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Review

Secondary immunodeficiencies and infectious considerations of biologic immunomodulatory therapies

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Key Messages

- Biologic immunomodulatory medications have rapidly expanded in the previous decades and are approved for a wide variety of conditions, necessitating that providers familiarize themselves with their indications and individual risks and adverse effects.
- Biologic medications target different pathways in the immune system and can impair host defense mechanisms, causing potential secondary immunodeficiency and increased risk of infection. The infectious risks and typical pathogens differ depending on the specific agent and its mechanism of action.
- Infectious risks with biologic medications can be mitigated by a comprehensive examination before therapy initiation and should include a thorough history of existing comorbid medical conditions, history of infections, screening for appropriate infections, assessment of risk for future infection, review of vaccination history, and optimizing immunization status.
- Treatment of secondary immunodeficiency and infections because of biologic medications may include timely antimicrobial therapy, antimicrobial prophylaxis, and possibly immunoglobulin replacement when indicated.

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ABSTRACT

Biologic immunomodulatory medications have rapidly expanded in the previous decades, providing new treatment options for individuals with a spectrum of oncologic, allergic, rheumatologic, and neurologic conditions. Biologic therapies alter immune function and can impair key host defense mechanisms, resulting in secondary immunodeficiency and increased infectious risks. Biologic medications can increase general risk for upper respiratory tract infections but can also be associated with unique infectious risks owing to distinct mechanisms of action. With the widespread use of these medications, providers in every area of medicine will likely care for individuals receiving biologic therapies and understanding their potential infectious complications can help mitigate these risks. This practical review discusses the infectious implications of biologics by class of medication and provides recommendations regarding the examination and screening both before therapy initiation and while the patient is receiving the medication. With this knowledge and background, providers can reduce risk whereas patients receive the treatment benefits of these biologic medications.

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Introduction

Biologic immunomodulatory medications, defined here as monoclonal antibodies (mAbs) and fusion proteins, have advanced the treatment landscape of many oncologic, allergic, rheumatologic, and neurologic conditions. For immunologists, biologic modifiers have allowed precision medicine-based therapy for the growing number of monogenic primary immune dysregulation disorders.[1] The number of biologics has rapidly expanded in the last 2 decades and continues to multiply, with more than 70 mAbs used in clinical practice.[2] Providers in every specialty will likely encounter and care for patients receiving biologic medications.

The overarching goal of biologic therapies is to restore balance between pro- and anti-inflammatory responses of the immune system. An overabundance of proinflammatory response with loss of self-tolerance can result in autoimmune disease, whereas too much anti-inflammatory response will lead to infectious and neoplastic complications. Biologic medications typically work in 3 different ways: (1) soluble receptor antagonism acting as decoy receptors inhibiting free cytokines, (2) cell surface receptor antagonist preventing cytokine-mediated receptor activation, and (3) through a combination of soluble cytokine and bound receptor inhibition.

Given that biologics target several cytokines and cellular interactions within the immune system and can impair important host defense functions (Figs 1 and 2), secondary immunodeficiency and increased infectious risk are important considerations. Providers should be aware of the general and unique infectious risks and preventative measures for the different biologics. In this study, we aim to provide for the clinician a practical review of the more widely used biologic medications, including their mechanism of action, indication for use, infectious implications, and recommendations for monitoring and screening for infectious complications.

Tumor necrosis factor-α Inhibitors

Tumor necrosis factor-α (TNF-α) is a potent proinflammatory cytokine of innate immunity and is involved in the pathophysiology of a myriad of inflammatory conditions. Tumor necrosis factor-α inhibitors (TNFi) were among the first biologics used to treat autoimmune disorders, and include mAbs adalimumab, golimumab, infliximab, and certolizumab and the soluble TNF-receptor etanercept (Fig 1, Table 1). Tumor necrosis factor-α inhibitors are currently approved for treating a range of autoimmune diseases including rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (JIA), inflammatory bowel disease (IBD), psoriasis, psoriatic arthritis (PsA), ankylosing spondylitis, hidradenitis suppurativa, and uveitis.[3–8] Although TNFi are highly effective and have revolutionized treatment of many autoimmune conditions, leading to improved outcomes, infectious risks are a significant consideration.[2,9,10] Many factors contribute to an individual's risk, including age, comorbid medical conditions, and use of adjunctive immunosuppressive therapies.[9–11]

