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Literature Review

Infections in Patients with Systemic Lupus Erythematosus: The Contribution of Primary Immune Defects Versus Treatment-Induced Immunosuppression

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Abstract

Patients with systemic lupus erythematosus experience high rates of infections. The use of immunosuppressive drugs to treat the disease, along with the fact that both the innate and adaptive branches of the immune system are compromised, account for the development of infections. In this communication, we briefly discuss the aberrant function of the immune system in patients with systemic lupus erythematosus and review the occurrence of infections that have been reported in clinical trials conducted to develop new therapeutics. Understanding the immune dysfunction in patients with systemic lupus erythematosus and the appearance of infections while trying to control the disease using immunosuppressive or immunomodulatory drugs should help limit infections and mitigate the associated morbidity and mortality.

Keywords: Systemic lupus erythematosus, infections, immunosuppression

Introduction

Patients with systemic lupus erythematosus (SLE) display a compromised immune system due to abnormalities affecting both the innate and adaptive components of the immune response.[1] In addition, treatment invariantly involves using immunosuppressive drugs. Both the immunocompromised status and drugs used to treat patients with SLE contribute to increased susceptibility to acute and chronic infections, leading to increased morbidity and mortality.[2] While new therapeutic approaches have been introduced or are under investigation, it should be noted that they also possess immunosuppressive properties and thereby increase the vulnerability of patients to infections.[3]

Apart from the heightened susceptibility to infections in individuals with SLE, it is important to keep in mind that infections can trigger disease flares by stimulating the innate immune system or by cross-reacting with receptors of the adaptive immune cells. This can complicate the diagnostic process and the selection of appropriate treatment. Diagnosis may present challenges because symptoms, such as fever, lymphadenopathy, pulmonary infiltrates, skin and mucosal rashes, and coagulopathy, may be shared by a disease flare and an ongoing infection.[2] Accordingly, it is important to maintain a high level of clinical vigilance when it comes to diagnosing and treating infections in individuals with SLE. The enhanced recognition and treatment of infections in individuals with SLE during the past 4 decades have significantly improved the survival rates.[4] This review will present a discussion of the increased susceptibility of patients with SLE to infections as a result of their immunocompromised status as well as the infections that result from the use of immunosuppressive drugs.

Immune Defects Leading to Increased Risk to Infections

Patients with SLE are vulnerable to infectious agents because of deficiencies in both the adaptive and innate immune systems.[1] (Table 1)

Cells of the Innate Immune Response

Several abnormalities in neutrophils, macrophages, and monocytes have been reported in individuals with SLE. Monocytes exhibit impaired engulfment of apoptotic cells and reduced phagocytic activity.[5] The antigen-presenting function of the macrophage/monocyte system is also defective.[2] Production of superoxide following Fcγ receptor-mediated phagocytosis, which is important in the defense against infectious agents, is impaired.[6] This can be further compromised by autoantibodies against the Fcγ receptors.[7] The

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Table 1. SLE immune dysfunctions predisposing to infection

Cells, Proteins, and Cytokines	Relation to Infections
Monocytes/macrophages	• Reduced capacity to phagocytose apoptotic cells • Reduced phagocytic activity
Neutrophils	• Neutropenia • Impaired chemotaxis • Diminished phagocytic capacity • Impaired reactivity to IL-8 cytokine signaling resulting in less efficient mobilization and a decreased granulocyte response • Defective response to secondary stimuli • Impaired neutrophil function against infection • Increased upregulation and overproduction of NETs, resulting in excessive release of phagocytic intracellular proteins and inflammatory cytokines. This, in turn, fosters local collateral damage in the form of endothelial damage and vascular injury.
Lymphocytes	• Lymphopenia (mostly CD4+ lymphopenia) • Reduced production of IL-2 and IFN-γ • Impaired T-cell cytotoxic capacity • Low immunoglobulin levels and immunoglobulin subclass deficiencies • Antibodies against Fcγ receptor • Defects in maturation of B-cell maturation
NK cells	• Decreased numbers and function
Cytokine dysregulation	• Increased TNFα production • Increased IL-10 • Decreased IL-2 production • Decreased G-CSF
Complement system	• Hypocomplementemia • Complement C1-q deficiency • Mannose-binding lectin pathway polymorphisms • Immune complexes' utilization of complement proteins diminishes the quantity of available complement for regular defense purposes • Reduction in complement system components which impairs patients' ability to combat encapsulated microorganisms effectively • Reduced expression of CR1 on polymorphonuclear cells leads to a diminished recognition by phagocytes

CD, cluster of differentiation; CR1, complement receptor type 1; IFN-γ, interferon gamma; Ig, immunoglobulins; IL, interleukin; G-CSF, granulocyte colony-stimulating factor; NET, neutrophil extracellular traps; NK, natural killer; SLE, systemic lupus erythematosus; TNFα, tumor necrosis factor alpha.

phagocytic function of macrophages and neutrophils may be influenced by autoantibodies targeting the 3 subclasses of Fcγ receptors (FcγRI, FcγRII, FcγRIII). These autoantibodies can further disrupt the immune system because Fcγ receptors are expressed on the surface membrane of B cells, natural killer cells, and specific γδT cells.[8]

