Waldron PE, Kirkcaldy RD, Weston EJ, Bernstein KT, Jones SC, Bersoff-Matcha SJ. 2019. Disseminated gonococcal infections in patients receiving eculizumab: a case series. Clin Infect Dis 69:596–600. https://doi.org/10.1093/cid/ciy958.
1221. Socie G, Caby-Tosi MP, Marantz JL, Cole A, Bedrosian CL, Gasteyger C, Mujeebuddin A, Hillmen P, Vande Walle J, Haller H. 2019. Eculizumab in paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome: 10-year pharmacovigilance analysis. Br J Haematol 185:297–310. https://doi.org/10.1111/bjh.15790.
1222. McNamara LA, Topaz N, Wang X, Hariri S, Fox L, MacNeil JR. 2017. High risk for invasive meningococcal disease among patients receiving eculizumab (Soliris) despite receipt of meningococcal vaccine. MMWR Morb Mortal Wkly Rep 66:734–737. https://doi.org/10.15585/mmwr.mm6627e1.
1223. Parikh SR, Lucidarme J, Bingham C, Warwicker P, Goodship T, Borrow R, Ladhani SN. 2017. Meningococcal B vaccine failure with a penicillin-resistant strain in a young adult on long-term eculizumab. Pediatrics 140:e20162452. https://doi.org/10.1542/peds.2016-2452.
1224. Lebel E, Trahtemberg U, Block C, Zelig O, Elinav H. 2018. Post-eculizumab meningococcaemia in vaccinated patients. Clin Microbiol Infect 24:89–90. https://doi.org/10.1016/j.cmi.2017.07.011.
1225. Bouts A, Monnens L, Davin JC, Struijk G, Spanjaard L. 2011. Insufficient protection by Neisseria meningitidis vaccination alone during eculizumab therapy. Pediatr Nephrol 26:1919–1920. https://doi.org/10.1007/s00467-011-1929-3.
1226. Alashkar F, Vance C, Herich-Terhürne D, Preising N, Dührsen U, Röth A. 2017. Serologic response to meningococcal vaccination in patients with paroxysmal nocturnal hemoglobinuria (PNH) chronically treated with the terminal complement inhibitor eculizumab. Ann Hematol 96:589–596. https://doi.org/10.1007/s00277-017-2924-y.
1227. Tubach F, Salmon D, Ravaud P, Allanore Y, Goupille P, Bréban M, Pallot-Prades B, Pouplin S, Sacchi A, Chichemanian RM, Bretagne S, Emilie D, Lemann M, Lorthololary O, Mariette X, Research Axed on Tolerance of Biotherapies Group. 2009. Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: the three-year prospective French Research Axed on Tolerance of Biotherapies registry. Arthritis Rheum 60:1884–1894. https://doi.org/10.1002/art.24632.
1228. Aikawa NE, Rosa DTA, Del Negro GMB, Moraes JCB, Ribeiro ACM, Saad CG, Silva CA, Bonfá E. 2016. Systemic and localized infection by Candida species in patients with rheumatic diseases receiving anti-TNF therapy. Rev Bras Reumatol Engl Ed 56:478–482. https://doi.org/10.1016/j.rbre.2015.08.004.
1229. Andersen NN, Jess T. 2014. Risk of infections associated with biological treatment in inflammatory bowel disease. World J Gastroenterol 20:16014–16019. https://doi.org/10.3748/wjg.v20.i43.16014.
1230. Mariette X, Gottenberg J-E, Ravaud P, Combe B. 2011. Registries in rheumatoid arthritis and autoimmune diseases: data from the French registries. Rheumatology 50:222–229. https://doi.org/10.1093/rheumatology/keq368.
1231. Burmester GR, Panaccione R, Gordon KB, McIlraith MJ, Lacerda A. 2013. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. Ann Rheum Dis 72:517–524. https://doi.org/10.1136/annrheumdis-2011-201244.