Overall infectious risk is different among TNFi, with the highest risk associated with infliximab, followed by adalimumab, and the lowest risk with etanercept.[2,10,12,13] Given the key and pleiotropic role of TNF-α in host defense, its inhibition can increase risk for common viral and bacterial infections and to a lesser extent, opportunistic fungal and rare parasitic infections.[11] A French national registry found that 40% of infections were viral; 33% were bacterial; 22% were fungal, and the remaining 4% were parasitic in patients receiving TNFi.[14] Herpes simplex virus (HSV), hepatitis B virus (HBV), and varicella zoster virus reactivation have been reported and are important considerations when administering TNFi.[15,16] Hepatitis B virus reactivation rates in patients positive for HB surface antigen (HBsAg) are higher with the mAb (12%-39%) than with etanercept (1%-5%).[17]

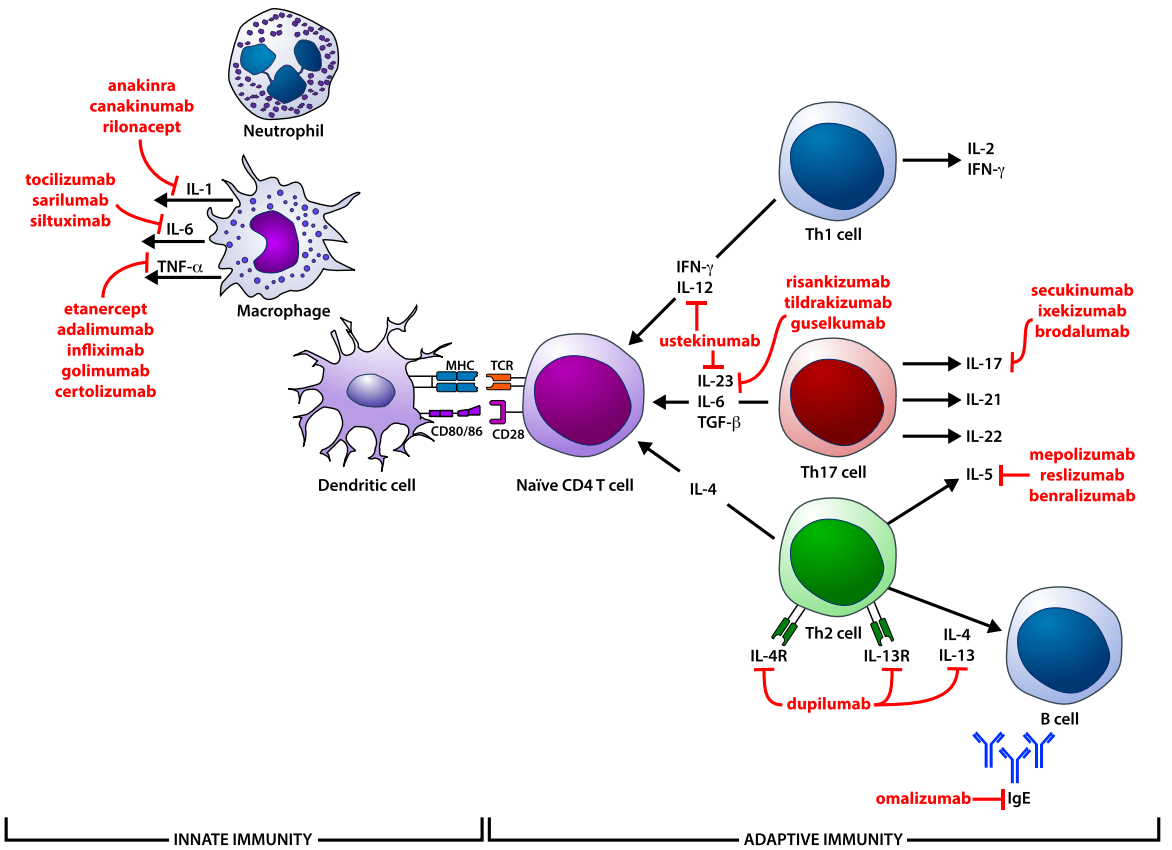

Figure 1. Overview of cytokine-targeting and anti-immunoglobulin E biologic immunomodulatory therapies.