Neutrophil counts are frequently decreased in patients with SLE, and their function can also be defective.[1,9] For more than 50 years, there has been evidence suggesting impaired phagocytosis by polymorphonuclear leukocytes.[10] Sera from patients with SLE and active disease suppress the opsonization of protein A-containing *Staphylococcus aureus*.[11] Neutrophil numbers and function may be diminished by complement-activating antineutrophil antibodies and, in some cases, antibodies targeting myeloid precursors.[12] Moreover, some SLE patients possess circulating autoantibodies targeting the neutrophil adhesion glycoproteins αMβ2, antibodies that may inhibit the receptor function of Mac-1 proteins.[13]

The presence of excessive amounts of immune complexes in the circulation is likely the primary cause of persistent neutrophil activation during active phases of the disease.[14] As a consequence of prior neutrophil activation, patients with SLE might display impaired neutrophil function in response to infections. Increased levels of neutrophil apoptosis contribute to the probability of functional neutropenia and serve as an additional source of autoantigens. Abnormal levels of neutrophil extracellular traps (NETs), a host defense mechanism designed to trap pathogens, have been extensively documented in patients with SLE. Production of NET becomes even more pronounced during infections, resulting in an excessive release of autoantigens and cytokines, which contribute to collateral damage from vascular and endothelial injury.[15] Furthermore, SLE neutrophils exhibit decreased responsiveness to IL-8, potentially leading to inadequate mobilization and a limited granulocyte response.[16]

The function and numbers of Natural Killer (NK) cells are notably diminished, especially during phases of disease exacerbation. Circulating NK antibodies can also induce cytotoxic effects, resulting in decreased NK numbers.[17–22]

In summary, cells of the innate immune system display compromised function through multiple mechanisms.

Lymphocytes

Lymphocytes in patients with SLE present a number of abnormalities.[17,22–25] Lymphopenia, particularly cluster of differentiation (CD) 4 cytopenia, is frequent. There is a reduction in the production of key cytokines, such as interleukin (IL)-2 and interferon-γ, while the production of cytokines with proinflammatory properties, including IL-17, is increased.[26]

Despite the evident polyclonal B-cell activation and hyperglobulinemia in lupus patients, B cells seem to maintain proper functionality. An early study revealed that CD8 T cells from lupus patients were unable to control and eliminate autologous B cells infected with the Epstein–Barr virus (EBV). As a result, there is a continuous expansion of antibody and autoantibody production. The number of CD8 T cells able to bind EBV antigen is diminished in the circulating blood of lupus patients.[27] The failure of $CD8^+$ T cells to control other viruses can explain the increased susceptibility of SLE patients to viral infections.

To demonstrate that systemic autoimmunity accounts for an inherently immunocompromised status, Lieberman and Tsokos[28] infected lupus-prone mice with the intracellular parasite

T. gondii. Lupus-prone mice succumbed early because their T cells failed to produce interferon gamma (IFN-γ), a cytokine that is needed for the proper defense against *T. gondii*.

Among $CD8^+$ T cells, a unique subset ($CD8^+CD38^{high}$ T cells) is expanded in patients with SLE.[29–31] CD38 is an ectoenzyme that degrades nicotinamide dinucleotide (NAD) and, through distinct molecular mechanisms, suppresses the expression of molecules that are responsible for the expression of cytotoxic activity, such as CD107, perforin, and granzymes.[32–34] In a cross-sectional study, infections occurred at high rates almost exclusively with a $CD8^+CD38^{high}$ T cell subset. Indeed, $CD8^+CD38^{high}$ T cells display limited, if not absent, cytotoxic activity.[35] Further, this $CD8^+CD38^{high}$ T cell subset displayed limited mitomicrophagy and lysosomal activity. Of great translational value is the finding that CD8-targeted delivery of a CD38 small drug inhibitor suppressed hepatitis in lupus-prone mice infected with lymphocytic choriomengitis virus.[36]

In a prospective evaluation of 80 patients with SLE, we found that the patients with an expanded $CD8^+CD38^{high}$ T cell subpopulation experienced more infectious events than the remaining patients (unpublished data).

In individuals with SLE, T-cell abnormalities encompass diminished cytotoxic capacity as assessed by allogeneic cell-mediated lymphol-ysis, along with reduced NK cell activity. Early studies had shown that IL-2 can restore allogeneic and NK cell cytotoxicity.[37] More recently, a study involving 665 lupus patients revealed that treatment with low-dose IL-2 therapy reduces by threefold the incidence of infections in SLE patients.[38]

Complement System

Genetic deficiency in various components of the complement pathways not only increases the risk of developing SLE but also predisposes individuals to infections.[39] Immune complexes formed in patients with SLE can consume complement proteins, leading to a reduction in the available complement for formal defense mechanisms. Complement 1q is involved in the clearance of apoptotic material, and patients with C1q deficiency have heightened vulnerability to bacterial and viral infections.[40,41] Also, certain mannan-binding lectin deficiencies have been linked to impaired opsonization. Increased consumption of complement components in SLE patients further impairs their ability to combat encapsulated microorganisms.[42]