1232. Yonekura CL, Oliveira RDR, Titton DC, Ranza R, Ranzolin A, Hayata AL, Duarte A, Silveira IG, Carvalho H, Moraes JCB, Abreu MM, Valim V, Bianchi W, Brenol CV, Pereira IA, Costa I, Macieira JC, Miranda JRS, Guedes-Barbosa LS, Bertolo MB, Sauma M, Silva MBG, Freire M, Scheinberg MA, Toledo RA, Oliveira SKF, Fernandes V, Pinheiro MM, Castro G, Vieira WP, Baaklini CE, Ruffino-Netto A, Pinheiro G, Laurindo IMM, Louzada-Junior P. 2017. Incidence of tuberculosis among patients with rheumatoid arthritis using TNF blockers in Brazil: data from the Brazilian Registry of Biological Therapies in Rheumatic Diseases (Registro Brasileiro de Monitoracao de Terapias Biologicas—BiobadaBrasil). Rev Bras Reumatol Engl Ed 57(Suppl 2):477–483. https://doi.org/10.1016/j.rbre.2017.05.005.
1233. Downey C. 2016. Serious infection during etanercept, infliximab and adalimumab therapy for rheumatoid arthritis: a literature review. Int J Rheum Dis 19:536–550. https://doi.org/10.1111/1756-185X.12659.
1234. Filler SG, Yeaman MR, Sheppard DC. 2005. Tumor necrosis factor inhibition and invasive fungal infections. Clin Infect Dis 41:S208–S212. https://doi.org/10.1086/430000.
1235. Toh S, Li L, Harrold LR, Bayliss EA, Curtis JR, Liu L, Chen L, Grijalva CG, Herrinton LJ. 2012. Comparative safety of infliximab and etanercept on the risk of serious infections—does the association vary by patient characteristics? Pharmacoepidemiol Drug Saf 21:524–534. https://doi.org/10.1002/pds.3238.
1236. Sandborn WJ, Lee SD, Randall C, Gutierrez A, Schwartz DA, Ambarkhane S, Kayhan C, Pierre-Louis B, Schreiber S, Lichtenstein GR. 2014. Long-term safety and efficacy of certolizumab pegol in the treatment of Crohn's disease: 7-year results from the PRECiSE 3 study. Aliment Pharmacol Ther 40:903–916. https://doi.org/10.1111/apt.12930.
1237. Meza-Meneses P, Vilar-Compte D, Cornejo-Juarez P, Volkow P. 2016. Incidence of infectious complications in patients with non-Hodgkin lymphoma receiving rituximab-containing chemotherapy. Open Forum Infect Dis 3:2337. https://doi.org/10.1093/ofid/ofw172.1884.
1238. Focosi D, Tuccori M, Blandizzi C, Del Tacca M, Petrini M. 2009. Incidence of progressive multifocal leukoencephalopathy in non-Hodgkin lymphoma patients treated with rituximab. Blood 114:3675. https://doi.org/10.1182/blood.V114.22.3675.3675.
1239. Kolstad A, Holte H, Fosså A, Lauritzsen GF, Gaustad P, Torfoss D. 2007. Pneumocystis jirovecii pneumonia in B-cell lymphoma patients treated with the rituximab-CHOEP-14 regimen. Haematologica 92:139–140. https://doi.org/10.3324/haematol.10564.
1240. Brusamolino E, Rusconi C, Montalbetti L, Gargantini L, Uziel L, Pinotti G, Fava S, Rigacci L, Pagnucco G, Pascutto C, Morra E, Lazzarino M. 2006. Dose-dense R-CHOP-14 supported by pegfilgrastim in patients with diffuse large B-cell lymphoma: a phase II study of feasibility and toxicity. Haematologica 91:496–502.
1241. Jiang X-Q, Fang L, Mei X-D, Wang X-J, Bao M-H. 2013. Pneumocystis jiroveci pneumonia in patients with non-Hodgkin's lymphoma after rituximab-containing regimen: two cases of report and literature review. J Thoracic Dis 5:E162–E166. https://doi.org/10.3978/j.issn.2072-1439.2013.08.35.
