

# Infectious Complications Associated with Monoclonal Antibodies and Related Small Molecules

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**INTRODUCTION**

**Biologics in the Treatment of Disease**

Modern therapeutics is experiencing an explosion in the development of drugs directed at specific molecular targets for the treatment of disease. As our knowledge of molecular pathogenesis grows, the fabrication of “designer molecules,” such as monoclonal antibodies and small molecules, against key steps in disease pathways has led to astounding clinical responses, remission, and cure of previously untreatable or intractable illnesses (67, 166, 192). The term “biologic” or “biological” in a broader sense applies to any biologically derived product, but for the purposes of this review, it refers to the class of drugs which includes monoclonal antibodies, receptor analogues, and chimeric small molecules designed to bind to or mimic their molecular targets (67). These drugs have obvious advantages over conventional therapy in terms of potency, specificity, and theoretically decreased side effects, since the product is engineered to bind to or interfere with a distinct molecular target (107, 166). While biologics for the most part represent a considerable boon to physicians and patients alike, they are not without their own unique set of problems, which clinicians must be aware of in order to utilize them with maximum benefit.

**A Brief History of Monoclonal Antibodies and Receptor Analogues**

Ever since Köhler and Milstein (91) first described the production of hybridomas producing specific antibodies, monoclonal antibodies have become a cornerstone of both basic and clinical research and have since made the transition to the clinical arena (107). The first monoclonal antibody used in the treatment of disease was muromonab, a murine anti-CD3 immunoglobulin G2a (IgG2a) antibody used for prophylaxis or treatment of allograft rejection (161). Advances in DNA recombinant technology also led to the development of the first chimeric receptor analog protein, etanercept (130). Further advances in molecular techniques allowed for the manipulation of genetic sequences, producing chimeric murine-human constructs, such as infliximab and rituximab, which contain the human effector portion of the antibody and the murine antigen binding portion, and fully “humanized” monoclonal antibodies with only the antigen binding site sequences derived from mouse genes, such as daclizumab and omalizumab, which are less likely to induce an immune reaction than purely murine antibodies (166). Since then, more than 20 monoclonal antibodies have been approved for therapeutic use in humans, along with other biologic products, from recombinant receptors to fusion proteins with higher potencies and specificities (67, 181). Tables 1, 2, and 3 give summaries of the agents and their effects.

**Biologics and Infection**

As more biologic agents become available for clinical use, certain drugs that interfere with natural immunity have led to concerns regarding increased rates of both common and un-

usual infections among treated patients (58). This is not surprising, particularly in the case of agents that interfere with tumor necrosis factor alpha (TNF- $\alpha$ ) as well as for monoclonal antibodies against specific subsets of leukocytes (Fig. 1) (57, 67, 83, 189). While most monoclonal agents and related biologics are generally safe, a working knowledge of the infectious complications associated with these is essential in order to apprise the patient of the risks involved in embarking on such a course of therapy as well as to maintain vigilance for these adverse events.

One of the major problems in determining causality between biologic therapy and infection is the fact that, in some cases, the underlying disease process itself along with concurrent therapy can cause immunosuppression. This is the case for patients with cancer, autoimmune diseases, and inflammatory conditions such as rheumatoid arthritis (RA). In the case of rare infections, a true association can never be proven definitively due to the small number of events. Even in randomized placebo-controlled trials and in large open-label studies, it is difficult to attribute the increased risk of infection to the biologic alone due to a large number of confounders, especially since trials are powered to measure efficacy, not safety (18, 138).

The aim of this review is to present a comprehensive overview of the infectious risks of all U.S. Food and Drug Administration (FDA)-approved monoclonal antibodies. In addition, we review some related FDA-approved small molecules that are used for the treatment of inflammatory diseases and which may pose some infectious risk. The target audience includes infectious disease specialists who may be called upon to help manage infectious complications as well as general practitioners who may be involved in the care of patients treated with these agents. We have not attempted a comprehensive review of indications, dosing, or adverse events other than infections associated with the use of these agents, and specialists intending to use these for therapy are advised to review product label inserts and more comprehensive literature regarding the specific agent.

**Concurrent Infections and Immune Reconstitution**

In the event of a serious infectious complication, the most logical course of action is to discontinue use of the biologic. This may not always be feasible and may necessitate a longer course of treatment for a particular infection. Moreover, biologics, especially monoclonal antibodies, tend to have long half-lives and may therefore result in a substantial delay from the time of discontinuation to the time of recovery of immune function (53). Finally, the discontinuation of immunosuppressive therapy may result in a paradoxical worsening of the infection as the immune system recovers and reacts to persistent but heretofore unrecognized antigens—a phenomenon termed immune reconstitution inflammatory syndrome in the human immunodeficiency virus (HIV)/AIDS literature (149, 185). Awareness of these special problems is essential for the successful clinical application of biologics.

TABLE 1. Summary of FDA-approved monoclonal antibodies and selected small molecules and their risks of infection

Drug name (trade name, manufacturer)	Type	Target	Indication	Risk of serious infection	Serious infections	Comments
Adalimumab (Humira, Abbott)	Human IgG1	TNF- $\alpha$	RA, JRA, AS, PA, PP, CD	Yes for granulomatous disease	Serious pulmonary bacterial infections, TB, candidiasis, CMV infection, toxoplasmosis, and nocardiosis	Black box for infections
Infliximab (Remicade, Centocor Inc.)	Chimeric IgG1	TNF- $\alpha$	RA, AS, PA, PP, CD, UC	Yes for granulomatous disease	Pneumonia, sepsis, TB, infections with MOTT, listeriosis, histoplasmosis, candidiasis, aspergillosis, cryptococcosis, salmonellosis, toxoplasmosis, brucellosis, bartonellosis, leishmaniasis, coccidiomycoses, leprosy, CMV infection, HBV reactivation	Black box for infections
Certolizumab pegol (Cimzia, UCB Inc.)	Humanized Fab' antibody fragment conjugated to polyethylene glycol	TNF- $\alpha$	CD	Yes for granulomatous disease	Serious pulmonary bacterial infections, TB, viral and fungal infections	Black box for infections
Etanercept (Enbrel, Immunex)	Human dimeric fusion protein	TNF- $\alpha$	RA, JRA, AS, PA, PP	Yes for granulomatous disease but less than that with monoclonal antibodies, yes in combination with anakinra	Serious bacterial infections, TB, infections with MOTT, listeriosis, histoplasmosis, candidiasis, aspergillosis, cryptococcosis, nocardiasis, protozoal and VZV infection	Black box for infections
Abatacept (Orencia, Bristol-Myers Squibb)	Fusion protein	T-cell costimulation inhibitor	RA, JRA	Yes, in combination with etanercept and other DMARDs, less clear for monotherapy	Pneumonia, sepsis, aspergillosis, sinusitis, candidiasis, bronchitis, skin and soft tissue infections, viral infections with HSV and VZV	Black box for infections
Anakinra (Kineret, Amgen)	Nonglycosylated IL-1 receptor	IL-1	RA	Yes	Pneumonia, cellulitis, TB, unspecified mycobacterial and fungal infections	Black box for infections
Rilonacept (Arcalyst, Regeneron)	Dimeric fusion protein IL-1 inhibitor	IL-1	CAPS	Yes	Meningitis, MOTT infection, severe bronchitis	Black box for infections
Efalizumab (Raptiva, Genentech)	Humanized IgG1	CD11a	PP	Yes, although most infections tend to be mild	Pneumonia, cellulitis, abscesses, sepsis, <i>Legionella</i> pneumonia, necrotizing fasciitis, TB, PML	Black box for infections
Alefacept (Amevive, Astellas)	Fusion protein	Inhibits T-cell activation	PP	Probable, inconsistent association from clinical trials	Celulitis, abscess, wound infections, toxic shock, pneumonia, appendicitis, cholecystitis, gastroenteritis, MOTT infection, influenza virus, HCV, and herpesvirus infections	Causes decrease in CD4 <sup>+</sup> and CD8 <sup>+</sup> cells
Alemtuzumab (Campath, Genzyme Corp.)	Humanized IgG1	CD52	CLL, TPL, NHL	Yes, causes prolonged lymphopenia	Overwhelming bacteremia, pneumonia, meningitis, CMV, VZV, and HSV infections, PCP, PML, adenovirus infection, acanthamebiasis, toxoplasmosis, histoplasmosis, cryptococcosis, aspergillosis, <i>Fusarium</i> infection, <i>Scedosporium</i> infection, BK virus infection, HHV-6 infection, candidiasis, parvovirus infection, mucormycosis, TB, <i>Balamuthia mandrillaris</i> infection, MOTT infection, BCGosis, <i>Rhodococcus</i> infection, HBV reactivation	Black box for infections, prophylaxis for PCP and herpesviruses
<sup>90</sup> Y-ibritumomab tiuxetan (Zevalin, Biogen Idec Pharmaceuticals Corp.)	Radiolabeled murine IgG1	CD20	NHL	Yes, causes prolonged cytopenias	pneumonia, sepsis, cellulitis, colitis, diarrhea, empyema, osteomyelitis, pericarditis, viral pneumonia and viral hepatitis	Blackbox for prolonged and severe cytopenias
Rituximab (Rituxan, Genentech)	Chimeric human-murine IgG1	CD20	RA, NHL	Yes for PML and hepatitis B, less clear for other infections	Serious bacterial infections, PML, parvovirus, CMV, HSV, and disseminated VZV infections, HBV and HCV reactivation	Black box for PML
<sup>131</sup> I-tositumomab (Bexxar, Corixa Corp.)	Radiolabeled murine IgG2	CD20	NHL	Yes, causes prolonged cytopenias	Pneumonia, septicemia, bronchitis, skin infections, viral infections	Black box for prolonged and severe cytopenias
Gemtuzumab ozogamicin (Mylotarg, Wyeth Pharmaceuticals Inc.)	Humanized IgG4 conjugated to calicheamicin	CD33	AML	Yes, from prolonged neutropenia	Sepsis, pneumonia, HSV infection, usual opportunistic infections with neutropenia, unusual pathogens include <i>Staphylococcus hominis</i> , <i>Agrobacterium radiobacter</i> , <i>Acinetobacter lwoffii</i> , <i>Rhodococcus</i> , and <i>Pantoea agglomerans</i>	Black box for prolonged and severe cytopenias