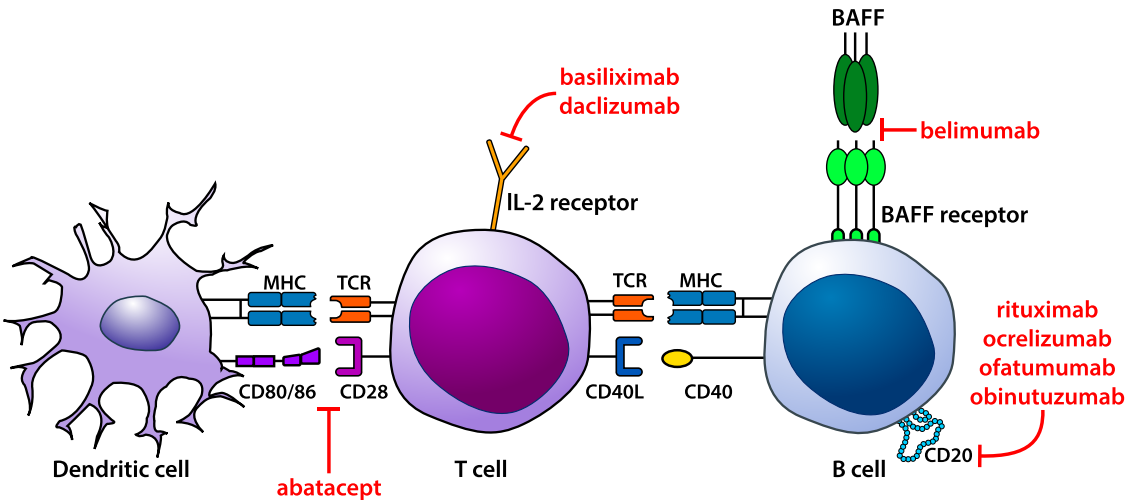

Figure 2. Biologic immunomodulatory therapies targeting key T-cell and B-cell receptors and molecules.

Tumor necrosis factor-activated macrophages are critical in phagocytosing and killing mycobacteria and controlling granuloma formation and maintenance.[18] Reactivation of latent tuberculosis infection (LTBI) is therefore a well-known concern with TNFi, with the greatest risk occurring with infliximab. One meta-analysis determined the absolute rate of tuberculosis (TB) infection in patients with RA treated with infliximab was 0.7%.[10,19] Tumor necrosis factor-α also enhances neutrophil fungicidal activity, and invasive fungal infections have been observed with TNFi use, including *Histoplasma, Candida, Pneumocystis, Aspergillus*, and *Cryptococcus*.[20]

Given the infectious risk profile of TNFi, clinicians need to perform screening before starting treatment. A thorough history should be performed and include vaccination status and special attention for TB exposure and chronic viral infections.[21] Testing for TB, HBV, hepatitis C virus (HCV), varicella zoster virus, and human immunodeficiency virus should be completed before therapy initiation. Prophylactic anti-HBV therapy is recommended for patients with higher risk of reactivation. Patients treated specifically for IBD may also need stool testing for *Clostridiodes difficile* and *Strongyloides* if in a high prevalence area.[22] The need for routine vaccinations should be reviewed, and all recommended vaccinations based on age and immune status ideally administered before treatment. Vaccine responses may be weakened, and live-attenuated vaccines are typically avoided with TNFi. If disease activity allows, TNFi therapy should be held 1 dosing interval before and 4 weeks after live-attenuated vaccine administration.[23]

Although TNFi have drastically improved the outcomes of patients with several inflammatory conditions, they are not without modest infectious risks. Patients should undergo a thorough infectious history, individualized screening for infection, and optimization of immunization status before therapy initiation. Because of the manifest effectiveness of TNFi in many inflammatory conditions, however, the benefit of TNFi therapy outweighs the risk when measures are taken to mitigate infectious complications.

Interleukin-1 Inhibitors

The interleukin (IL)-1 pathway is a crucial part of the response of the innate immune system to infection, and dysregulated IL-1 activity also plays a role in autoinflammatory conditions. Three agents that block the IL-1 pathway are anakinra, canakinumab, and rilonacept (Fig 1, Table 1).[2,24] Anakinra is approved for treatment of RA, neonatal-onset multisystemic inflammatory disease, and deficiency of IL-1 receptor antagonist. Canakinumab is approved for treatment of systemic JIA, adult-onset Still's disease, and several periodic fever syndromes: cryopyrin-associated periodic syndromes, familial Mediterranean fever, hyperimmunoglobulin D syndrome or mevalonate kinase deficiency, and TNF-receptor associated periodic syndrome. Rilonacept is currently approved for cryopyrin-associated periodic syndromes, deficiency of IL-1 receptor antagonist, and recurrent pericarditis.

