

Biologic Agents and Secondary Immune Deficiency



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KEYWORDS

- Secondary immune deficiency • Biologics • Immunosuppression
- Monoclonal antibodies • TNF- α inhibitors • Anti-inflammatory

KEY POINTS

- Biologics are protein-based pharmaceuticals derived from living organisms or their products, and are widely used in treatment of autoimmune and autoinflammatory diseases.
- The use of biologics has become the standard of care for many pediatric rheumatologic conditions because of their efficacy in disease remission.
- TNF- α inhibitors are the oldest and best studied with regard to immune suppression and possible infectious consequences.
- Pediatricians need to be aware of immune suppression caused by biologics and the spectrum of infections that should be screened for before use (especially TB) and during use.
- Specific guidelines for screening, measures to reduce risk, and precautions to be given to patients on biologics do not yet exist for children, and are needed.

Biologics block inflammatory pathways, which reduce pathologic inflammation through various mechanisms including cytokine inhibition, nonclonal cell deletion, and co-stimulatory inhibition. It is not surprising that this immune suppression raises concern for secondary immunodeficiency and increased risk of infection. Clinical studies by Keyser,¹ Rutherford and colleagues,² Bradshaw and colleagues,³ Carneiro and colleagues,⁴ and Lee and colleagues⁵ have investigated and detailed the association of these therapies with opportunistic infections and malignancies.

Biologics are classified by their mode of action. The first biologic developed and approved for the treatment of rheumatoid arthritis (RA) was the tumor necrosis factor

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alpha (TNF- α) inhibitor etanercept. Other subsequent TNF- α inhibitors include certolizumab, adalimumab, infliximab, and golimumab. Other classes of biologics include B cell inhibitors (rituximab), interleukin 1 (IL-1) inhibitors (anakinra), IL-6 inhibitors (sarilumab and tocilizumab [TCZ]), and cytotoxic T lymphocyte-associated antigen 4 (CTLA4) co-stimulator inhibitors (abatacept/Orencia).

We discuss the mechanism of action of the currently approved biologics and summarize the studies on immune suppression from biologics, most of which have been conducted patients with rheumatology.

TUMOR NECROSIS FACTOR ALPHA INHIBITORS

TNF- α is a cytokine that modulates the host response in the acute phase of infection and induces production of IL-1, IL-2, IL-6, IL-8, monocyte chemoattractant protein-1, gas chromatography-mass spectrometry, and adhesion molecules such as E-selectin and vascular cell adhesion molecule 1.⁶ TNF- α inhibitors remove TNF- α from the extracellular environment. They have been shown to be effective in treating RA, juvenile idiopathic arthritis (JIA), inflammatory bowel disease, and the spondyloarthropathies. By inhibiting TNF- α , these biologic agents also inhibit the initiation of an inflammatory response and may leave the body susceptible to infection. Furthermore, the diagnosis of a bacterial infection may not be made as quickly because of the lack of certain clinical features (ie, fever or elevated C-reactive protein). The association between TNF- α inhibitors and infection has been well established in the literature, and in 2011 a black box warning was issued to warn providers and adult patients about the risk of serious infections when using these products.

Etanercept is a dimeric fusion protein with 2 TNF- α receptors linked to the Fc portion of human immunoglobulin G1 (IgG1). It was the first anti-TNF agent to be approved by the Food and Drug Administration (FDA) for the treatment of RA. Over the past 16 years, its short-term safety profile has been investigated in many clinical trials in patients with RA, psoriatic arthritis, and psoriasis.⁷⁻¹⁰ There are 2 major clinical trials that looked at the use of etanercept in RA; the TEMPO¹¹ and COMET studies.¹²

The TEMPO study, published in February 2004, included 522 patients. The percentage of serious infection (not defined in the study) was 4% in all groups: those receiving methotrexate (MTX) alone, those receiving a combination of etanercept and MTX, and those receiving etanercept monotherapy. This study did not identify the infections that developed. Six malignant diseases were noted. One patient in each group had basal cell carcinoma, and there was 1 case of breast cancer, melanoma, and rectal cancer in the etanercept group. There were no cases of central demyelinating diseases, blood dyscrasias, or multiple sclerosis.