Bevacizumab (Avastin, Genentech)	Humanized IgG1	VEGF	CRCa, NSCLCa, BrCa	Yes, severe neutropenia in combination with chemotherapy; intraocular injection without evidence of increased risk	Sepsis, anaerobic liver abscess with <i>Bacteroides fragilis</i> , <i>Fusarium</i> nasal septal infection, endophthalmitis, intraocular injection including <i>Bacillus cereus</i> and coagulase-negative <i>Staphylococcus aureus</i> , abscess, sepsis	Black box for intestinal perforation, sometimes with abscess
Cetuximab (Erbixux, Bristol-Myers Squibb and Imclone)	Chimeric human-murine IgG1	ErbB1	CRCa, HNCa	Yes, dermatologic toxicity with infectious sequelae	Paronychia caused by <i>Staphylococcus aureus</i> , abscess, sepsis	
Panitumumab (Vectibix, Amgen)	Human IgG2	ErbB1	CRCa	Yes, dermatologic toxicity with infectious sequelae	Paronychia, abscess, sepsis	
Trastuzumab (Herceptin, Genentech)	Human IgG1	HER2	BrCa	Yes, in combination with certain chemotherapeutic regimens	Febrile neutropenia	
Basiliximab (Simulect, Novartis)	Chimeric human-murine IgG1	CD25	Renal transplant rejection prophylaxis	Increased risk with triple regimens for CMV, otherwise no difference versus placebo	Bacterial, CMV, and HSV infections, aspergillosis, nocardiosis, candidiasis, and protozoal infections	
Daclizumab (Zenapax, Hoffmann-la Roche)	Humanized IgG1	CD25	Renal transplant rejection prophylaxis	Probable, inconsistent association from clinical trials, with overall incidence no different from that with placebo, although severe infections were more common	Nocardiosis, legionellosis, MOTT infection, TB, viral infection with CMV, BK virus, adenovirus, HSV, RSV, or influenza virus, fungal infections with <i>Aspergillus</i> , <i>Scedosporium</i> , <i>Cunninghamella</i> , and <i>Candida</i>	
Muromonab (Orthoclone-OKT3, Ortho Biotech)	Murine IgG2	CD3	Solid organ transplant rejection	Yes, but no different from that with high-dose steroids	Bacterial infections, including <i>Listeria</i> , <i>Nocardia</i> , and MOTT infections; infections with <i>Aspergillus</i> , <i>Candida</i> , <i>Cryptococcus</i> , or dermatophytes; PCP; infections with <i>Toxoplasma gondii</i> , CMV, EBV, HSV, hepatitis viruses, VZV, adenovirus, enterovirus, RSV, and parainfluenza virus	
Abeiximab (Reopro, Centocor Inc.)	Fab' fragment of chimeric human-murine IgG1	GP1Ib/IIIa	Adjunct for PCI	No, incidence of pneumonia is slightly higher than that with placebo ( <i>P</i> value not reported)	Pneumonia	
Natalizumab (Tysabri, Biogen Idec Pharmaceuticals Corp.)	Humanized IgG4	$\alpha$ 4-Integrin	MS, CD	Yes with PML, less clear for other infections	PML, herpesvirus infections, influenza, <i>Cryptosporidium</i> diarrhea, bacterial pneumonias and UTIs, PCP, <i>Mycobacterium avium-intracellulare</i> infection, <i>Aspergillus</i> and <i>Burkholderia cepacia</i> infections	Black-box warning for PML, restricted distribution
Omalizumab (Xolair, Genentech)	Humanized IgG1	IgE	Asthma	Theoretical increased risk of parasitic infection, not substantiated in clinical trials	Otitis media	
Palivizumab (Synagis, Medimmune)	Humanized IgG1	F protein of RSV	RSV prophylaxis	No	None	
Arcitumomab (CEA-Scan, Immunomedics)	Fab' fragment of murine IgG1 radioconjugated to <sup>90m</sup> Tc	CEA	Detection of CRCa	No	None	
Fanolesomab (NeuroSpec, Palatin Technologies)	<sup>90m</sup> Tc-radiolabeled murine IgM	CD15	Equivoval appendicitis	No	None	
Capromab pendetide (Prostascint, Cytogen)	IgG	PSMA	Detection of recurrence of prostate cancer	No	None	
<sup>90m</sup> Tc-nofetumomab merpentan (Veriuma, Boehringer Ingelheim)	<sup>90m</sup> Tc-radiolabeled murine IgG2	CAA	SCLCa staging	No	None	Transient decrease in neutrophil count; withdrawn from market

<sup>a</sup> TNF- $\alpha$ , tumor necrosis factor alpha; RA, rheumatoid arthritis; IRA, juvenile rheumatoid arthritis; AS, ankylosing spondylitis; PA, psoriatic arthritis; PP, plaque psoriasis; CD, Crohn's disease; CMV, cytomegalovirus; UC, ulcerative colitis; MOTT, *Mycobacterium* species other than *M. tuberculosis*; HBV, hepatitis B virus; IL-1, interleukin-1; HSV, herpes simplex virus; VZV, varicella zoster virus; CAPS, cryopyrin-associated periodic syndrome; PML, progressive multifocal leukoencephalopathy; HCV, hepatitis C virus; CLL, B-cell chronic lymphocytic leukemia; TPL, T-cell prolymphocytic leukemia; NHL, non-Hodgkin's lymphoma; PCP, *Pneumocystis jirovecii* pneumonia; AML, acute myelogenous leukemia; VEGF, vascular endothelial growth factor; CRCa, colorectal cancer; NSCLCa, non-small-cell lung cancer; BrCa, breast cancer; HNCa, head-and-neck cancer; RSV, respiratory syncytial virus; EBV, Epstein-Barr virus; PCI, percutaneous coronary intervention; MS, multiple sclerosis; CEA, carcinoembryonic antigen; PSMA, prostate-specific membrane antigen; CAA, carcinoma-associated glycoprotein antigen; SCLCa, small-cell lung cancer.