A significant number of patients exhibit low levels of CR1, the complement receptor for C3b, on the plasma membrane of erythrocytes.[40,43] It is possible that during disease flares, these levels are further decreased because they are occupied by immune complexes.[44] Additionally, there is a decreased expression of CR1 on polymorphonuclear cells, and the presence of autoantibodies against CR1 has also been identified. Reduced expression of CR1 on these cells can lead to weakened phagocytosis.[45] CR1 on erythrocytes transports immune complexes to the spleen, the main harbor of reticuloendothelial cells. Dysfunction of the spleen has been reported in patients with SLE. Up to 5% of SLE patients exhibit functional hyposplenism, which leads to an elevated risk of infections caused by encapsulated microorganisms and bacteria like *Haemophilus* sp., *Salmonella*, and *Pneumococci*.[46-48]

Compromised Anatomic Barriers to Infectious Agents

Anatomic lesions in patients with SLE caused by the disease itself present additional risk factors for infection. Skin lesions can compromise the integrity of the protective epidermal and other skin layers, increasing the vulnerability to secondary infections. The presence of skin lesions in SLE patients creates an entry point for pathogens, raising the risk of infection. Small vessel injury and glomerular scarring in the kidneys can lead to urinary tract infections (UTIs).[2] End-stage renal disease and pulmonary fibrosis in patients with SLE can compromise the defensive capacity of the host against pathogens.[1] In the gastrointestinal mucosa, capillary vasculitis may enable the leakage of pathogens into the circulation, thus increasing the risk of sepsis.[49] These anatomic lesions in SLE patients significantly contribute to the heightened vulnerability to different types of infections. Managing these risk factors and promptly addressing any infections that arise are crucial in the comprehensive care of individuals with SLE.

Epidemiology and Types of Infections

Epidemiology

Infections play a substantial role in the morbidity and mortality of lupus patients. They are responsible for a substantial proportion of hospitalizations (13%-37%) and approximately one-third of overall deaths.[50] (Table 2) Infection rates, types of infectious agents, and gravity of infections differ between developed and developing countries. *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Candida* infections are more prevalent in developing nations. The occurrence of tuberculosis is significantly lower in developed countries. In general, infectious diseases are known to be more prevalent and pose twice the risk in developing countries.[51] The majority of epidemiologic studies on the incidence and mortality of infections in patients with SLE have relied on inpatient data. In a study involving nearly 175 000 SLE-related hospitalizations in the USA in 2016, infections were the primary cause of in-hospital mortality (38.18%), with cardiac disease ranking second (12.04%).[52]

Bacterial Infections

Bacterial infections are prominent in SLE patients and account for two-thirds of infections. Most bacterial infections are caused by opportunistic bacteria. Retrospective studies worldwide (North America, India, Africa, Europe, and Asia) have reported pathogens such as *Escherichia coli, Streptococcus pneumoniae, Staphylococcus aureus, Salmonella enterica,* and mycobacteria species. Although these bacteria can be found in the general population, they tend to induce more severe infections in patients with SLE. Colonization by these bacteria has the potential to exacerbate the ongoing autoimmune response and/or trigger new disease flares. In SLE, the respiratory and urinary tracts, along with the skin, are the common infection sites, representing over 60% of reported cases.[51,76–78]

Viral Infections

SLE patients have an increased susceptibility for viral diseases. Viruses like EBV, cytomegalovirus (CMV), and parvovirus B19 may trigger the development of SLE. Herpes zoster (HZ) is the most prevalent viral infection in SLE patients, with an incidence of 6-32/1000 person-years.[51] HZ occurs when the varicella-zoster virus reactivates from dorsal root ganglia following primary infection. Cellular immune mechanisms primarily regulate this latent virus, and its reactivation can occur when CD8 cytotoxic cell function is compromised. SLE patients have a 2-3 times higher incidence of HZ compared to the general population.[79]

Fungal Infections

Invasive fungal infections are being increasingly reported in patients with SLE. In a study of 24 541 SLE patients, 445 fungal infections were recorded with 26.7% lethality. Among the fungi, *Candida* (52.8%), *Cryptococcus* (18.2%), and *Aspergillus* (18.2%) were the common pathogens.[80]

Coronavirus Disease 2019

Most SLE patients are not at increased risk of contracting coronavirus disease 2019 (COVID-19). Nevertheless, SLE patients may have taken