1242. Becerra E, Cambridge G, de la Torre I, Leandro MJ. 2012. Long-term

safety of rituximab in patients with rheumatoid arthritis. Int J Clin Rheumatol 7:383–390. https://doi.org/10.2217/ijr.12.31.
1243. van Vollenhoven RF, Emery P, Bingham CO, Keystone EC, Fleischmann RM, Furst DE, Tyson N, Collinson N, Lehane PB. 2013. Long-term safety of rituximab in rheumatoid arthritis: 9.5-year follow-up of the global clinical trial programme with a focus on adverse events of interest in RA patients. Ann Rheum Dis 72:1496–1502. https://doi.org/10.1136/annrheumdis-2012-201956.
1244. Clifford DB, Ances B, Costello C, Rosen-Schmidt S, Andersson M, Parks D, Perry A, Yerra R, Schmidt R, Alvarez E, Tyler KL. 2011. Rituximab-associated progressive multifocal leukoencephalopathy in rheumatoid arthritis. Arch Neurol 68:1156–1164. https://doi.org/10.1001/archneurol.2011.103.
1245. Rovin BH, Furie R, Latinis K, Looney RJ, Fervenza FC, Sanchez-Guerrero J, Maciuca R, Zhang D, Garg JP, Brunetta P, Appel G, LUNAR Investigator Group. 2012. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis Rheum 64:1215–1226. https://doi.org/10.1002/art.34359.
1246. Terrier B, Amoura Z, Ravaud P, Hachulla E, Jouenne R, Combe B, Bonnet C, Cacoub P, Cantagrel A, de Bandt M, Fain O, Fautrel B, Gaudin P, Godeau B, Harle JR, Hot A, Kahn JE, Lambotte O, Larroche C, Leone J, Meyer O, Pallot-Prades B, Pertuiset E, Quartier P, Schaerverbeke T, Sibilia J, Somogyi A, Soubrier M, Vignon E, Bader-Meunier B, Mariette X, Gottenberg JE. 2010. Safety and efficacy of rituximab in systemic lupus erythematosus: results from 136 patients from the French AutoImmunity and Rituximab registry. Arthritis Rheum 62:2458–2466. https://doi.org/10.1002/art.27541.
1247. Tony H-P, Burmester G, Schulze-Koops H, Grunke M, Henes J, Kötter I, Haas J, Unger L, Lovric S, Haubitz M, Fischer-Betz R, Chehab G, Rubbert-Roth A, Specker C, Weinerth J, Holle J, Müller-Ladner U, König R, Fiehn C, Burgwinkel P, Budde K, Sörensen H, Meurer M, Aringer M, Kieseier B, Erfurt-Berge C, Sticherling M, Veelken R, Ziemann U, Strutz F, von Wussow P, Meier FM, Hunzelmann N, Schmidt E, Bergner R, Schwarting A, Eming R, Hertl M, Stadler R, Schwarz-Eywill M, Wassenberg S, Fleck M, Metzler C, Zettl U, Westphal J, Heitmann S, Herzog AL, Wiendl H, Jakob W, Schmidt E, Freivogel K, Dörner T, GRAID investigators. 2011. Safety and clinical outcomes of rituximab therapy in patients with different autoimmune diseases: experience from a national registry (GRAID). Arthritis Res Ther 13:R75. https://doi.org/10.1186/ar3337.
1248. Cohen SB, Tanaka Y, Mariette X, Curtis JR, Lee EB, Nash P, Winthrop KL, Charles-Schoeman C, Thirunavukkarasu K, DeMasi R, Geier J, Kwok K, Wang L, Riese R, Wollenhaupt J. 2017. Long-term safety of tofacitinib for the treatment of rheumatoid arthritis up to 8.5 years: integrated analysis of data from the global clinical trials. Ann Rheum Dis 76:1253–1262. https://doi.org/10.1136/annrheumdis-2016-210457.