TABLE 2. Reported serious infections with biologics by etiologic agent

Etiologic agent or disease	Therapeutic agent associated with serious infection
Bacteria.....	Adalimumab Infliximab Certolizumab pegol Etanercept Abatacept Anakinra Riloncept Efalizumab Alefacept Alemtuzamab <sup>90</sup> Y-ibritumomab tiuxetan Rituximab <sup>131</sup> I-tositumomab Gemtuzumab ozogamicin Bevacizumab Cetuximab Panitumumab Trastuzumab Basiliximab Daclizumab Muromonab Abciximab Natalizumab Palivizumab
TB.....	Adalimumab Infliximab Certolizumab pegol Etanercept Abatacept Anakinra Efalizumab Alemtuzamab Daclizumab
MOTT.....	Infliximab Etanercept Certolizumab pegol Anakinra Riloncept Alefacept Alemtuzamab Daclizumab Muromonab Natalizumab
Viruses.....	Adalimumab Infliximab Certolizumab pegol Etanercept Abatacept Alefacept Alemtuzamab <sup>90</sup> Y-ibritumomab tiuxetan Rituximab <sup>131</sup> I-tositumomab Gemtuzumab ozogamicin Basiliximab Daclizumab Muromonab Natalizumab
PML.....	Alemtuzamab Rituximab Natalizumab
Fungi.....	Adalimumab Infliximab Etanercept Abatacept Anakinra Alemtuzamab Bevacizumab Basiliximab Daclizumab Muromonab Natalizumab
Parasites.....	Adalimumab Infliximab Etanercept Anakinra Alemtuzamab Basiliximab Muromonab Natalizumab

TABLE 3. Approximate levels of evidence of risk of infection

Level of risk and drug <sup>a</sup>
Increased risk (meta-analysis or postmarketing cases with strong pattern of risk, consistent post hoc phase III randomized controlled trial (RCT) analysis showing risk)
Adalimumab Infliximab Certolizumab pegol Etanercept Abatacept* Anakinra Riloncept Efalizumab Alemtuzamab <sup>90</sup> Y-ibritumomab tiuxetan Rituximab <sup>131</sup> I-tositumomab Gemtuzumab ozogamicin Bevacizumab** Cetuximab Panitumumab Trastuzumab** Natalizumab
Probable risk (most post hoc phase III RCT analysis and postmarketing studies show risk or trend to risk)
Alefacept Basiliximab Daclizumab Muromonab
Possible risk (case reports and trend toward increased infection but inconsistent in big RCTs, reported cases with confounders, or theoretical risk)
Abciximab Omalizumab Palivizumab
No risk
Arcitumomab Fanolesomab Capromab pendetide <sup>99m</sup> Tc-nofetumomab merpentan

<sup>a</sup> \*, in combination with other agents, probable risk for monotherapy; \*\*, in combination with chemotherapeutic agents, possible risk as monotherapy.

**BIOLOGICS FOR RHEUMATOLOGIC DISEASES AND OTHER INFLAMMATORY CONDITIONS**

**TNF-α Inhibitors**

TNF-α inhibitors represent a major breakthrough in the treatment of rheumatologic diseases and diseases of immune dysregulation (27, 123). TNF-α is a cytokine that plays a central role in establishing and maintaining the inflammatory response against infection (49, 57, 140, 189). TNF-α has both soluble and transmembrane forms, both of which are biologically active and are produced by a wide variety of cells, including macrophages, natural killer cells, granulocytes, fibroblasts, and T cells. Both forms interact with two distinct types of receptors, TNF receptor 1 (TNFR1) and TNFR2, either or both of which are found in practically all cells in the human body other than red blood cells (177). TNF-α blockade results in the interruption of TNFR-mediated functions, which include cell activation and proliferation, cytokine and chemokine production, and the formation and maintenance of granulomas

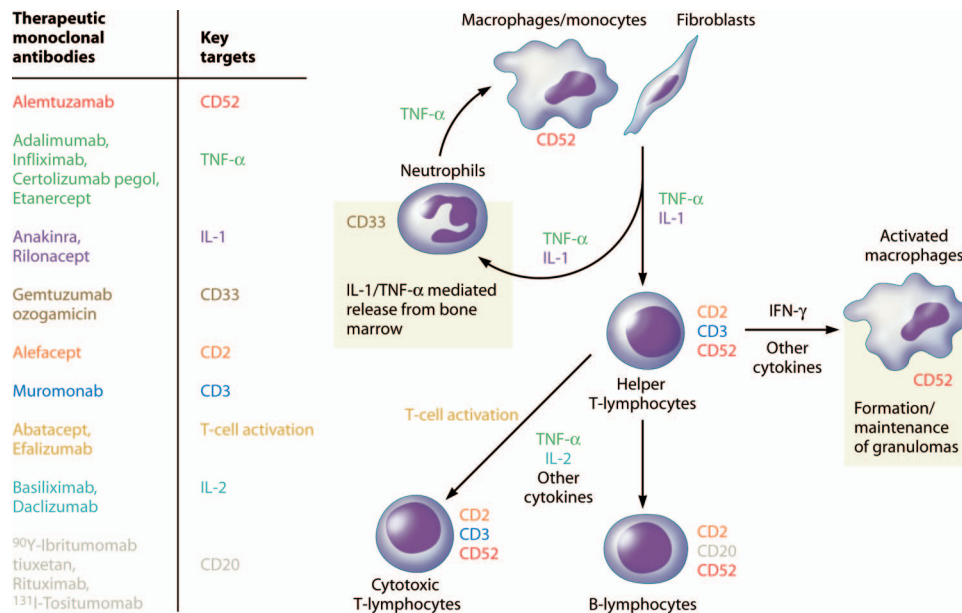


FIG. 1. Outline of human immunologic responses showing key targets of monoclonal antibodies that may suppress immune responses and enhance the risk for infection. Immune targets and therapeutic agents are color coded. CD, cluster of differentiation; TNF-α, tumor necrosis factor alpha; IL-1, interleukin-1; IFN-γ, gamma interferon; IL-2, interleukin-2.

(49, 57, 177, 189). It is therefore not surprising that TNF-α inhibitors have been shown to increase the risk of granulomatous infections, most importantly tuberculosis (TB) (188, 196). There are currently four TNF-α antagonists approved for treatment, including two monoclonal antibodies, one Fab' fragment, and one soluble receptor, namely, adalimumab, infliximab, certolizumab pegol, and etanercept, respectively.