Studies in patients being treated with IL-1 inhibitors have overall been favorable and reassuring from an infectious perspective. In 1 large study in patients with RA treated with anakinra, infections occurred in 12% of the placebo-treated group compared with 15% to 17% of those receiving anakinra, with mild respiratory infections being most common.[25] Similarly, in studies in anakinra and canakinumab in which patients also received concomitant immunosuppression, infections were most commonly upper respiratory tract infections (URTI), with severe infections occurring less frequently.[26–29]

Given a potential risk and case reports of TB reactivation with IL-1 inhibition, providers should consider screening for LTBI before starting therapy.[30] Patients should be up to date on all nonlive vaccinations according to age.[31,32] Avoiding live vaccinations while receiving IL-1 inhibitors is recommended, so ensuring an individual is up to date before therapy initiation, if disease activity allows, would be ideal.[33]

Overall infectious risk is low with IL-1 inhibitors, and respiratory infections are the most observed infectious complication. Although overall risk is considered minimal, individuals should be examined for their own particular factors such as diabetes, underlying lung disease, or treatment with additional immunosuppression that may increase risk for more serious complications[28,29,34] and will also help individualize screening and medication monitoring.

Interleukin-6 Inhibitors

Interleukin-6 is critically important to both innate and adaptive immune responses and is implicated in several different acute and chronic inflammatory processes. Given its multifaceted role in the immune system, IL-6 inhibition has been used to treat several different systemic rheumatic inflammatory conditions.[2,35]. Approved IL-6 pathway inhibitors include tocilizumab and sarilumab, mAbs against the IL-6 receptor, and siltuximab, an mAb against the IL-6 cytokine (Fig 1, Table 1). Tocilizumab is approved for RA resistant to first-line disease-modifying antirheumatic drugs, giant cell arteritis, polyarticular and systemic JIA, and cytokine release syndrome from chimeric antigen receptor-T cell therapy. Sarilumab is approved for RA

Table 1
Infectious Considerations and Recommended Screening for Biologic Agents

Class of biologic	Reference product brand name	Food and Drug Administration-approved indications	Unique infections considerations	Recommended screening before initiation
TNF inhibitors				
Adalimumab	Humira	RA, pJIA, Crohn's disease, UC, psoriasis, PsA, AS, uveitis, hidradenitis suppurativa	Reactivation of LTBI Reactivation of viral hepatitis Less commonly fungal infection	Testing for TB, HBV, HCV, VZV, and HIV Consider stool testing for *Clostridiodes difficile* and *Strongyloides* in patients with IBD Review vaccination history and provide non-live vaccinations
Certolizumab	Cimzia	RA, Crohn's disease, psoriasis, PsA, AS		
Etanercept	Enbrel	RA, pJIA, psoriasis, PsA, AS		
Golimumab	Aria, Simponi	RA, pJIA, PsA, AS, UC		
Infliximab	Remicade			
IL-1 Inhibitors				
Anakinra	Kineret	RA, NOMID, DIRA	Mild upper respiratory tract viral infections	Consider testing for TB Review vaccination history and provide non-live vaccinations
Canakinumab	Ilaris	Systemic JIA, AOSD, CAPS, FMF, HIDS/MKD, TRAPS		
Rilonacept	Arcalyst	DIRA, recurrent pericarditis		
IL-6 Inhibitors				
Tocilizumab	Actemra	RA, giant cell arteritis, pJIA, systemic JIA	Upper respiratory tract viral infections Bacterial skin infections	Consider testing for TB and HBV Review vaccination history and provide non-live vaccinations
Sarilumab	Kevzara	RA		
Siltuximab	Sylvant	Castleman's disease		
IL-12/IL-23 Inhibitors				
Risankizumab	Skyrizi	Crohn's disease, psoriasis, PsA	Upper respiratory tract viral infections and nasopharyngitis Monitor for *Candida* infections	Testing for TB and HBV Review vaccination history and provide non-live vaccinations
Tildrakizumab	Ilumya	Psoriasis		
Guselkumab	Tremfya	Psoriasis, PsA		
Ustekinumab	Stelara	Crohn's disease, UC, psoriasis, PsA		
IL-17 Inhibitors				
Secukinumab	Cosentyx	Psoriasis, PsA, AS, ERA	Upper respiratory tract viral infections Increased risk of *Candida* infections	Testing for TB Consider antifungal prophylaxis for patients with chronic candidiasis Review vaccination history and provide non-live vaccinations
Ixekizumab	Taltz	Psoriasis, PsA, AS		
Brodalumab	Siliq	Psoriasis		
IL-4/IL-13 Inhibitors				
Dupilumab	Dupixent	Atopic dermatitis, asthma, CRSwNP, EoE, PN	Potential increased risk for parasitic infections	Examine and treat for parasitic infections Review vaccination history and provide non-live vaccinations
IL-5 Inhibitors				
Mepolizumab	Nucala	CRSwNP, EGPA, HES, severe asthma with eosinophilic phenotype	Potential increased risk for parasitic infections	Examine and treat for parasitic infections Review vaccination history and provide non-live vaccinations
Reslizumab	Cinqair	Severe asthma with eosinophilic phenotype		
Benralizumab	Fasenra	Severe asthma with eosinophilic phenotype		
Anti-IgE Therapy				
Omalizumab	Xolair	Moderate-to-severe persistent asthma, CSU, nasal polyps	Potential increased risk for parasitic infections	Examine and treat for parasitic infections Review vaccination history and provide non-live vaccinations