Table 2. Infection as the Leading Cause of Death in SLE

Lead Author (Reference)	Duration (Years)	Number of Patients	Number of Deaths	Death Caused by Infections (%)	Published Year
Wallace et al[53]	30	609	128	21	1981
Rosner et al[54]	13	1103	222	33	1982
Huicochea Grob et al[55]	23	65	14	29	1996
Kim et al[56]	4	544	43	33	1999
Jacobsen et al[57]	20	513	122	21	1999
Mok et al[58]	24	186	9	67	2000
Rodriquez et al[59]	34	662	161	27	2000
Bernatsky et al[60]	30	9547	1255	5	2006
Wadee et al[61]	15	226	55	44	2007
Nossent et al[62]	5	2500	91	57	2007
Al Arfaj et al[63]	30	624	25	48	2009
Goldblatt et al[64]	29	104	67	25	2009
Feng et al[65]	11	1956	116	25.9	2011
K McElhoneet al[66]	3	382	37	37.8	2014
Dubula et al[67]	6.5	167	24	62.5	2015
Tektonidou et al[50]	63	20 318	2179	33	2015
Chen et al[68]	10	3815	84	57	2016
Budhoo et al[69]	9.5	408	53	49.1	2016
Padjen et al[70]	10	967	90	33	2018
Wu et al[71]	10	29 510	360	65.8	2019
Dhital et al[52]	1	174 105	3405	38.1	2019
Ingvarsson et al[72]	25	175	60	15	2019
Gonzalez Lucero et al[73]	8	353	32	43.17	2020
Bultink et al[74]	25	4356	442	32	2021
Moghaddam et al[75]	18	6092	451	25	2022

more restrictive measures, including isolation, for fear of having a worse outcome if they contracted COVID-19.[81] The COVID-19 Global Rheumatology Alliance (C-19-GRA) registry, consisting of over 20 000 patients with rheumatic diseases and COVID-19, provided data suggesting that SLE patients with moderate or high disease activity, as well as those taking specific medications (such as moderate or high doses of prednisone, rituximab, and immunosuppressive drugs like Azathioprine (AZA), mycophenolate mofetil (MMF)/mycophenolic acid (MPA),Cyclophosphamide (CYC), and tacrolimus (TAC)), experience more unfavorable outcomes compared to a reference group of individuals receiving methotrexate.[82,83]

A recent extensive analysis conducted on the medical records from primary care of over 17 million adults found that individuals diagnosed with autoimmune diseases like SLE, rheumatoid arthritis (RA), or psoriasis had heightened susceptibility to COVID-19-related mortality. It is important to note that this increased risk persists even after adjusting for demographic characteristics and comorbidities. Nonetheless, the study did not take into account medication use, nor did it assess SLE as a distinct disease.[83]

In an extensive analysis by Ugarte-Gil et al,[83] the C19-GRA and European Alliance of Associations for Rheumatology (EULAR) COVID-19 registries were examined to assess the outcomes of patients with rheumatic diseases, including SLE, from March 2020 to June 2021. The study included a total of 1606 individuals with SLE. Using a multivariable model, the study reported that older age, male sex, high prednisone doses, absence of current treatment, comorbidities, and more severe COVID-19 outcomes were linked to moderate to high disease activity in SLE patients. Furthermore, after adjusting for sex and age, it was reported that MMF, rituximab, and CYC were linked to worse outcomes in comparison to hydroxychloroquine. On the other hand, methotrexate and belimumab were associated with favorable outcomes.

Type-I interferons (IFNs-I) are excessively produced in SLE patients, and they play an essential role in early viral infection control. Autoantibodies against interferon-α (IFN-α) have been observed in SLE patients, but their exact significance remains unclear, whether they are pathogenic, protective, or merely indicative of a general autoreactivity tendency.[84–87] A cohort of over 600 SLE patients was examined for the presence of serum antibodies against IFN-α. Neutralizing and non-neutralizing IFN-α antibodies were found in 3.3% and 8.4% of individuals with SLE, respectively. Neutralizing antibodies were associated with decreased levels of IFN-α in the serum and a lower risk of developing active disease. However, they did increase the susceptibility to severe COVID-19 pneumonia and HZ. Severe COVID-19 pneumonia in SLE patients was primarily associated with the combined neutralization of various IFNs-I, but IFN-α autoantibodies did not affect the humoral immunogenicity of COVID-19 vaccines.[88]

Infections Caused by Treatment

Treatment choices for SLE are limited to corticosteroids and various immunosuppressive drugs. While these drugs demonstrate efficacy in managing SLE, they also raise the susceptibility to infections. Lupus patients treated with immunosuppressive agents appear to have a higher vulnerability to infections in comparison to individuals with other rheumatic diseases receiving similar treatment.[89] This suggests that while immunosuppressive agents contribute to a higher infection risk, they are not the sole determining factor.[89] Immunosuppressive treatment in patients with SLE has a double impact on immunity. While it suppresses the activity of abnormal cells, it can also normalize other features of the immune system. For instance, in untreated patients, the migration of the neutrophil is significantly decreased. However, treatment can normalize neutrophil migration,[90] and high doses of corticosteroids can enhance Fc receptor-mediated mononuclear phagocyte function. Consequently, patients receiving therapy may demonstrate enhanced neutrophil migration and phagocytic function in contrast to untreated SLE patients.[91] The risk of infection in SLE can vary according to the type of immunosuppression used. We will review studies investigating drugs used to treat patients with SLE and

studies attempting to introduce new biologics and small drugs.