The COMET study, published in August 2008, examined 2 groups; an MTX monotherapy group and a combined treatment group receiving etanercept and MTX. Almost 92% of patients in the MTX group and 90% in the combined group reported an adverse event. The most common adverse events were nausea and nasopharyngitis. Serious adverse events (SAEs) occurred in 12.7% of patients in the MTX-only group and 12% of patients in the combined group. The most common SAEs included worsening of RA, breast cancer, chest pain, pneumonia, cholelithiasis, interstitial lung disease, disc protrusion, and hip arthroplasty. One patient died of acute respiratory failure. Eight patients in the MTX group and 5 in the combined group developed serious infections. Herpes zoster was seen in 1 patient in the MTX group. There were no cases of tuberculosis (TB) or demyelinating diseases. There were 8 malignant diseases reported. None of these were found to be related to MTX or etanercept.

The TEMPO and COMET studies demonstrated that etanercept is generally well tolerated in RA, but SAEs are still evident. In the British Society for Rheumatology Biologics Registry for Rheumatoid Arthritis prospective observational study in 2001, etanercept was shown to have the lowest incidence of TB compared with the other TNF- α inhibitors.¹³ A similar result was seen in a study in 2009, which demonstrated that etanercept had a lower risk of causing reactivation TB than infliximab or adalimumab.¹⁴ In a long-term clinical trial over 8 years of patients on etanercept, the safety profile was shown to be similar to that seen in studies over a shorter time frame.¹⁵ Registries continue to assess long-term risk and harm of etanercept in patients with rheumatologic conditions.¹⁶

Adalimumab is a human monoclonal antibody that blocks the effects of TNF- α . Adalimumab was the first therapeutic monoclonal antibody against TNF- α that had 100% human peptide sequences and is thereby indistinguishable in function and structure from human IgG1.¹⁷ There were 4 randomized double-blinded placebo-controlled clinical trials were used for the original application of this medication: the ARMADA,¹⁸ DE019,¹⁹ DE011,²⁰ and STAR studies.²¹

The ARMADA study, published in January 2003, examined a group of patients taking adalimumab and MTX or MTX with a placebo over 24 weeks. Infections occurred at a similar rate in the patients treated with adalimumab (1.55/patient-year) and those treated with a placebo (1.38/patient-year). Two patients in the adalimumab group developed pneumonia and remained in the study. One patient in the treatment group developed adenocarcinoma of the colon. No other cancers were reported, no drug-related toxicity occurred, and no patients developed TB or lupus-like syndrome.

In the DE019 study, published in May 2004, adalimumab was used alone at a dosage of 20 mg once a week, or 40 mg every other week with MTX, in 618 patients over 52 weeks.

The rate of SAEs was 14.3%. More patients (3.8%) treated with adalimumab reported serious infections requiring hospitalization compared with the placebo group (0.5%). There was a statistically significant difference between the percentage of patients reporting serious infections who received adalimumab 40 mg every other week and the placebo group. However, there was no statistically significant difference between the rates of serious infections in the group that received adalimumab weekly and the placebo group. On entry, 2.6% of patients receiving adalimumab and 3.5% of patients receiving placebo were positive for purified protein derivative (PPD).

One patient in the treatment group receiving adalimumab 40 mg every other week was diagnosed with primary TB, withdrew from the study, and was treated. Before the start of the study this patient had a normal chest radiograph and was negative for PPD.

One patient in the group that received 40 mg adalimumab every other week developed a histoplasmosis infection. Another patient in the 40-mg group developed herpes zoster and encephalitis. Four patients receiving adalimumab developed cancers; non-Hodgkin lymphoma, adenocarcinoma, breast cancer, and testicular seminoma, respectively. One patient in the 20-mg treatment group had worsening of a central demyelinating illness. There were 2 deaths in the 40-mg treatment group, 1 attributed to urosepsis and 1 from multiple fractures. There was 1 death in the 20-mg treatment group related to complications of chemotherapy for the treatment of lymphoma. No deaths occurred in the placebo group.

The DE011 study, published in May 2004, investigated adalimumab as monotherapy at varying dosages and frequency of treatment. Over 26 weeks, 544 patients with RA were separated into groups receiving adalimumab: 20 mg every other week, 20 mg weekly, 40 mg every other week, 40 mg weekly, or a placebo. Adalimumab was well tolerated, and most adverse events were mild or moderately severe. The

rate of adverse events was 2.23 patients/patient-year in the adalimumab-treated group and 2.60 patients/patient-year in the placebo group. There was no statistically significant difference in the rates of SAEs between the placebo group and the adalimumab-treated group (0% and 2.3% of patients, respectively). In addition, there were no dose-related statistically significant adverse events for those in the adalimumab group. There were no cases of TB. There was an equal rate of malignancies between the treatment and placebo group, and they were deemed to be unrelated to the study drug.