Abbreviations: AOSD, adult-onset Still's disease; AS, ankylosing spondylitis; CAPS, cryopyrin-associated periodic syndromes; CRSwNP, chronic rhinosinusitis with nasal polyposis; CSU, chronic spontaneous urticaria; DIRA, deficiency of interleukin-1 receptor antagonist; EGPA, eosinophilic granulomatosis with polyangiitis; EoE, eosinophilic esophagitis; ERA, enthesitis related arthritis; FDA, food and drug administration; FMF, familial Mediterranean fever; HBV, hepatitis B virus; HCV, hepatitis C virus; HES, hypereosinophilic syndrome; HIDS, hyperimmunoglobulin D syndrome; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; IL, interleukin; JIA, juvenile idiopathic arthritis; MKD, mevalonate kinase deficiency; NOMID, neonatal-onset multisystemic inflammatory disease; pJIA, polyarticular juvenile idiopathic arthritis; PN, prurigo nodularis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TB, tuberculosis; TNF, tumor necrosis factor; TRAPS, tumor necrosis factor receptor associated periodic syndrome; UC, ulcerative colitis; VZV, varicella zoster virus.

resistant to disease-modifying antirheumatic drugs, and siltuximab for multicentric Castleman's disease.

Understanding of the infectious complications of IL-6 inhibitors is largely derived from studies with tocilizumab, in which most infections reported are skin and URTIs, without reported cases of TB.[36] Although fewer, studies with sarilumab and siltuximab have revealed similar findings, with upper respiratory infection being most commonly observed.[37,38] Those receiving tocilizumab had a higher risk of serious bacterial infection and skin and soft tissue infection than did patients with RA being treated with TNFi, but there was no difference for infections requiring hospitalization.[39] In contrast to some of the other mAb agents, reactiviating LTBI has not been associated with tocilizumab, and reactivation of viral hepatitis has also not been consistently associated with IL-6 inhibition.[9,40]

Skin and respiratory infections are most observed with IL-6 inhibitors, so providers should pay particular attention to these organ systems before initiating therapy, and appropriate counseling should be provided to patients. Providers may have a lower threshold to initiate antimicrobial therapy for presumed bacterial pneumonia or cellulitis in patients receiving IL-6 inhibitors. Vaccination history should be reviewed to confirm the patient is up to date on all nonlive vaccinations according to age.[31,32] Live vaccines should not be administered.[23] Some groups do advocate screening for TB and HBV in all patients, but providers may decide to take an individualized approach on the basis of both being rarely observed in studies.[41] In summary, IL-6 inhibitors have advanced treatment of numerous inflammatory conditions, but they are not without infectious risk, specifically respiratory and skin infections, requiring thorough screening and vigilant monitoring to diminish likelihood of complications.

Interleukin-12/Interleukin-23 Inhibitors

The IL-12 and IL-23 cytokines play a key role in T-cell differentiation and are important drivers in autoimmunity. Currently, 3 agents

selectively block IL-23, and 1 blocks both IL-12 and IL-23 (Fig 1, Table 1). Risankizumab, tildrakizumab, and guselkumab are mAbs targeting the P19 subunit of IL-23 and are indicated in moderate-to-severe plaque psoriasis. Ustekinumab is a human immunoglobulin (Ig) G1 mAb targeting the P40 subunit of both IL-12 and IL-23 and is indicated for moderate-to-severe plaque psoriasis, active PsA, and treatment-resistant Crohn's disease.[2]

Because the IL-12/23 pathways are involved in T- and natural killer-cell activation, it is plausible that IL-12/23 inhibition can increase infection risk, particularly from intracellular pathogens. Recent trials have shown that nasopharyngitis and URTIs are the most common infections with IL-12/23 inhibitor therapy.[42] Trials of guselkumab in patients with psoriasis, however, showed comparable low rates of nasopharyngitis and URTIs with those of groups receiving adalimumab and placebo.[43–45] Additional studies support minimal risk of intracellular pathogen and viral infections with IL-12/23 inhibitors.