Evaluation for TB risk factors, tuberculin skin testing, and a baseline chest X-ray, as indicated, should be performed prior to initiation of therapy, and if the patient tests positive, chemoprophylaxis for latent TB should be initiated prior to the start of treatment with TNF-α inhibitors. A cutoff of 5 mm of induration for tuberculin skin testing is recommended, since patients treated with these agents are considered immunosuppressed (196). Monitoring for active TB should also be done while patients are on TNF-α inhibitors, including those who tested negative for latent TB (145, 174; Humira [adalimumab] package insert [Abbott Laboratories, North Chicago, IL, February 2008] [http://www.fda.gov/cder/foi/label/2008/125057s114lbl.pdf]; Remicade [infliximab] package insert [Centocor Inc., Malvern, PA, April 2007] [http://www.fda.gov/cder/foi/label/2007/103772s5189lbl.pdf]; Enbrel [etanercept] package insert [ImmuneX Corporation, Thousand Oaks, CA, March 2008] [http://www.fda.gov/medwatch/safety/2008/enbrel\_pi.pdf]; Cimzia [certolizumab pegol] package insert [UCB Inc., Smyrna, GA, April 2008] [http://www.fda.gov/cder/foi/label/2008/125160s000lbl.pdf]). Newer gamma interferon release assays have been advocated to enhance screening efficacy, although the effectiveness of this approach is still being evaluated (174). Anti-TNF therapies carry different risks for TB, either as a consequence of the mechanism of action alone (infliximab versus etanercept) or as a consequence of pharmacokinetics as well (adalimumab versus etanercept) (147, 186). Saliu et al. (147) showed with whole-blood assays that the proportion of TB-responsive CD4 cells was reduced by both adalimumab and inflix-

imab, albeit at significantly different rates (70% versus 49%), along with antigen-induced gamma interferon production, but again at significantly different rates (70% versus 64%), while etanercept had no effect on either parameter. Interleukin-10 (IL-10) production was equally suppressed by all three drugs. No significant apoptosis was induced. Murine models of chronic TB have shown that treatment with a TNF-α receptor analog allowed for control of disease, while treatment with a TNF-α monoclonal antibody resulted in death within a month and in disruption of granulomas (33, 134). Finally, a recent review by Wallis (188) outlining the risks of TB showed a 1.3- to 5.9-fold increased risk with infliximab versus etanercept and a 1.8- to 14.6-fold increased risk with adalimumab versus etanercept. Time to developing TB was likewise shorter with infliximab than with etanercept (1:1.7 to 1:4.6). Using Markov and Monte Carlo simulation computer models, Wallis (187) attempted to determine the respective contributions of the reactivation of latent TB versus new TB infection. He found that while both infliximab and etanercept presented high risks for new TB infection, the rate of reactivation of latent TB was 12 times higher for infliximab than for etanercept.

Recently, the FDA mandated the strengthening of existing warnings on all TNF-α agents for increased risk of serious fungal infections, especially histoplasmosis. It also stressed that empirical antifungal therapy should be considered for at-risk patients, particularly those living in the Ohio and Mississippi River valleys, since delays in recognition and treatment of at least 21 cases of histoplasmosis of the 240 reported cases have led to 12 deaths (180).

Hepatitis B virus (HBV) reactivation has likewise occurred with TNF-α antagonists, and while product labels are equivocal regarding the safety of concomitant antivirals, limited data suggest that prophylaxis with lamivudine seems to be effective and well tolerated (118, 143). In general, it is not recommended that TNF-α antagonists (or any other potentially im-

munosuppressive agents, for that matter) be started in patients with active infections, and caution should be used for patients with a history of chronic or recurrent infections. Furthermore, while there are no data specifically pertaining to immunologic responses to live vaccines or the secondary transmission of infection from live vaccines in patients receiving TNF- $\alpha$  inhibitors, administration of these agents is not recommended during anti-TNF treatment (Humira package insert; Remicade package insert; Enbrel package insert; Cimzia package insert).

**Adalimumab.** Adalimumab is a fully human IgG1 monoclonal antibody against TNF- $\alpha$  currently licensed for use against juvenile idiopathic arthritis, RA, Crohn's disease, ankylosing spondylitis, chronic plaque psoriasis, and psoriatic arthritis (27, 123; Humira package insert). Infectious complications observed while undergoing adalimumab therapy include serious pulmonary bacterial infections, TB, candidiasis, cytomegalovirus (CMV) infection, toxoplasmosis, and nocardiosis (27, 44). One case of reversal reaction with leprosy has been reported (122). Early trials and safety data analyses have been inconsistent in showing a link between adalimumab and a higher risk of serious infection (101; Humira package insert). However, pooled analysis of postmarketing reports seems to indicate an increase in the risk of infections, particularly granulomatous diseases such as TB (101, 188).

**Infliximab.** Infliximab is a human-murine chimeric monoclonal antibody that binds both trimeric and monomeric forms of soluble TNF- $\alpha$  as well as transmembrane TNF- $\alpha$  and is indicated for the treatment of RA and Crohn's disease (57, 189; Remicade package insert). Infliximab has consistently been linked to an increased risk of granulomatous infection, particularly TB (21, 174, 189), as well as to an increase in overall infections (101; Remicade package insert). Other infections observed with infliximab use include infections with *Mycobacterium* species other than *Mycobacterium tuberculosis* (MOTT), *Histoplasma capsulatum*, *Candida* species, *Listeria*, *Aspergillus* species, *Cryptococcus neoformans*, *Nocardia* species, *Salmonella* species, *Toxoplasma gondii*, *Brucella* species, *Bartonella* species, *Leishmania donovani*, *Coccidioides immitis*, CMV, and *Mycobacterium leprae* (12, 149, 156, 189). Immune reconstitution has been reported for TB (11, 56) and MOTT infection (149), and reversal reactions were seen in two patients with leprosy (156).

**Certolizumab pegol.** Certolizumab pegol is a recombinant humanized Fab' antibody fragment conjugated to polyethylene glycol which is specific for human TNF- $\alpha$  and indicated for the treatment of Crohn's disease (113; Cimzia package insert). It has currently completed phase III trials for the treatment of RA as well (85, 163). It is similar to the monoclonal antibodies infliximab and adalimumab in that it binds to both soluble and membrane-bound TNF- $\alpha$ , but it neither binds nor fixes complement and it does not induce cell-mediated toxicity in vitro, since it does not have an Fc receptor (113). Certolizumab carries the same black-box warnings for infection as do all TNF- $\alpha$  blockers. Controlled clinical studies have shown an increased rate of infection among patients treated with certolizumab compared to patients treated with placebo (38% versus 30%) (Cimzia package insert). Phase III data on Crohn's disease specifically show higher rates of serious infections in both the induction and maintenance phases, but these are comparable to the rates reported with other TNF- $\alpha$  inhibitors and are

generally low (2 to 3%). These infections included bacterial, viral, and fungal infections as well as TB (151, 155). Phase III trials of certolizumab in combination with methotrexate for RA showed similar safety data, with mostly mild infections, particularly respiratory tract infections and urinary tract infections (UTIs), with serious infections ranging from 2 to 3% versus 0% for placebo (163) and from 5 to 7% versus 2% for placebo (85), respectively.

**Etanercept.** Etanercept is a fully human dimeric fusion protein consisting of two molecules of the extracellular ligand-binding portion of human TNFR2 attached to the Fc domain of human IgG1 and is approved for the treatment of juvenile RA (JRA), RA, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis (53, 150, 189; Enbrel package insert). While early trials showed no definitive increased risk of overall infection compared to placebo (as opposed to infliximab) (101), a number of opportunistic infections have subsequently been observed with increased incidence, including TB, MOTT infection, and listeriosis (83, 149, 150, 189). Other granulomatous infections reported in higher numbers than those for placebo include histoplasmosis, candidiasis, aspergillosis, cryptococcosis, nocardiosis, and salmonellosis (180, 189). The use of etanercept in combination with other biologics, specifically anakinra and abatacept, has resulted in higher rates of infectious complications without added benefit in terms of therapeutic response (65, 194).

#### Other Biologics for Rheumatologic Diseases and Inflammatory Conditions

**Abatacept.** Abatacept is a fully human soluble fusion protein made up of the extracellular domain of human cytotoxic T lymphocyte-associated antigen 4 linked to the modified Fc portion of human IgG1 and is indicated for the treatment of refractory RA and JRA (119, 194; Orenia [abatacept] package insert [Bristol-Meyers Squibb Company, Princeton, NJ, March 2007] [<http://www.fda.gov/cder/foi/label/2007/125118s0016lbl.pdf>]). It acts by selectively modulating the CD80/CD86-CD28 costimulatory signal required for full T-cell activation. Infections most commonly associated with abatacept use are upper respiratory tract infections, although in early trials there was no difference in the incidence of infection compared to that with placebo (194). In phase III trials, the incidence of serious infections was either the same or higher than that with placebo (119, 154). A meta-analysis showed no association between serious infections and abatacept treatment for RA (148). Pneumonia, septicemia, aspergillosis, sinusitis, candidiasis, bronchitis, skin and soft tissue infections, and infections with herpes simplex virus (HSV) and varicella zoster virus (VZV) have all been reported during treatment with abatacept (94, 119, 154, 194). It seems that combination treatment with biological disease-modifying antirheumatic drugs (DMARDs) such as etanercept is more likely to lead to an adverse event, including infection, than abatacept used in combination with a nonbiological DMARD (194). A tuberculin skin test is recommended by the manufacturer prior to the initiation of abatacept. If the test is positive, the patient should receive chemoprophylaxis for latent TB prior to the start of treatment (Orenia package insert).