The STAR study, published in December 2003, investigated adalimumab in combination with several anti-RA drugs, including methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, and prednisolone, sometimes with more than 1 of these drugs being used with adalimumab, as opposed to disease-modifying antirheumatic drugs (DMARDs—a category of drugs defined by their use in rheumatologic disease rather than by their mode of action) and a placebo. The study included 318 patients over 24 weeks and found no statistically significant differences in SAEs, or severe or life-threatening adverse events leading to withdrawal between the adalimumab plus DMARDs group and the placebo plus DMARDs group.

Infliximab (Remicade), is a chimeric human and mouse peptide sequence monoclonal antibody to TNF- α . The ASPIRE²² and BeSt²³ trials investigated the safety and efficacy of infliximab in patients with early RA. The ATTRACT²⁴ study examined patients with an established history of 7 to 9 years of RA taking infliximab.

The ATTRACT study, published in November 30, 2000, included 428 patients with established RA of 7.2 to 9 years in duration which persisted despite treatment with MTX for 3 months or longer. There were 2 treatment groups, those that received MTX alone and those that received infliximab and MTX. SAEs occurred in 21% of MTX group and 17% in the infliximab and MTX group. The frequency of serious infections was also similar (8% and 6%, respectively, of the MTX and infliximab plus MTX groups). The most common adverse events were upper respiratory tract infections, pharyngitis, sinusitis, and headache. Five patients receiving infliximab developed cancer; basal cell carcinoma, and rectal carcinoma. Eight deaths occurred during the trial, 3% in the MTX-only group and 1% in the infliximab plus MTX group.

The ASPIRE trial, published in November 2004, examined the efficacy of infliximab in over 1000 patients with early moderate to severely active RA. These patients were examined over a 54-week period. SAEs were more prevalent in the MTX-infliximab group than the MTX-placebo group; the rates were 14% and 11%, respectively. Pneumonia occurred more frequently in those treated with infliximab than those with MTX alone. Most of the 15 cases (or 2%) in the infliximab group were community acquired pneumonias. Active TB was diagnosed in 4 patients from the infliximab treatment groups. Three of the 4 had pulmonary TB. Four patients in the infliximab group were diagnosed with a malignancy during the trial. Four patients died during the study, 2 were from the group treated with infliximab. None of the deaths were thought to be related to the study drugs.

The BeSt study, published in October 2005, was a randomized trial that examined 508 patients with recently diagnosed RA. Patients were divided into 4 groups. The first group received monotherapy, the second group received step-up combination therapy, the third group received combination therapy with tapered high-dose prednisone, and the fourth received initial combination therapy with infliximab. Nine patients in group 4 had latent TB and received isoniazid before infliximab. There were no new cases of TB or opportunistic infections reported in this study. Six patients in the infliximab group experienced SAEs, which included pulmonary embolism, septic arthritis,

transient cardiac ischemia, peripheral vascular disease, MTX pneumonitis, and pneumonia.

Certolizumab is a recombinant polyethylene glycolylated fragment of a humanized anti-TNF monoclonal antibody with high affinity to TNF. The affinity of certolizumab for TNF- α is stronger than adalimumab and infliximab. The safety of certolizumab in RA has been evaluated in 7 major clinical trials. These clinical trials include FAST4WARD,²⁵ RAPID 1,²⁶ RAPID 2,²⁷ Study 014,²⁸ REALISTIC,²⁹ CERTAIN,³⁰ and DOSEFLEX.³¹ In these studies treatment-emergent adverse events (AEs) occurred after the first time the subject received the study drug and for up to 12 weeks after the last dose.

The RAPID 1 trial was published in October 2008. This study investigated placebo versus treatment with 200 and 400 mg certolizumab pegol (CZP). The overall rate of treatment AEs for the placebo group was 125.9 per 100 patient-years. In the 200-mg CZP group it was 96.6 per 100 patient-years, and in the 400-mg CZP group it was 94.6 per patient-years. Most AEs were mild or moderate. Infections led to the withdrawal of the study drug in 6 patients in each of the CZP dosage groups. No patients in the placebo group discontinued the study drug due to infection. The most common infections reported were urinary tract infections, upper respiratory tract infections, and nasopharyngitis. Between the groups, the frequency of infectious AEs was comparable. SAEs were observed more frequently in the CZP groups than the placebo group. The most frequent serious infections were gastroenteritis, urinary tract infections, lower respiratory tract infections, and TB. SAEs occurred in 5.3 (per 100 patient-years) in the CZP 200 mg group, 7.3 in the 400 mg CZP group, and 2.2 in the placebo group. Five patients living in Eastern Europe who received CZP developed TB; 3 of whom had a positive PPD at baseline, another was a worker in a TB clinic. One hundred and seventy-two patients who had a PPD equal to or greater than 5 mm were enrolled in the study. Malignant neoplasms were found in 12 patients (1 receiving placebo [1.1 per 100 patient-years; thyroid neoplasm], 7 receiving 200 mg of CZP). There were no clinically or statistically significant differences between the 2 CZP dosage groups. The 8 instances of AEs related to death were deemed unrelated or unlikely to be related to CZP.