Hydroxychloroquine

Chloroquine and hydroxychloroquine were initially developed as antimalarial drugs, but they have also been proven to be effective in treating autoimmune diseases, particularly SLE. In addition to their antimalarial properties, they exhibit antibacterial, antifungal, and antiviral effects, achieved through a pH-dependent iron deficiency and the ability to increase lysosomal pH, which hampers the proliferation of intracellular organisms. Chloroquine and hydroxychloroquine demonstrate antibacterial activity against *Staphylococcus aureus, Mycobacterium tuberculosis, Salmonella typhi,* and *Escherichia coli*, while also exhibiting antifungal properties against *Cryptococcus*, *Histoplasma,* and *Aspergillus*.[92]

There is no evidence suggesting an enhanced risk of infection associated with the use of hydroxychloroquine. Yet, certain studies[93-95] have reported a significant protective effect against infections in patients with SLE, including those with lupus nephritis (LN). Furthermore, a comprehensive analysis encompassing 44 trials involving more than 9000 patients revealed that treatment with hydroxy chloroquine resulted in a reduced susceptibility to infections when compared to other medications such as methotrexate, placebo, rituximab, low-dose belimumab, medium-dose belimumab, and high-dose belimumab. These results emphasize the potential benefits of hydroxy chloroquine in mitigating the risk of infection in SLE patients.[3]

Methotrexate

Methotrexate inhibits purine and thymidylic acid synthesis and interferes with DNA synthesis, repair, and cell replication.[96] Despite the immunomodulatory properties of methotrexate, the doses used to treat rheumatologic diseases are not significantly immunosuppressive, and typically they do not lead to opportunistic infections unless the patients simultaneously receive high doses of steroids or other immunosuppressive agents.[96] A meta-analysis of 12 randomized controlled trials with more than 1100 subjects reported that methotrexate was associated with an elevated risk of infections among patients with RA but not in people suffering from other inflammatory rheumatic diseases.[97] In patients taking methotrexate who develop an infection, it is recommended to continue the medication for mild infections that do not require antibiotics; the same holds for patients going through low-risk surgery. For moderate infections necessitating antibiotics, it is advisable to withhold methotrexate until finishing the use of antibiotic and symptoms are resolved. In cases of severe infections requiring hospitalization or parenteral antibiotics, methotrexate should be suspended until antibiotic treatment is finished, inflammatory markers return to normal, and symptoms are solved. In patients with severe infections, particularly those with renal disease, early administration of intravenous folinic acid rescue may also prove advantageous.[98]

Azathioprine

Azathioprine is a prodrug that undergoes rapid metabolism in the intestinal tract, liver, and erythrocytes to form 6-mercaptopurine, which is responsible for the immunosuppressive and toxic effects of AZA.[99] One-tenth of individuals with rheumatic diseases who are treated with AZA may experience infections.[100] The likelihood of bacterial infections is heightened when leukopenia is present, while viral infections, notably HZ, can affect up to 6% of patients receiving treatment. Additionally, AZA may worsen chronic viral hepatitis in certain individuals.[101]

A systematic review and meta-analysis of 9898 participants reported that AZA demonstrated a higher level of safety when compared to glucocorticoids. However, it was observed that the combination of CYC followed by AZA increased the likelihood of experiencing infections. TAC exhibited superior efficacy in preventing serious infections compared to CYC, AZA, and MMF combined with TAC, as well as CYC followed by AZA.[3] Currently, there are no established guidelines guiding when to discontinue AZA in the presence of infections. The determination should be personalized, considering factors like the gravity and recurrence of infections, existing medical conditions, and concurrent usage of other medications.

Mycophenolate

Mycophenolate (MMF) mofetil is a prodrug converted to mycophenolic acid (MPA) (active form). MPA inhibits the production of guanine nucleotides, impairs DNA synthesis, and consequently reduces lymphocyte proliferation and antibody production. There is evidence that it reduces fibroblast proliferation, resulting in antifibrotic activity.[102]

The occurrence of infections in individuals with rheumatic diseases who receive MMF treatment is supported by limited evidence. However, insights from studies in animal models[103] and trials in patients with renal allografts[104] suggest that MMF can offer protection against *Pneumocystis jirovecii*. Notably, though, the use of MMF has been linked to HZ in heart transplant recipients,[105] and renal allograft recipients have an increased frequency of tissue-invasive CMV infections.[106] It is important to acknowledge that these findings may not directly apply to individuals with rheumatologic conditions.

A retrospective study of SLE patients reported that UTIs were associated with the use of prednisone and CYC, while upper airway infections correlated with the use of prednisone, MMF, and cyclosporine. Glucocorticoids were generally associated with increased infection risk.[107] In a meta-analysis, MMF showed lower overall infection risk compared to CYC in non-Asian populations treated for LN. Mycophenolate mofetil therapy should be avoided during active systemic or life-threatening infections due to its effects on the immune system and the potential risk of neutropenia.[108]

Cyclophosphamide

Cyclophosphamide is a DNA-alkylating agent that exerts cytotoxic effects on both replicating and resting lymphocytes. It reduces the number of B and T lymphocytes, leading to decreased lymphocyte proliferation, modulation of cell activation, and reduced antibody production. As a result, it suppresses cellular and humoral immunity.[109] It increases the risk of infections by suppressing the bone marrow, which can result in neutropenia and/or lymphopenia. Additionally, CYC interferes with normal neutrophil and lymphocyte function, even in the absence of reductions in cell counts. Patients treated with CYC who develop neutropenia (defined as neutrophil < 1500/μL), especially when combined with high doses of glucocorticoids, are at a high risk of infection.[110]