**Anakinra.** Anakinra is a recombinant, nonglycosylated form of the human IL-1 receptor antagonist with a single methionine residue

added at the amino terminus. It is approved for the treatment of RA (35, 37; Kineret [anakinra] package insert [Amgen Manufacturing Limited, Thousand Oaks, CA, April 2004] [<http://www.fda.gov/cder/foi/label/2004/103950s5039lbl.pdf>]). Murine models with IL-1 knockouts have demonstrated reduced survival after challenge with several bacterial species, one fungal species, one parasitic species, and one virus (influenza virus) (182). Overall, infection-related adverse events in humans treated with anakinra were similar to those with placebo and were mostly upper respiratory tract infections (37, 68). However, there seemed to be an increased risk of serious infections compared to that with placebo (2.1% versus 0.4%) in at least one study (48), although a smaller trial did not show an increased risk (37). The product label also asserts a higher risk of serious infections in patients with asthma (4% versus 0%), although post hoc analysis of the largest phase III trial showed that this difference did not reach statistical significance (154; Kineret package insert). There is an increased risk of serious infections in combination with etanercept (3.7 to 7.4% versus 0% for placebo), so combination therapy with other biologics is not recommended (65; Kineret package insert). Only one case of reactivation of TB has been reported in the literature (160), and anakinra therapy does not generally seem to put patients at higher risk of TB or other opportunistic infections, although labeling information alludes to risks for mycobacterial and fungal infections which were not further specified (Kineret package insert). One case of visceral leishmaniasis in a child with JRA after 6 months of anakinra treatment has been reported and was treated successfully (92). Mirkinson et al. (115) observed that a patient with biopsy-proven human herpesvirus 6 (HHV-6) encephalitis who then developed JRA showed improvement in the manifestations of arthritis as well as improved neurologic symptoms after treatment with anakinra. The authors proposed a link between IL-1, JRA, and HHV-6.

**Riloncept.** Riloncept is a fully human dimeric fusion protein made up of the extracellular component of the IL-1 receptor and the Fc portion of IgG1, and it binds circulating IL-1 $\alpha$  and IL-1 $\beta$  with very high affinities, thereby acting as a long-acting IL-1 inhibitor (70, 73; Arcalyst [riloncept] package insert [Regeneron Pharmaceuticals, Tarrytown, NY, February 2008] [<http://www.fda.gov/cder/foi/label/2008/125249lbl.pdf>]). It is approved for the treatment of cryopyrin-associated periodic syndromes, including familial cold autoinflammatory syndrome and Muckle-Wells syndrome (Arcalyst package insert). Two sequential placebo control phase III studies of 47 patients with cryopyrin-associated periodic syndromes showed a higher reported incidence of infection in study 1, with mostly mild upper respiratory tract infections (48% versus 17% for placebo), but not in study 2 (18% versus 22%) (73). Severe infections reported for patients using riloncept included *Streptococcus pneumoniae* meningitis, MOTT infection, and severe bronchitis (73; Arcalyst package insert). No cases of TB have been reported, although the label advises testing and treatment for latent TB prior to the initiation of therapy (Arcalyst package insert).

**Efalizumab.** Efalizumab is a monoclonal humanized recombinant IgG1 antibody against the  $\alpha$ -subunit (CD 11a) of lymphocyte or leukocyte function-associated antigen type 1 (LFA-1) and is indicated for the treatment of psoriasis (97; Raptiva [efalizumab] package insert [Genentech, Inc., South San Francisco, CA, June 2005] [[http://www.fda.gov/cder/foi/label/2005/125075\\_0031\\_lbl.pdf](http://www.fda.gov/cder/foi/label/2005/125075_0031_lbl.pdf)]). LFA-1 is a mediator of T-cell activation in lymph nodes, the transfer of these T cells

from the circulation to cutaneous sites of inflammation, and the reactivation of T cells in the dermis and epidermis (98). Infections reported in trials during treatment with efalizumab were generally mild to moderate in severity and were mostly upper respiratory tract infections, gastroenteritis, and HSV infections (98, 126). Most trials have reported no significant difference in the incidence of infection versus that with placebo, although at least one trial and a large case series reported slightly higher incidences of infection-related adverse events (158). Serious infections requiring hospitalization during treatment with efalizumab included pneumonia, cellulitis, abscess, sepsis, and necrotizing fasciitis, while opportunistic infections reported included TB, a case of disseminated *Cryptococcus* infection (178), and a case of legionellosis (126; Raptiva package insert).

**Alefacept.** Alefacept is a fully human fusion protein of LFA-3 and IgG1 that binds to CD2, inhibits T-cell activation and proliferation, and induces the selective apoptosis of memory T cells, which are important in the pathogenesis of psoriasis (69, 71; Amevive [alefacept] package insert [Astellas Pharma US, Inc., Deerfield, IL, October 2006] [<http://www.fda.gov/cder/foi/label/2006/125036s071lbl.pdf>]). Alefacept has been shown to decrease circulating CD4 and CD8 T-cell populations, and placebo-controlled studies showed a higher rate of serious infections requiring hospitalization (Amevive package insert). However, subsequent studies have failed to definitively demonstrate this association, and no opportunistic infections were reported during large clinical trials (55, 69, 71). Infections observed during treatment with alefacept include upper respiratory infections, HSV, VZV, and hepatitis C virus (HCV) infections, influenza, pneumonia, gastroenteritis, skin and soft tissue infections, and one case of MOTT infection (69, 136). Alefacept is contraindicated for patients with HIV because it decreases circulating CD4 lymphocytes. Monitoring of CD4 lymphocyte counts is recommended during therapy, and alefacept should be withheld if the circulating CD4 count decreases below 250 cells/ $\mu$ l (Amevive package insert).

## BIOLOGICS FOR MALIGNANCIES

### Antilymphocyte Antibodies

**Alemtuzumab.** Alemtuzumab is a fully humanized IgG1 against CD52 and is used in the treatment of B-cell chronic lymphocytic leukemia, T-cell prolymphocytic leukemia, and non-Hodgkin's lymphoma. It forms an antibody-antigen complex which induces the lysis of lymphocytes and other cells expressing CD52 (108; Campath [alemtuzumab] package insert [Genzyme Corp., Cambridge, MA, September 2007] [<http://www.fda.gov/cder/foi/label/2007/103948s5070lbl.pdf>]). Infections that have occurred during the course of large studies and also in case reports include overwhelming bacteremia, pneumonia, meningitis, infections with CMV, VZV, and HSV, *Pneumocystis jirovecii* pneumonia (PCP), progressive multifocal leukoencephalopathy (PML), acanthamebiasis, *Balamuthia mandrillaris* toxoplasmosis, histoplasmosis, cryptococcosis, aspergillosis, invasive fungal infection (with *Fusarium*, *Rhizopus*, or *Scedosporium*), viral infection (with BK virus, HHV-6, parvovirus, or adenovirus), candidiasis, mycobacterial infection (TB, MOTT infection, or bacillus Calmette-Guérin [BCG] in-



fection), and *Rhodococcus* infection (1, 30, 108, 112, 127, 175). Chronic HBV carriers have also experienced severe flare-ups. Since treatment with alemtuzumab results in severe and prolonged lymphopenia, prophylaxis against PCP and herpesviruses is indicated for a minimum of 2 months after completion of therapy or until CD4 counts are  $\geq 200$  cells/ $\mu$ l (Campath package insert).