1249. Strand V, Ahadieh S, French J, Geier J, Krishnaswami S, Menon S, Checchio T, Tensfeldt TG, Hoffman E, Riese R, Boy M, Gomez-Reino JJ. 2015. Systematic review and meta-analysis of serious infections with tofacitinib and biologic disease-modifying antirheumatic drug treatment in rheumatoid arthritis clinical trials. Arthritis Res Ther 17:362. https://doi.org/10.1186/s13075-015-0880-2.
1250. Cohen S, Curtis JR, DeMasi R, Chen Y, Fan H, Soonasra A, Fleischmann R. 2018. Worldwide, 3-year, post-marketing surveillance experience with tofacitinib in rheumatoid arthritis. Rheumatol Ther 5:283–291. https://doi.org/10.1007/s40744-018-0097-3.
1251. Winthrop KL, Lebwohl M, Cohen AD, Weinberg JM, Tyring SK, Rottinghaus ST, Gupta P, Ito K, Tan H, Kaur M, Egeberg A, Mallbris L, Valdez H. 2017. Herpes zoster in psoriasis patients treated with tofacitinib. J Am Acad Dermatol 77:302–309. https://doi.org/10.1016/j.jaad.2017.03.023.
1252. Curtis JR, Xie F, Yun H, Bernatsky S, Winthrop KL. 2016. Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis. Ann Rheum Dis 75:1843–1847. https://doi.org/10.1136/annrheumdis-2016-209131.
1253. Winthrop KL, Park SH, Gul A, Cardiel MH, Gomez-Reino JJ, Tanaka Y, Kwok K, Lukic T, Mortensen E, Ponce de Leon D, Riese R, Valdez H. 2016. Tuberculosis and other opportunistic infections in tofacitinib-treated patients with rheumatoid arthritis. Ann Rheum Dis 75:1133–1138. https://doi.org/10.1136/annrheumdis-2015-207319.
1254. Souto A, Maneiro JR, Salgado E, Carmona L, Gomez-Reino JJ. 2014. Risk of tuberculosis in patients with chronic immune-mediated inflammatory diseases treated with biologics and tofacitinib: a systematic review and meta-analysis of randomized controlled trials and long-term extension studies. Rheumatology (Oxford) 53:1872–1885. https://doi.org/10.1093/rheumatology/keu172.
1255. Genovese MC, Kremer J, Zamani O, Ludivico C, Krogulec M, Xie L, Beattie SD, Koch AE, Cardillo TE, Rooney TP, Macias WL, de Bono S, Schlichting DE, Smolen JS. 2016. Baricitinib in patients with refractory rheumatoid arthritis. N Engl J Med 374:1243–1252. https://doi.org/10.1056/NEJMoa1507247.
1256. Dougados M, van der Heijde D, Chen YC, Greenwald M, Drescher E, Liu J, Beattie S, Witt S, de la Torre I, Gaich C, Rooney T, Schlichting D, de Bono S, Emery P. 2017. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. Ann Rheum Dis 76:88–95. https://doi.org/10.1136/annrheumdis-2016-210094.
1257. Taylor PC, Keystone EC, van der Heijde D, Weinblatt ME, Del Carmen Morales L, Reyes Gonzaga J, Yakushin S, Ishii T, Emoto K, Beattie S, Arora V, Gaich C, Rooney T, Schlichting D, Macias WL, de Bono S, Tanaka Y. 2017. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. N Engl J Med 376:652–662. https://doi.org/10.1056/NEJMoa1608345.
1258. Keystone EC, Genovese MC, Schlichting DE, de la Torre I, Beattie SD, Rooney TP, Taylor PC. 2018. Safety and efficacy of baricitinib through 128 weeks in an open-label, longterm extension study in patients with rheumatoid arthritis. J Rheumatol 45:14–21. https://doi.org/10.3899/jrheum.161161.
1259. Tanaka Y, Ishii T, Cai Z, Schlichting D, Rooney T, Macias W. 2018. Efficacy and safety of baricitinib in Japanese patients with active rheumatoid arthritis: a 52-week, randomized, single-blind, extension study. Mod Rheumatol 28:20–29. https://doi.org/10.1080/14397595.2017.1307899.