The FAST4WARD study was published in June 2009. There were no cases of opportunistic infections, including TB. No cases of systemic lupus erythematosus (SLE) were reported and there were no deaths.

The RAPID 2 trial was published in June 2009. The RAPID 2 trial again looked at CZP 200 and 400 mg and a placebo group. In the placebo group, 3.2% of patients experienced SAEs compared with 7.3% in the CZP group. Serious infections did not occur in the placebo group, whereas 3.2% of patients in the 200-mg CZP group and 2.4% of patients in the 400-mg CZP group were affected. Serious infections included erysipelas, TB, gastroenteritis, tooth abscess, postoperative wound infection, and urosepsis. Five patients in total developed TB and they were in the CZP group. One case of malignant neoplasm occurred in each group. Two patients died during the study, both from the CZP groups. Neither of the deaths were reported as related to the study drug.

Study 014 was published in July 2012. This study investigated patients receiving CZP with MTX and those receiving placebo with MTX. SAEs were reported in 12.9% of patients in the CZP + MTX group and 10.1% of patients in the placebo + MTX group. The rates of infections were higher in the CZP + MTX group (26.6%), which was statistically significant ($P = .026$), in comparison with the MTX + placebo group (14.3%). Serious infections were reported in 3 patients in the CZP + MTX group and 2 patients in the MTX + placebo group. There were no cases of TB, malignancies, SLE, or deaths in the study.

The REALISTIC study was published in December 2012. They compared CZP versus placebo. The most common SAEs were infections in 2.6% of patients in the CZP group and 1.9% of patients in the placebo group. There were 2 cases of *Aspergillus* infection in the CZP group. There were no cases of TB. There were 4 cases of malignant neoplasms in the CZP group. These neoplasms included carcinoid tumor, adenocarcinoma of the pancreas, skin melanoma, and uterine sarcoma. There were 2 malignant neoplasms in the placebo group: breast cancer and skin melanoma. There were 2 deaths in the CZP group. One death was because of sigmoid diverticulitis and the other because of necrotizing pneumonia, and both deaths were stated to possibly be related to CZP.

The CERTAIN trial, published in December 2013, investigated CZP and placebo groups. The rates of each type of AE were comparable in both groups. SAEs were reported in 5.2% of patients in the CZP group. These included irritable bowel syndrome, otitis media, polyarthritis, RA, sepsis, and disc protrusion. SAEs were reported in 7.1% of patients in the placebo group. These included pneumonia, tendon rupture, joint effusion, cerebrovascular accident, Wegener's, pleurisy, breast cancer, and basal cell carcinoma.

The DOSEFLEX trial was published in February 2015 and examined patients who received CZP. The most common AEs were infections, which were present in 54% of patients. The most common infections were upper respiratory tract infections. SAEs were found in 8.7% of patients. The most common SAE was infection, followed by connective tissue disorders and cardiac disorders. There was 1 case of malignant melanoma and 1 case of basal cell carcinoma. There were no deaths and no reported cases of TB.

In a Cochrane meta-analysis of 22 randomized controlled trials from 2002 to 2012, certolizumab was found to have a relative risk of 2.29, which was comparable with the relative risk of other TNF- α inhibitors. However, this study was limited because there were fewer patients treated with certolizumab compared with some of the other TNF- α inhibitors.³² Also, when compared with the other TNF- α inhibitors in this study, CZP was not associated with an increased risk of malignancies, infections, or cardiovascular events.³³ The opportunistic infections that were studied in this review were TB, oral or esophageal candidiasis, herpes simplex, herpes zoster, Epstein-Barr virus, *Nocardia*, and cytomegalovirus.

Golimumab, or Simponi, is a human anti-TNF drug that was approved by the FDA in 2009 for the treatment of RA, ankylosing spondylitis, and psoriatic arthritis. There were 2 large, double-blinded, randomized trials that investigated the efficacy and safety of golimumab in patients with RA: the GO-BEFORE³⁴ and GO-FORWARD³⁵ studies.