Patients treated with IL-23 inhibitors do not have increased risk of TB and have low rates of TB reactivation.[46,47] In a pooled study assessing the safety of guselkumab and anti-TB treatment, no cases of active TB including reactivation of LTBI were reported in patients with or without LTBI treated for up to 2 years.[48,49] A few cases of HBV reactivation in patients who are HBsAg positive and have herpes zoster infection have been reported, but these have not been shown in large clinical trials.[50]

Inhibition of IL-23 also results in indirect inhibition of IL-17. Interleukin-17 is important in immune defense against fungal and extracellular bacterial infections. Consequently, some studies report an increased incidence of mucocutaneous *Candida* infections with ustekinumab at 2.3%. The risk of mucocutaneous *Candida* infections, however, seems to be lower with ustekinumab than with direct IL-17 inhibitors.[51,52]

In conclusion, the data for IL-12/IL-23 inhibitors suggest an increased risk of URTIs. Although the risk of TB and HBV reactivation seems low, it is recommended to screen for latent and active TB before therapy initiation, and antiviral prophylaxis is recommended in patients who are HBsAg positive, respectively.[2] If possible, routine vaccinations should also be completed before starting therapy.

Interleukin-17 Inhibitors

Interleukin-17 is a proinflammatory cytokine produced mainly by CD4+ T helper 17 (T_H17) cells and is essential in defense against bacteria and fungi by phagocytic cell recruitment and activation. T helper 17 cells and IL-17 also play a key role in the pathogenesis of several autoimmune diseases. Secukinumab and ixekizumab are anti-17A mAbs, and brodalumab is an anti-IL17 receptor mAb (Fig 1, Table 1). Interleukin-17 inhibitors are currently approved to treat plaque psoriasis, PsA, and ankylosing spondylitis.

Given the role of the IL-17 pathway in antifungal immunity, IL-17 inhibitor therapy is, not surprisingly, associated with an increased risk of mild candidiasis infection.[2,53] Similarly to primary immunodeficiencies with impaired T_H17-mediated immunity, IL-17 inhibitors are associated with an increased susceptibility to chronic mucocutaneous candidiasis.[54] Consistent with previous studies, a recent global real-world observational study found a strong association between IL-17 inhibitors and cutaneous, oropharyngeal, and esophageal candidiasis. Incidence rates were 4% to 6.5% for brodalumab, 1.7% to 4.7% for secukinumab, and 3.3% for ixekizumab. The risk of *Candida* infection was 4- to 10-fold higher in patients treated with IL-17 inhibitors than in patients treated with TNFi. The *Candida* infections, however, were successfully treated with antifungals and did not lead to therapy discontinuation, resistant candidiasis, or increased morbidity.[51]

Interleukin-17 inhibitors are generally considered safe in patients with LTBI.[47] A pooled cohort study in more than 12,000 patients treated with secukinumab for 5 years reported 13 patients (0.1%) with LTBI as an adverse effect. Of those 13 patients, 6 had previous positive LTBI, and 7 were new findings. No active TB cases were reported. These results suggest that new LTBI is rare during long-term secukinumab treatment.[55] Secukinumab has very rarely been associated with opportunistic infections such as herpes zoster, toxoplasmosis, and *Mycobacterium avium* complex infections.[56] Similarly to other biologic agents, 2 large studies showed an increased risk of URTIs with IL-17 inhibitors.[57,58]

In summary, patients treated with IL-17 inhibitors are at increased risk of *Candida* infections compared with other biologic agents. The risk of other infections, including URTIs and opportunistic infections, however, is similar to that of other classes. Before therapy initiation, screening for latent and active TB is recommended. In addition, patients should be screened and treated for mucocutaneous candidiasis before and during IL-17 inhibitor therapy. Antifungal prophylaxis can be considered in patients with recurrent or chronic candidiasis. However, more studies are needed to identify potential predisposing risk factors.[2,51]

Interleukin-4/Interleukin-13 and Interleukin-5 Inhibitors and Anti-immunoglobulin E Therapy

Type 2 immune responses are critical for host defense against parasitic infections and when dysregulated, can underpin allergic inflammation. Type 2 cytokines include IL-4, IL-5, and IL-13, which promote eosinophil recruitment and IgE production.[59] Dupilumab is an mAb that inhibits IL-4 and IL-13 signaling by targeting the shared receptor subunit IL-4Rα (Fig 1, Table 1).[59,60] Mepolizumab, reslizumab, and benralizumab target the IL-5 pathway, and omalizumab is an anti-IgE mAb (Fig 1, Table 1).[59,60] These medications are approved to treat a spectrum of atopic disorders, including, but not limited to, atopic dermatitis, asthma, chronic rhinitis with nasal polyposis, eosinophilic esophagitis, chronic spontaneous urticaria, eosinophilic granulomatosis with polyangiitis, and hypereosinophilic syndrome.[59]