**Ibritumomab tiuxetan.**  $^{90}\text{Y}$ -ibritumomab tiuxetan is a chimeric molecule composed of ibritumomab, a murine anti-CD20 IgG2a monoclonal antibody, conjugated to tiuxetan, a chelator that attaches to  $^{90}\text{Y}$  (106; Zevalin [ibritumomab tiuxetan] package insert [Biogen Idec Inc., Cambridge, MA, March 2008] [<http://www.fda.gov/cder/foi/label/2008/125019s1351bl.pdf>]). It is used as radioimmunotherapy for non-Hodgkin's lymphoma and has been shown to have superior response rates compared to rituximab (see below) (42, 45, 106), but it has a higher rate of infectious complications (197). Most infections encountered are likely a result of prolonged and severe cytopenias and include unspecified upper respiratory tract infections, UTIs, gastroenteritis, and pneumonia, and less frequently, sepsis, cellulitis, infectious diarrhea and colitis, empyema, osteomyelitis, pericarditis, viral pneumonia, and viral hepatitis (191, 197; Zevalin package insert).

**Rituximab.** Rituximab is a chimeric human-mouse IgG1 anti-CD20 monoclonal antibody used in the treatment of non-Hodgkin's lymphoma and other B-cell malignancies, as well as RA (87, 148; Rituxan [rituximab] package insert [Genentech, Inc., South San Francisco, CA, January 2008] [<http://www.fda.gov/cder/foi/label/2008/103705s52561bl.pdf>]). Treatment with rituximab results in rapid depletion of both malignant and nonmalignant CD20-positive cells and leads to depletion of normal B cells which can last for 2 to 6 months. However, serum immunoglobulin levels seem to remain stable after a conventional cycle of treatment (87). It is not consistently associated with an increased risk of bacterial infections (38, 86, 87, 148). However, there have been reports of reactivation of hepatitis B and exacerbation of hepatitis C (43, 46, 159). Sera et al. (159) reported an HBV surface antigen (HBsAg)-negative, anti-HBV surface antibody (anti-HBsAb)-positive patient converting to HBsAg-positive status with acute hepatitis during rituximab therapy, and they suggested prophylaxis with lamivudine in both HBsAg-positive and HBsAg-negative (with evidence of previous infection, i.e., anti-HBV core antibody) patients prior to initiation of rituximab therapy, despite the presence of anti-HBsAb. Rare opportunistic infections, such as PML (17, 28, 128) and parvovirus, CMV, HSV, and disseminated VZV infections, have been reported for rituximab used for treatment of malignancy (87; Rituxan package insert), but until recently, no opportunistic infections were observed when it was used for treatment of RA (38, 86, 148; [http://www.fda.gov/medwatch/safety/2008/rituxan\\_DHCP\\_Final%209411700.pdf](http://www.fda.gov/medwatch/safety/2008/rituxan_DHCP_Final%209411700.pdf)). A case of PML in an RA patient was recently reported but was confounded by concurrent therapy for oropharyngeal cancer as well as treatment with methotrexate and steroids ([http://www.fda.gov/medwatch/safety/2008/rituxan\\_DHCP\\_Final%209411700.pdf](http://www.fda.gov/medwatch/safety/2008/rituxan_DHCP_Final%209411700.pdf)). Patients at possibly higher risk of developing PML on rituximab therapy include those with systemic lupus erythematosus as well as those who are receiving hematopoietic stem cell transplantation and highly cytotoxic chemotherapy (28, 51, 128).

**Tositumomab.**  $^{131}\text{I}$ -tositumomab is a radiolabeled murine IgG2a monoclonal antibody against CD20 used in the treatment of non-Hodgkin's lymphoma and other B-cell malignancies

(Bexxar [tositumomab and iodine-131 tositumomab] package insert; Corixa Corp., Seattle, WA, December 2004).  $^{131}\text{I}$  labeling offers the advantage of targeting adjacent antigen-negative and nontargeted antigen-positive malignant cells because beta radiation travels about 0.4 mm and gamma radiation allows the quantification of the total radiation delivered (184). The major toxicity of tositumomab is neutropenia, which represents the major risk factor for infectious complications (42, 74, 184). Infections reported for patients treated with tositumomab include bacterial and viral upper respiratory tract infections as well as pneumonia (74).

### Anti-Myeloid Receptor Antibodies

**Gemtuzumab.** Gemtuzumab ozogamicin is a fully humanized anti-CD33 IgG4 monoclonal antibody conjugated with the cytotoxic antibiotic calicheamicin that is indicated for the treatment of CD33-positive acute myelogenous leukemia (8; Mylotarg [gemtuzumab ozogamicin] package insert [Wyeth Pharmaceuticals Inc., Philadelphia, PA, January 2006] [<http://www.fda.gov/cder/foi/label/2006/021174s0201bl.pdf>]). Infectious risk is related mostly to significant myelosuppression, since CD33 is also found on normal myeloid precursors, although this is reversible because pluripotent hematopoietic stem cells do not express CD33 and therefore are not affected (8). Infectious complications encountered during trials included sepsis from *Pseudomonas*, *Acinetobacter*, and *Klebsiella* infections, pneumonia, and neutropenic fever (7, 99, 164). Unusual pathogens reported with treatment include *Staphylococcus hominis*, *Agrobacterium radiobacter*, *Acinetobacter lwoffii*, *Rhodococcus*, and *Pantoea agglomerans* (142).

### Antiangiogenesis Antibodies

**Bevacizumab.** Bevacizumab is a recombinant humanized IgG1 monoclonal antibody against human vascular endothelial growth factor that is used in the treatment of advanced colorectal cancer, non-small-cell lung cancer, and breast cancer and is in trials for renal cancer (36, 144; Avastin [bevacizumab] package insert [Genentech, Inc., South San Francisco, CA, February 2008] [<http://www.fda.gov/cder/foi/label/2008/125085s1451bl.pdf>]). It has also been used as an intravitreal injection for the treatment of exudative age-related macular degeneration (81). Infectious risk has been demonstrated only in combination with chemotherapy as a result of severe neutropenia, while a black-box warning exists for intestinal perforation with or without abscess formation, presumably from the inhibition of endothelial cell proliferation and new blood vessel formation (36; Avastin package insert). Infectious complications associated with systemic bevacizumab include neutropenic fever, sepsis, and pneumonitis (36, 114; Avastin package insert). Case reports of anaerobic liver abscess with *Bacteroides fragilis* (100) and *Fusarium*-associated nasal septal perforation (144) have also been published. Intraocular injection has infrequently resulted in endophthalmitis (81, 109, 132), including at least one case each with *Bacillus cereus* (93) and coagulase-negative *Staphylococcus* (109), although an increased risk for endophthalmitis has not been demonstrated.

### ErbB Receptor Antibodies

**Cetuximab.** Cetuximab is a chimeric murine-human IgG1 monoclonal antibody against ErbB1 that is approved for colorectal and head-and-neck cancer and in trials for other ErbB1-expressing tumors. ErbB1, also known as epidermal growth factor receptor (EGFR), is constitutively expressed in many types of cancer as well as in normal epithelial tissues, including skin and hair follicles, such that blocking the activity of EGFR leads to inhibition of cell growth and induction of apoptosis and decreases matrix metalloproteinase and vascular endothelial growth factor production (52; Erbitux [cetuximab] package insert [Bristol-Meyers Squibb Company, Princeton, NJ, and Imclone Systems Incorporated, Branchburg, NJ, October 2007] [<http://www.fda.gov/cder/foi/label/2007/125084s103lbl.pdf>]). Infectious complications are largely related to cutaneous toxicity, resulting in acneiform eruptions and paronychia caused by *Staphylococcus aureus* (including methicillin-resistant *S. aureus*), which can lead to abscess formation and sepsis; these infections may represent secondary infection, while the primary process is unclear (19, 20, 75, 171).