A study of 100 patients with SLE found that infection occurred in 45% of CYC-treated patients compared to 12% of those treated with glucocorticoids alone. Bacterial infections were the most common, followed by opportunistic infections and HZ. Patients with infections were more likely to have multiple organ involvement, a lower nadir in the white blood cell count, and a higher maximum dose of corticosteroid than those without infection. Infections were equally prevalent in patients receiving oral or parenteral CYC but were more common when using sequential intravenous and oral therapy.[110] The use of CYC therapy should be avoided in the presence of active systemic or potentially life-threatening infections. The use of CYC in neutropenic patients should also be avoided unless neutropenia is likely immune-mediated.

Rituximab

Rituximab is an IgG1 monoclonal antibody that binds to CD20, a B-cell differentiation marker.[111] The biologic targets and depletes B cells from the pre-B to the mature B cell stage. Normalization of B cell numbers after treatment typically requires 6-9 months or longer.[112]

In a meta-analysis[113] of 19 observational studies and 2 trials (EXPLORER[114] and LUNAR[115]) which used rituximab to treat SLE patients, adverse reactions were detected in 16.8% of the patients. Among these events, infections were the most frequent, accounting for 63.1% of the cases.

In the EXPLORER trial,[114] the group receiving rituximab had a higher occurrence of severe neutropenia events (grade 3 and grade 4) at a rate of 7.7% in comparison to the placebo group, which had a rate of 3.4%, and higher cases of grade 4 neutropenia (6 versus 0). However, there was no significant correlation between neutropenia events and the occurrence of infectious events. The ratio of patients encountering infectious adverse events was comparable between the rituximab and placebo groups, with rates of 82.2% and 83.0%, respectively. The most commonly reported type of infection in both groups was upper respiratory tract infections (URTIs), accounting for 49.1% in rituximab patients and 46.6% in placebo patients. It is worth noting that the rituximab group had an increased frequency of herpesvirus (15.4%) compared to the placebo group (8.0%), including rare cases of oral and genital outbreaks as well as HZ infections (9.5% in the rituximab group and 3.4% in the placebo group). However, most of the herpesvirus infections were resolved within 1 month in approximately 66% of patients. Regarding serious infections, sepsis occurred in 2.3% of patients who received placebo and 1% of patients who received rituximab. Additionally, the placebo group had a higher proportion of patients developing serious infections (17.0%) compared to the rituximab group (9.5%). In the LUNAR trial,[115] within the rituximab group, there were 2 instances of death, one of which was attributed to sepsis resulting from a *Staphylococcus aureus* infection. Infections were reported in 62% of patients receiving rituximab and 64% of patients receiving placebo. Serious infections were observed in 19.2 patients in each group, including 3 cases of opportunistic infections. The hospitalization rates per 100 patients-year were similar between the 2 groups. In these trials, the most frequently observed infections involved the upper respiratory and urinary tracts or were caused by HZ.[113]

Obinutuzumab

Obinutuzumab is a type II anti-CD20 monoclonal antibody, distinct from the conventional type I antibody, rituximab. It binds to the CD20 antigen in a different manner, leading to enhanced antibody-dependent cellular cytotoxicity and direct elimination of B cells with reduced reliance on complement-dependent cytotoxicity. The NOBILITY trial, a randomized phase 2 study involving patients with LN, did not report a significant increase in serious infectious adverse events.[116]

Belimumab

Belimumab, an IgG1-lambda monoclonal antibody, neutralizes the B-lymphocyte stimulator (BLyS), inhibits the survival of B lymphocytes, and reduces B-cell-mediated immunity.[117] A systematic analysis of 6 studies with 2917 participants aged between 22 and 80 years comparing belimumab to placebo treatment did not report differences in terms of infections between the treatment and control groups.[118] Four studies involving 2185 participants[119-122] also did not report statistically meaningful differences in the incidence of serious infections between the belimumab and the placebo groups. In the BLISS-76 study,[119] a phase 3 randomized trial involving 819 patients, the proportions of serious or severe infections were similar between all treatment groups.

Interestingly, in 2018, Doria et al[123] reported lower infection rates in patients treated with belimumab. Similar protective effects were reported in Asian patients with SLE receiving belimumab.[124] In 2020, the BLISS-LN study, a 2-year randomized controlled trial of belimumab in LN, reported similar rates of serious infections across the treatment and control groups.[124]

Anifrolumab

Anifrolumab is a human monoclonal antibody designed to specifically target and inhibit the activity of type I IFN receptors, including IFN-α, IFN-β, and IFN-κ. These particular cytokines are frequently found at elevated levels in patients with lupus. By effectively inhibiting the function of IFNs-I, anifrolumab assists in diminishing the production of proinflammatory and immunomodulatory proteins associated with the immune response. This inhibition extends to the activation of B and T cells, the migration of immune cells, and the release of cytokines. Furthermore, anifrolumab decreases the expression of CD80 and CD83 on dendritic cells, providing additional correction of the aberrant immune responses in patients with SLE.[125] Anifrolumab was approved by Food and Drug Administration (FDA) in 2021 for managing moderate to severe SLE patients who are already receiving standard therapy and do not have severe active LN or neuropsychiatric SLE.