1260. Verstovsek S, Mesa RA, Gotlib J, Gupta V, DiPersio JF, Catalano JV, Deininger MW, Miller CB, Silver RT, Talpaz M, Winton EF, Harvey JH, Jr, Arcasoy MO, Hexner EO, Lyons RM, Paquette R, Raza A, Jones M, Kornacki D, Sun K, Kantarjian H, COMFORT-I Investigators. 2017. Long-term treatment with ruxolitinib for patients with myelofibrosis: 5-year update from the randomized, double-blind, placebo-controlled, phase 3 COMFORT-I trial. J Hematol Oncol 10:55. https://doi.org/10.1186/s13045-017-0417-z.
1261. Vannucchi AM, Kiladjian JJ, Griesshammer M, Masszi T, Durrant S, Passamonti F, Harrison CN, Pane F, Zachee P, Mesa R, He S, Jones MM, Garrett W, Li J, Pirron U, Habr D, Verstovsek S. 2015. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. N Engl J Med 372:426–435. https://doi.org/10.1056/NEJMoa1409002.
1262. Harrison CN, Vannucchi AM, Kiladjian JJ, Al-Ali HK, Gisslinger H, Knoops L, Cervantes F, Jones MM, Sun K, McQuitty M, Stalbovskaya V, Gopalakrishna P, Barbui T, COMFORT-II Investigators. 2016. Long-term findings from COMFORT-II, a phase 3 study of ruxolitinib vs best available therapy for myelofibrosis. Leukemia 30:1701–1707. https://doi.org/10.1038/leu.2016.148.

**Joshua S. Davis** (M.B.B.S., F.R.A.C.P., Ph.D.) is an infectious diseases physician at John Hunter Hospital in Newcastle, Australia, and a senior research fellow at the Menzies School of Health Research and Charles Darwin University in Darwin, Australia. He trained in clinical infectious diseases in Sydney, Newcastle, and Darwin and completed his Ph.D. in 2010 on the pathophysiology and epidemiology of sepsis. Professor Davis is a clinical triallist, with ongoing investigator-initiated trials in *S. aureus* bacteremia, sepsis, and prosthetic joint infection. He is the current president of the Australasian Society for Infectious Diseases.

**David Ferreira** (B.Med.) is a medical registrar currently based at John Hunter Hospital in Newcastle, Australia. He completed his medical degree at the University of New England in Armidale, NSW, and finished basic physician training at Liverpool Hospital, Sydney, Australia, achieving academic and physician awards. Passionate about evidence-based medicine, Dr. Ferreira has published in several fields, including cardiology, infectious diseases, nephrology, and hematology.

**Emma Paige** (M.B.B.S., F.R.A.C.P.) is an infectious diseases physician based at the Alfred Hospital in Melbourne, Australia. Dr. Paige completed her clinical training in infectious diseases in Melbourne and works across the breadth of clinical infectious diseases, including general infectious diseases, infections in immunocompromised hosts, and HIV medicine. She heads the Regional Infectious Diseases Service at Alfred Health and is involved in outreach work and teaching, and her research interests include infections in oncology and hematology patients.

**Craig Gedye** (M.B.B.S., F.R.A.C.P., Ph.D.) is a clinical oncologist at the Calvary Mater Hospital in Newcastle, Australia, and a laboratory cancer researcher at the University of Newcastle. Associate Professor Gedye trained in clinical oncology and laboratory science in New Zealand and subsequently spent time as a postdoctoral clinician researcher at the University of Toronto, Canada. He currently undertakes clinical, translational, and basic cancer research in melanoma, brain, prostate, bladder, and kidney cancers.

**Michael Boyle** (M.B.B.S., M.D., F.R.A.C.P., F.R.C.P.A.) is a clinical immunologist and the Chief of the Division of Medicine at John Hunter Hospital in Newcastle, Australia. Associate Professor Boyle has research interests in HIV infection and the epidemiology and pathophysiology of drug allergy and a broad interest and experience in the immunological aspects of human disease.