**Panitumumab.** Panitumumab is a fully human IgG2 monoclonal antibody against ErbB1 used in the treatment of advanced colorectal cancer (52, 105; June 2008, revision date. Vectibix [panitumumab] package insert [Amgen Inc., Thousand Oaks, CA, June 2008] [<http://www.fda.gov/cder/foi/label/2008/125147s026lbl.pdf>]). Infectious events observed with panitumumab treatment are similar to those with cetuximab, including acneiform eruptions and paronychia, and are generally mild. However, there seems to be an increased incidence of severe reactions when panitumumab is used in combination with other chemotherapy (105). Blocking EGFR can decrease neutrophil-driven inflammation but does not seem to interfere with antiviral pathways, particularly in the case of respiratory syncytial virus (RSV) (103).

**Trastuzumab.** Trastuzumab is a humanized recombinant monoclonal antibody directed against HER2, which is overexpressed by certain types of breast tumors (Herceptin [trastuzumab] package insert; Genentech, Inc., South San Francisco, CA, May 2008 [<http://www.gene.com/gene/products/information/pdf/herceptin-prescribing.pdf>]). HER2 (also called human epidermal growth factor receptor 2 or ErbB2) is structurally related to EGFR but has no known ligand, although there is evidence that it may be autoactivated, suggesting that HER2 alone can cause transformation if overexpressed (52). Infectious complications are generally mild, such as upper respiratory tract infections and UTIs, and no opportunistic infections have been reported in the literature (3, 176, 183), although an increase in the number of overall infections and degree of febrile neutropenia has been reported for combinations with certain chemotherapeutic agents, such as doxorubicin plus cyclophosphamide followed by paclitaxel plus trastuzumab (Herceptin package insert). Life-threatening interstitial lung disease has been reported, although it was not clearly identified as infectious in nature (129). Interestingly, ErbB2 activation has been implicated in demyelination induced by *Mycobacterium leprae*, and ErbB2 blockade has been shown to abrogate *M.*

*leprae*-induced myelin damage in both in vitro and in vivo models (172).

### BIOLOGICS FOR TREATMENT OF OTHER DISEASES AND OTHER INDICATIONS

#### Monoclonal Antibodies for Graft-Versus-Host Disease and Transplant Rejection

**Basiliximab.** Basiliximab is a chimeric murine-human IgG1 monoclonal antibody directed against the  $\alpha$ -chain of the IL-2 receptor (IL-2R $\alpha$  or CD25), is indicated as immunoprophylaxis in the prevention of rejection of renal transplants, and has been studied for prophylaxis in other solid organs (34, 84; Simulect [basiliximab] package insert [Novartis Pharmaceutical Corp., East Hanover, NJ, January 2003] [<http://www.fda.gov/cder/foi/label/2003/basnov010203LB.htm>]). CD25 blockade by basiliximab prevents IL-2-mediated activation of lymphocytes, a critical pathway in cell-mediated immune responses which is intimately involved in allograft rejection (Simulect package insert). No increased incidence of infection was reported with basiliximab versus placebo in initial trials for rejection (34, 82, 84). One study reported a higher incidence of CMV disease but a lower overall infection rate than that with antithymocyte globulin (ATG) (23). This increase in CMV disease was not borne out in a retrospective study involving presensitized patients (199). Infections observed during treatment with basiliximab include bacterial infections, particularly UTIs, infections with CMV and HSV, aspergillosis, nocardiosis, candidiasis, and protozoal infections (23). Among liver transplant patients, basiliximab-treated patients actually had a lower incidence of HCV recurrence and no difference in post-transplantation lymphoproliferative disease or CMV incidence (137). In cardiac transplant patients, basiliximab treatment had a lower incidence of infectious deaths than did ATG treatment (110).

**Daclizumab.** Daclizumab is a recombinant humanized IgG1 anti-CD25 monoclonal antibody that affects activated T cells through the IL-2R $\alpha$  chain and is indicated for induction therapy in the prevention of rejection in renal transplant recipients. It is also being studied for other solid organ transplant recipients (26, 76; Zenapax [daclizumab] package insert [Hoffman-La Roche Inc., Nutley, NJ, September 2005] [<http://www.fda.gov/cder/foi/label/2005/103749s5059lbl.pdf>]). The mechanism of action is the same as that for basiliximab. Infections associated with daclizumab for induction therapy are generally mild upper respiratory tract infections, and in comparison with ATG, daclizumab has a lower incidence of CMV viremia (26, 76). One retrospective study found a higher incidence of *Aspergillus* colonization and invasive disease than that with ATG in lung transplant patients, although the reason for this was not clear (80). When used for steroid-refractory graft-versus-host disease in combination with other immunosuppressive therapy, daclizumab was found to have an extremely high rate of opportunistic infections (95%), although there was lower mortality than that with ATG used for the same indication. These infections included the usual bacterial infections as well as *Nocardia*, *Legionella*, and MOTT infections, TB, viral infections (CMV, BK virus, adenovirus, HSV, RSV, and influenza virus), and invasive fungal infections (*Aspergillus*, *Scedospor-*

*rium*, *Cunninghamella*, and *Candida*) (131). When combined with cytolytic therapy in heart transplant patients, more patients treated with daclizumab died than those receiving placebo (six versus zero) (72). Finally, in heart transplant patients treated with daclizumab in combination with other immunosuppressive drugs, a progressive decline in pneumococcal polysaccharide antibodies in previously vaccinated individuals was observed during the year after transplantation (152).

**Muromonab.** Muromonab (OKT3) is a murine IgG2 monoclonal antibody against CD3 indicated for acute rejection in solid organ transplant recipients (161; Orthoclone-OKT3 [muromonab] package insert [Ortho Biotech, Raritan, NJ, November 2004] [[http://www.orthobiotech.com/orthobiotech/shared/OBI/PI/OKT3\\_PI.pdf](http://www.orthobiotech.com/orthobiotech/shared/OBI/PI/OKT3_PI.pdf)]). The interaction of muromonab with CD3, found in all T lymphocytes, blocks the generation and function of effector T cells and leads to a rapid decrease in the number of circulating CD3-positive cells. Binding of muromonab to T cells results in early activation, leading to cytokine release followed by the blocking of T-cell functions. T-cell function returns to normal after muromonab therapy, within about a week (Orthoclone-OKT3 package insert). Infection rates with muromonab were not significantly different from previous experience with non-monoclonal-antibody-containing regimens. However, there is evidence that the rates of post-transplantation lymphoproliferative disease and lymphoma are increased compared to those with antirejection regimens that do not employ muromonab therapy (117). Infections reported with OKT3 therapy include infections with *Listeria*, *Nocardia*, MOTT, *Aspergillus*, *Candida*, *Cryptococcus*, dermatophytes, PCP, *Toxoplasma gondii*, CMV, Epstein-Barr virus, HSV, hepatitis viruses, VZV, adenovirus, enterovirus, RSV, and parainfluenza virus but have not been significantly different in head-to-head studies from basiliximab and daclizumab or from high-dose steroids alone (29, 157; Orthoclone-OKT3 package insert). Because muromonab is usually administered with other immunosuppressive drugs, resulting in profound immunosuppression, the manufacturer suggests judicious use of anti-infective prophylaxis, including that directed against herpesviruses such as HSV and CMV (Orthoclone-OKT3 package insert).