Anifrolumab has been evaluated in several pivotal studies, including TULIP-1,[126] TULIP-2,[127] TULIP-LN,[128] and MUSE.[129] Across these studies, among patients treated with anifrolumab, the incidence of any adverse event varied from 85% to 89%, while the placebo groups exhibited rates ranging from 77% to 84%. The most commonly observed adverse events included URTI and nasopharyngitis. Notably, there was a higher frequency of HZ in the anifrolumab groups (5%-7%) compared to the placebo groups (1%-2%). However, the majority of HZ cases were not serious and did not necessitate cessation of treatment. All cases showed a favorable response to the appropriate treatment and generally resolved without any long-term complications.[125]

In the TULIP-LN study, a phase II randomized controlled study evaluating the efficacy and safety of anifrolumab in patients with active LN, the most common adverse events in the combined anifrolumab groups compared to the placebo group were HZ, UTI, and influenza. All HZ cases were cutaneous, with 13 localized and 3 disseminated. HZ cases tended to occur early in the trial and were successfully managed with conventional treatment. The occurrence of other adverse events of special interest was low in all of the treatment groups.[128] An evaluation of tolerability in an extension study[130] of those who participated in either TULIP 1 or TULIP 2 trials reported as most common adverse events, nasopharyngitis (9.7 versus 5.5 per 100 patient-year), UTI (8 versus 6), and URTI (8 versus 7) in the anifrolumab and placebo groups, respectively. Proportions of latent tuberculosis (2.3 versus 0.8) and influenza (2.2 versus 0.8) were enhanced in anifrolumab patients compared to placebo patients. It is worth noting that, in both groups, there were no occurrences of active tuberculosis, and in the anifrolumab group, no opportunistic infections were noted. During the 3 years, the rates of HZ per 100 patient-years were 3.4 in the anifrolumab group and 2.8 in the placebo group.

Litifilimab

Litifilimab is a humanized monoclonal antibody that specifically binds to the antibody-binding of blood dendritic cell antigen 2

(BDCA2), which is exclusively expressed on plasmacytoid dendritic cells. By targeting BDCA2, litifilimab suppresses the production of IFN-I. A phase II trial did not report alarmingly increased rates of infections.[131]

Tacrolimus, Cyclosporine, and Voclosporin

Cyclosporine and TAC are 2 immunosuppressive drugs used in the treatment of various immune-mediated diseases. Both drugs belong to the class of calcineurin inhibitors and exhibit similar suppressive effects on cell-mediated and humoral immune responses. While their primary action is on T helper cells, they may also inhibit T suppressor and T cytotoxic cells. Importantly, neither cyclosporine nor TAC causes significant clinical myelosuppression.[132]

In the context of treating LN or idiopathic membranous nephropathy, these drugs have been found to have a lower infection risk compared to glucocorticoids or other immunosuppressive agents. A meta-analysis of 38 randomized controlled trials involving 2066 patients reported that the combination of TAC and glucocorticoids was associated with a 48% lower risk of infection compared to intravenous CYC plus glucocorticoids. In contrast, intravenous CYC plus glucocorticoids was associated with a significantly higher risk of infection compared to TAC plus glucocorticoids, cyclosporine plus glucocorticoids, and oral CYC plus glucocorticoids.[133] Similar results were reported by another meta-analysis,[134] in which TAC showed a significantly decreased risk of serious infections when compared to glucocorticoids, CYC, MMF, and AZA. Overall, these studies highlight the relatively lower risk of infections associated with cyclosporine and TAC compared to other immunosuppressive drugs commonly used for treating SLE.

Voclosporin is a next-generation calcineurin inhibitor that shares structural similarities with cyclosporine, with a single amino acid difference that confers superior calcineurin inhibition and reduced plasma concentration variability. This distinction eliminates the need for therapeutic drug monitoring, which is typically required for other calcineurin inhibitors. In addition, voclosporin exhibits a more favorable effect on lipid and glucose concentrations compared to other drugs in the same class.[135] It received FDA approval in January 2021 for the treatment of LN in combination with MMF and glucocorticoids.

In the AURORA-I trial, a phase III multicenter randomized controlled study, infections and infestations emerged as the most common adverse events observed in the voclosporin and placebo groups, affecting 65% and 57% of patients, respectively. Most of the reported infections were of mild and moderate severity.[135] In the subsequent AURORA-II trial, which focused on evaluating the long-term safety and tolerability of voclosporin versus placebo in patients receiving treatment for an additional 24 months following the conclusion of the AURORA-I study, no unexpected safety concerns were identified in the voclosporin arm when compared to the control group. Moreover, similar proportions of serious adverse effects were reported in both groups.[136]

Atacicept

Atacicept, a fully human recombinant fusion protein, effectively inhibits B cell-stimulating factors, including APRIL (a proliferation-inducing ligand) and BLyS.[137] The APRIL-LN study, a phase II/III, randomized, double-blind, placebo-controlled 52-week trial, was terminated prematurely after enrolling 6 patients due to an unexpected decline in serum immunoglobulin G (IgG) levels and the occurrence of serious infections[137]. The APRIL-SLE[138] and ADDRESS II,[139] double-blind, placebo-controlled 52-week trials that evaluated the safety of atacicept and did not alert for serious infections.