There is particular concern for an increased risk of parasitic infection given the importance of type 2 immunity in defending against parasitic infections. Although parasitic infections were observed in 2.6% of pediatric patients receiving dupilumab in a randomized controlled trial (RCT) for asthma, these infections were mild, did not result in drug discontinuation, and were not considered related to dupilumab by trial investigators.[61] In addition, a meta-analysis of RCTs of dupilumab for atopic dermatitis showed that the rate of overall infections was similar to that of placebo.[62–64] Similarly, systematic reviews of RCTs for anti-IL-5 and anti-IgE therapies indicated no increased rate of adverse effects compared with placebo.[65] Most clinical trials were limited in that they occurred in modern settings and excluded individuals with parasitic infections. To better address the concern, an RCT of omalizumab was conducted in subjects with asthma and allergic rhinitis with a high risk of geohelminth infection.[66] There was slightly increased, but not statistically significant, risk for acquiring a parasitic infection compared with placebo.[66]

Previous studies have shown an increase rate of HSV exacerbation with dupilumab. In a pooled data analysis of 7 RTCs of dupilumab in atopic dermatitis, rates of HSV infections were slightly higher with dupilumab and mostly because of oral herpes. Clinically important infections like eczema herpeticum and zoster were less common with dupilumab.[67]

For agents targeting type 2 cytokines and IgE, safety has been shown, and infectious complications are overall rare. There are limited data regarding the safety and efficacy of live vaccines with these agents, but it is generally recommended to complete all age-appropriate vaccinations before initiating treatment and to avoid live

vaccines during treatment. Although there is no robust evidence of increased risk, examination and treatment for parasitic infections should be considered before starting therapy. Patients with recurrent HSV may also benefit from antiviral prophylaxis.

Anti–T-Lymphocyte Therapies

T-lymphocytes coordinate and regulate cell-mediated adaptive immunity and are paramount in response to intracellular organisms such as viruses, mycobacteria, and fungi.[2] Basiliximab is the 1 T-cell –targeted therapy marketed as an immunosuppressive agent. Basiliximab prevents T-lymphocyte activation by antagonism of CD25, the alpha subunit of the IL-2 receptor (Fig 2). Its only indication is for induction therapy in patients who undergo renal transplant.[68] The infectious risk of basiliximab is difficult to fully ascertain because it is typically used in conjunction with other immunomodulatory therapies. Studies in renal and liver transplant have had favorable findings when evaluating basiliximab vs placebo, with no increase in infection rates after the addition of basiliximab.[69–72]

Abatacept is another T-lymphocyte therapy and is a fusion molecule consisting of cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) and the Fc portion of IgG1. Abatacept prevents T-cell activation by blocking the costimulatory signal between antigen-presenting cells and T cells (Fig 2).[73] It is approved for use in RA, PsA, and JIA.

Reported infections with abatacept are largely respiratory and skin infections with common organisms. In 1 large meta-analysis, the rate of infection with abatacept was 3% vs 1.9% in the placebo group.[74] In a cohort study comparing abatacept with other biologics, there was no significant difference in risk of serious bacterial infection in the abatacept group compared with individuals receiving other biologics.[75] There are several reports of HBV reactivation in individuals receiving abatacept.[76–78] Regarding TB, there seems to be an exceptionally minimal risk of TB reactivation with abatacept therapy.[79,80]

Given that basiliximab is not typically used as a single agent, infection prevention strategies do not need to be altered with addition of basiliximab on the basis of the available evidence. Patients starting or receiving abatacept should be counseled on general infection prevention strategies. Depending on the individual, HBV serologies should be considered. There are no data to support the need for TB screening before abatacept initiation.[2]

Overall, the rates of viral, bacterial, or fungal infections have been observed to be no different with basiliximab compared with placebo. Abatacept is associated with low risk of infection, particularly skin or respiratory tract infections. Providers should be aware of the potential for HBV reactivation in patients on abatacept and provide appropriate monitoring and counseling. Vaccination history should be reviewed to optimize vaccinations before initiating therapy, and live vaccinations should be avoided while on therapy.[23]

Anti-B-Lymphocyte Therapies

B-lymphocytes are vital in adaptive immunity, with main functions including Ig production, antigen presentation, and T-cell activation/regulation.[2] Given their broad functions, B-lymphocytes have a key role in immune response to viral, bacterial, and fungal infections. Anti–B-lymphocyte therapies include 6 mAbs. Rituximab, ocrelizumab, ofatumumab, and obinutuzumab are mAbs directed against the CD20 antigen (Fig 2). Inebilizumab works against CD19 found primarily on B-cell precursors, and belimumab targets B-cell activating factor, which promotes the formation and survival of memory B cells and plasma cells (Fig 2). These agents are primarily approved for the treatment of several oncologic and autoimmune conditions.