#### Monoclonal Antibodies for Cardiovascular Disease

**Abciximab.** Abciximab is the Fab' fragment of a chimeric human-mouse monoclonal antibody against the glycoprotein IIb/IIIa receptor, which is responsible for platelet aggregation and is indicated as an adjunct in the treatment of acute coronary syndrome following percutaneous coronary intervention (13; Reopro [abciximab] package insert [Centocor B.V., Leiden, The Netherlands, November 2005] [<http://www.centocor.com/centocor/assets/reopro.pdf>]). At least one study showed a slightly higher incidence of pneumonia than that with placebo, although the mechanism and significance of this finding are unknown. Otherwise, no additional risk of infection has been associated with abciximab (Reopro package insert). In fact, there is in vitro and murine model evidence that glycoprotein IIb/IIIa inhibition protects against endothelial cell dysfunction and leukocyte adherence to the vascular wall during experimental endotoxemia (88, 190).

#### Monoclonal Antibodies for Neurologic Disease

**Natalizumab.** Natalizumab is a humanized recombinant IgG4 monoclonal antibody that binds to the  $\alpha 4\beta 1$  (very late activating antigen 4) and  $\alpha 4\beta 7$  integrins, found in all white blood cells except for neutrophils, and is indicated for the treatment of relapsing multiple sclerosis (MS) and Crohn's disease (169, 170; Tysarbi [natalizumab] package insert [Biogen Idec Inc., Cambridge, MA, January 2008] [<http://www.fda.gov/cder/foi/label/2008/125104s033lbl.pdf>]). The pathogenesis of MS is thought to be driven by the egress of inflammatory cells into the central nervous system from the peripheral blood, and natalizumab interferes with this process (89, 168). Natalizumab was voluntarily withdrawn from the market in 2005 following the development of PML caused by the JC polyomavirus in three patients, but it has now been reapproved for relapsing forms of MS and Crohn's disease (168; Tysarbi package insert). Analyses of previous clinical trials indicate that the risk of development of PML with natalizumab is estimated to be around 0.1% during a mean of 17.9 monthly doses (200). Measurement of immunologic parameters in treated patients has shown that natalizumab leads to a prolonged decrease in lymphocytes in the central nervous system, particularly CD4 T cells and B cells; this deficit persists for over 6 months (natalizumab half-life = 11 days) after treatment (168, 170) and could presumably be responsible for the increased risk for PML. Other infections reported with natalizumab include upper respiratory tract infections, bacterial pneumonias, and UTIs, as well as PCP and infections with *Cryptosporidium parvum*, *Mycobacterium avium* complex, *Aspergillus* species, HSV, influenza virus, and *Burkholderia cepacia*. Most trials show that the overall risk of infection is no different from that with placebo (Tysarbi package insert).

#### Monoclonal Antibodies for Pulmonary Disease

**Omalizumab.** Omalizumab is a chimeric humanized IgG1 monoclonal antibody that binds human IgE, is indicated for the treatment of asthma, and is in trials for allergic rhinitis and other eosinophil-associated disorders (50, 133; Xolair [omalizumab] package insert [Genentech, Inc., South San Francisco, CA, July 2007] [<http://www.fda.gov/cder/foi/label/2007/103976s5102lbl.pdf>]). Mild infections, including upper respiratory tract infections and viral infections, have been observed with omalizumab, but the incidence of infection was no different from that with placebo (Xolair package insert). Prolonged therapy has been shown to result in a sustained decrease in IgE levels, which could theoretically decrease immunity toward helminthic infections (58, 165). A trial in Brazil with patients at high risk for geohelminth infections showed a trend toward increased infection risk, but the risk was not statistically different from that with placebo (40).

**Palivizumab.** Palivizumab is a humanized monoclonal antibody (IgG1) against an epitope in the A antigenic site of the F protein of RSV and is indicated for the prevention of serious lower respiratory tract infection due to RSV in pediatric patients at high risk (173; Synagis [palivizumab] package insert [MedImmune Inc., Gaithersburg, MD, February 2007] [<http://www.fda.gov/cder/foi/label/2007/103770>]).

\_50961bl.pdf]). The incidences of upper respiratory tract infections, rhinitis, and otitis media were slightly increased compared to those with placebo in initial trials (Synagis package insert), although subsequent studies did not bear this out (146, 173). In a trial involving a second course of palivizumab in the subsequent year, an increased incidence of otitis media was noted in the group receiving a second course compared to the group receiving a single course and placebo, although this was judged not to be related to palivizumab by the investigators (121). At present, there is no evidence that palivizumab increases susceptibility to infection.

### Monoclonal Antibodies for Imaging

**Arcitumomab.** Arcitumomab is the  $^{99m}\text{Tc}$ -labeled Fab' fragment of the anti-CEA IgG1 murine monoclonal antibody IMMU-4 and is indicated for detection of advanced colorectal cancer in conjunction with other diagnostic modalities (47; CEA-Scan [arcitumomab] package insert [Immunomedics, Inc., Morris Plains, NJ, August 1999] [<http://www.cea-scan.com/inserts/pckginstr.htm>]). Initial trials for approval, using mostly single-dose infusions, as well as serial administration in subsequent trials did not show any associated infection-related adverse events (54, 193). While arcitumomab has been shown to have similar accuracy to that of fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) in detecting local recurrence of cancer, FDG-PET is clearly superior in detecting distant metastasis and so the use of the anti-CEA scan is less preferred (195).

**Technitium fanolesomab.**  $^{99m}\text{Tc}$ -fanolesomab is a murine anti-CD15 IgM monoclonal antibody labeled with  $^{99m}\text{Tc}$  which was approved for imaging of equivocal cases of acute appendicitis and was in trials for use in imaging osteomyelitis and occult infection (6, 90, 104, 162; Neutro-Spec [fanolesomab] package insert [Palatin Technologies, Inc., Cranbury, NJ, July 2004] [<http://www.fda.gov/cder/foi/label/2004/1039281bl.pdf>]). The drug was withdrawn from the market in 2005 following two fatalities and reports of serious cardiovascular complications during postmarketing surveillance (90). Shortly after infusion, a transient drop in the absolute neutrophil number has been observed, but no infectious complications have been attributed to Tc-fanolesomab (102, 104).

**Capromab pendetide.** Capromab pendetide is an indium-111-radiolabeled murine monoclonal antibody (7E11-C5.3) covalently joined to a linker-chelator molecule directed against human prostate-specific membrane antigen and is used in the detection of recurrence in patients with prostate cancer (95, 116; Proscint [capromab pendetide] package insert [Cytogen Corporation, Princeton, NJ, October 1996] [<http://www.fda.gov/cder/foi/label/1996/capcyt102896lab.pdf>]). No infections have been associated with capromab use during single and repeated infusions, although some patients have developed fever and local site irritation (95, 135).

**Nofetumomab.**  $^{99m}\text{Tc}$ -nofetumomab merpentan is the Fab' fragment of the IgG2 murine antibody NR-LU-10 against carcinoma-associated glycoprotein antigen radioconjugated with  $^{99m}\text{Tc}$  and is indicated as a diagnostic imaging agent for staging patients with lung cancer, particularly as an adjunct when results from other studies are equivocal; it has also been evalu-

ated for use with other carcinomas (10, 22, 167; Verluma [nofetumomab] package insert [Dr. Karl Thomae GmbH, Ingelheim, Germany, August 1996] [<http://www.fda.gov/cder/foi/label/1996/nofedrck082096lb.pdf>]). No infectious complications have been associated with this agent.

### THE FUTURE: PANDORA'S BOX OR HORN OF PLENTY?

Based on the human genome, it is estimated that there are about 6,000 to 8,000 targets of pharmaceutical interest, with around 300 currently targeted by existing drugs (96). The science of monoclonal antibodies and the development of small molecules that target important cellular steps or factors, coupled with further advances in recombinant protein technology, create nearly infinite possibilities to manipulate disease pathways. The ongoing development of drugs that target specific pathways of the immune system, such as the JAK/STAT pathway and other immunoreceptors such as those involved in antigen recognition and processing, as well as those targeting complement, will give rise to agents with profound effects on immune function and risk for infections (96, 166). As more and more biologics find their way into our therapeutic armamentarium, the challenge becomes not whether a drug exists to treat a disease but which is the most appropriate with the lowest number of side effects, not the least of which are infectious complications.

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