Abatacept

Abatacept, a selective costimulation modulator, targets CD80 and CD86 on antigen-presenting cells, leading to the inhibition of T-cell activation. This selectivity blocks the specific interaction between CD80/CD86 receptors and CD28, effectively suppressing T cell proliferation and the immune response of B cells.[140,141]

A multicenter, exploratory, double-blind, placebo-controlled phase IIb trial conducted over 2 months in SLE patients with polyarthritis, discoid lesions, pleuritis, and/or pericarditis reported a slightly higher rate of infections in the treatment group.[140] Similar rates of infections were also reported in another 12-month randomized phase II/III trial.[141]

Ustekinumab

Ustekinumab is a monoclonal antibody that specifically targets the shared p40 subunit common to interleukins IL-12 and IL-23.[142] In a phase II, multicenter, double-blind, randomized controlled trial, infections were the most commonly reported side effects, but they occurred equally in the treatment and control groups.[142] Similarly, in the phase III study, which was terminated for lack of efficacy, the rate of infections was comparable in the treatment and control groups.[143]

Baricitinib

Baricitinib is an oral inhibitor of janus kinases (JAKs) 1 and 2, intracellular enzymes that participate in stimulating hematopoiesis and immune cell functions. Many critical cytokines implicated in the pathophysiology of lupus, including IFNs-I, IL-6, IL-12, and IL-23, depend on the activation of JAKs for intracellular signaling.[144]

In a 24-week phase II clinical trial evaluating the effectiveness, safety, and tolerance of oral baricitinib in individuals with active SLE, the occurrence of serious infections was increased in the baricitinib 4 mg group (6% of the patients) compared to both the 2 mg (2% of the patients) and the placebo groups (1%).[144]

Iberdomide

Iberdomide is a cereblon modulator that acts by promoting the degradation of the transcription factors Ikaros and Aiolos, which affect immune-cell development and homeostasis.[145] In a phase II trial, the iberdomide groups experienced more frequent urinary, upper respiratory tract infections, and neutropenia in a dose-dependent manner. Infections with herpesvirus, fungi, and varicella-zoster virus were reported in the iberdomide groups.[145]

Deucravacitinib

Deucravacitinib is a selective, orally administered allosteric inhibitor that targets TYK2, an intracellular kinase that plays a crucial role in mediating the signaling of critical cytokines involved in the pathophysiology of lupus. These cytokines include IFNs-I, as well as IL-10, IL-12, and IL-23.[146] A study that evaluated the efficacy of deucravacitinib reported increased rates of URTI and UTI but not significant differences in the incidence of HZ infections. Also, there were no cases of opportunistic infections or tuberculosis.[146]

Considerations to Mitigate Infections in Patients with Systemic Lupus Erythematosus

Preventive strategies are crucial to reduce the risk of infection in SLE patients. It is strongly advised that lupus patients receive immunizations as part of their preventive care. This includes vaccines against seasonal influenza, pneumococcal infections (both PCV13 and PPSV23), tetanus, HZ, and HPV. While the live vaccine Zostavax is available for HZ, a non-live vaccine known as Shingrix has been approved by the FDA in the United States since 2017. Shingrix is considered safer and more effective

for preventing shingles in the general population,[147] but there are no reports on its use in patients with SLE. Live attenuated vaccinations for measles, mumps, rubella, varicella zoster, and yellow fever should be evaluated for appropriate administration in select SLE patients before initiating therapy with immunosuppressive drugs.

Before starting treatment with immunosuppressive agents, it is crucial to identify and treat any chronic infections, like HIV, hepatitis B and C, and tuberculosis. This will help minimize the risk of worsening infections while receiving immunosuppressive therapy.

Due to the variable and unknown state of immunosuppression in SLE patients, any suspected infection should be treated promptly. An elevated C-reactive protein level may indicate a bacterial infection rather than a disease flare. Timely recognition and treatment of sepsis are essential. Validated scoring systems can help identify patients at higher risk of poor outcomes, allowing for more targeted interventions in emergency room settings and hospitals.[148]

Monitoring SLE patients for cytopenias induced by drugs and other adverse effects is crucial. This approach enables physicians to take an engaged participation in minimizing avoidable infections. Blood tests to assess immunoglobulin levels in individuals with SLE may also assist in recognizing patients with a higher risk of infections. In certain cases of severe infection or specific exposure to infectious agents, intravenous immunoglobulin may have a role in treating patients with hypogammaglobulinemia.[1]

For lupus patients receiving high doses of glucocorticoids (exceeding a daily dose of 30 mg of prednisone or its equivalent), prophylactic therapy to prevent *Pneumocystis jirovecii* infection is often recommended.

Implementing these preventive strategies and closely monitoring lupus patients can significantly reduce the risk of infections and their associated complications and improve the overall management of the disease.

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