The risks and type of infectious complications are similar across this drug group except for belimumab. By neutralizing B-cell activating factor, belimumab reduces B-cell differentiation and survival but does not fully deplete B-cell numbers. This may be a reason belimumab has lower infectious risks than the B-cell depleting therapies. The overall rates of serious infection reported with belimumab are comparable with rates with placebo.[81,82] This contrasts with the remaining agents in this group in which infectious risks are more significant.

Of the B-lymphocyte targeting therapies, rituximab has been studied the most in depth regarding infectious complications. Given the similar target and mechanism of action, however, the infectious risks are considered similar across agents. Reported risk does vary on the basis of indication, with higher rates observed for treatment of hematologic malignancy than of autoimmune disease, which is likely because of higher cumulative dose and more concomitant immunosuppressive therapy.[83–85] The indication for treatment will also likely affect screening and monitoring.

Rituximab carries a Food and Drug Administration black box warning for HBV reactivation. Hepatitis B virus reactivation occurs less often in those with autoimmune disease being treated with rituximab than in those with malignancy, with 1 long-term study in 3595 patients with RA not having a single case of HBV reactivation.[86,87] The rates of HBV reactivation vary greatly on the basis of indication and concomitant immunosuppressive therapy. Rituximab also has a Food and Drug Administration black box warning for progressive multifocal leukoencephalopathy (PML). In 1 large report of confirmed PML cases in patients who received rituximab, reported occurrence was very low in patients with RA, with 2.56 cases per 100,000 with RA.[88]

Apart from viral infections and reactivation, bacterial infections are a concern in patients receiving anti–B-lymphocyte therapies. Bacterial infections were the most common infectious complication of patients treated with rituximab for malignancies, with *Escherichia coli* and coagulase-negative staphylococci being the 2 most common organisms.[89] Other types of infections have also been reported. Fungal infections are uncommon with rituximab, although *Pneumocystis* pneumonia has been reported in case reports and case series and other studies finding increased risk in patients with lymphoma.[90–92] Unlike many other biologic agents, TB is a rare complication.[93]

Hypogammaglobulinemia after B-cell depleting therapy may include low IgG, IgM, and IgA levels. A subset of children and adults develop secondary immunodeficiency and persistent hypogammaglobulinemia and failure of B-cell recovery that can persist for years, predisposing to serious infections and potentially requiring Ig replacement.[94] One large study in children and young adults receiving rituximab revealed 13% with low IgG levels, and 33% had persistently low IgM levels 1 year after stopping rituximab.[95] Possible risk factors for developing persistent or symptomatic hypogammaglobulinemia include low Ig levels at baseline, cumulative dose, and concomitant immunosuppression.[96,97]

Before initiation of therapy, screening for HBV infection, given the risk of reactivation, and screening for HCV infection are recommended. This can guide the need for any vaccinations or whether antiviral therapy is indicated. Routine vaccinations should be up to date before starting therapy, ideally giving vaccinations several weeks before therapy initiation. Live vaccinations are contraindicated while receiving anti–B-lymphocyte therapies.[23] Immunoglobulin levels and B-cell numbers should be monitored before, during, and after treatment.

Although anti–B-lymphocyte agents are effective for several oncologic and autoimmune conditions, they are associated with secondary immunodeficiency, including persistent hypogammaglobulinemia and increased infectious risk including bacterial infection, viral hepatitis reactivation, and PML. Providers must be vigilant about the patient's individual risk factors, with close monitoring while patients are receiving this therapy.

Conclusion

Biologic immunomodulatory therapies have contributed to a paradigm shift and revolutionized the treatment of numerous inflammatory conditions over the preceding decades. Although their therapeutic effectiveness is absolute, appropriate vigilance is necessary owing to safety concerns with the potential for secondary immunodeficiency and increased infectious risk. There is a general increased infectious risk in addition to specific risk profiles given the unique mechanisms of action for the different classes. Although not covered in this review, another area of rapid growth is small molecule inhibition including janus kinase inhibitors and proteasome inhibitors, each with their own unique infectious risk profiles.[98,99] As immunomodulatory therapies continue to expand, providers caring for patients receiving biologic and other immunomodulatory medications should familiarize themselves with the associated risks and the recommended or required screenings before use. Other individual risk factors such as concomitant immunosuppressive therapy, age, and comorbid medical conditions should also be factored into determination of risk and screening. Ultimately, the benefit of these therapies must be weighed with each agent's risk profile. With appropriate screening and monitoring, these risks can be mitigated, and patients can safely and effectively receive biologic agents.

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