The GO-BEFORE study was published in June 2008, and separated patients into 4 groups; group 1 patients received MTX plus placebo, group 2 received golimumab 100 mg plus placebo, group 3 received golimumab 50 mg plus MTX, group 4 received golimumab 100 mg plus MTX. The most common SAEs were pneumonia, anemia, and serious infections. SAEs were reported in 6.9%, 3.2%, 6.3%, and 6.3%, respectively, of the 4 groups. Tuberculosis of the spine was diagnosed in a patient in group 2, 33 days after she received golimumab. However, the spinal lesion was present before the patient started the study. Two patients died during the study; neither were attributed to the study drug. Malignancies developed in 4 patients; 1 with Hodgkin lymphoma, 2 with breast cancer, and 1 with squamous cell skin cancer. Overall the incidence of SAEs and serious infections was low. However, there was a higher incidence of patients who developed serious infections in the golimumab 100 mg with MTX group in comparison with the other groups.

The GO-FORWARD study was published in December 2008 and separated patients into 4 groups. The groups varied on the dosages of golimumab and whether or not MTX was used. Patients were followed for 2 years, and 22.6% of golimumab-treated patients developed SAEs. Serious infections were the most common SAEs. Two patients in the 100 mg golimumab plus placebo group developed active TB, and 4 patients in the same group died during the 2-year duration of the study. The causes of death were sepsis, hepatic failure, circulatory insufficiency, and complicated respiratory distress following acute pulmonary edema, which occurred after open cholecystectomy. Two placebo-treated patients and 14 golimumab-treated patients developed malignancy.

OTHER CLASSES OF BIOLOGICS

TCZ targets the IL-6 receptor, thus inhibiting the inflammatory cascade. It is 1 of the newer biologics studied for the treatment of adult patients with RA with a refractory response to DMARDs. Because of its newer status the risk of infections with treatment of TCZ is less well studied. The 2 long-term extension studies that investigated the efficacy and safety of TCZ were the SUMMACTA³⁶ and the BREVACTA³⁷ trials.

SUMMACTA, published in January 2014, demonstrated a similar safety profile between intravenous and subcutaneous administration of TCZ. The rate of serious infections was 3.6 per 100 patient-years in the TCZ group versus 1.5 per 100 patient-years in the MTX group. The most common serious infections included pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis, and bacterial sepsis.

The BREVACTA trial, published November 2014, was a 24-week, double-blinded study in patients with active RA and inadequate response to DMARDs. Patients received TCZ 162 mg or placebo every other week, and 4.6% of patients in the treatment group and 3.7% of patients in the placebo group experienced SAEs. The most common SAE was infection in both groups. Three patients died during the study, all in the TCZ group, and the deaths were reported as related to the drug. Deaths were from *Haemophilus influenzae* sepsis, sepsis secondary to gastrointestinal causes, and complications of a lower respiratory tract infection, respectively. Three malignancies occurred in the treatment group, which were deemed unrelated to the study medication.

Rituximab is an anticluster of differentiation 20 (CD20) monoclonal antibody that recognizes B cell lineage from the pro-B cell onward. Cell death is caused by complement-mediated and antibody-mediated cytotoxicity targeting peripheral B cells. It is used to treat patients with RA, but also leukemia, lymphoma, and antibody-driven disorders such as hemolytic anemia and systemic lupus erythematosus. Although there have been reported cases of patients on rituximab who developed serious infections, these individuals were also treated with biologic agents and/or TNF- α inhibitors.³ An increased risk of infection is evident in patients with lymphoma or other hematological malignancies on rituximab maintenance therapy, but no similar data exist for patients with RA.³⁸ Progressive multifocal leukoencephalopathy is an opportunistic central nervous system (CNS) infection that may develop in 1 per 25,000 patients with RA treated with rituximab.³⁹

Abatacept is a T cell co-stimulator modulator with CTLA-4 linked to human IgG1. It blocks binding of CD80/CD86 to T cell CD28 and therefore blocks co-stimulation.⁴⁰ The incidence of serious infections was roughly 2% over 26 weeks and 2.5% to 3% in more than 1 year of medication use.⁴⁰ In a trial that compared the use of abatacept with MTX and infliximab, versus MTX as a sole treatment, there was a lower rate of

serious infections with abatacept treatment.⁴¹ In a meta-analysis the incidence of serious infections in patients with RA taking abatacept was 2.5%, which was not a significant increase.

REACTIVATION OF LATENT TUBERCULOSIS AND OTHER INFECTIONS

The reactivation of latent TB is a well-studied infectious adverse effect of TNF- α inhibitors.³ However, etanercept has lower risk of causing reactivation TB than either infliximab or adalimumab.¹⁴ Individuals with TB on TNF inhibitors are more likely to develop extrapulmonary and CNS complications, such as meningitis and tuberculomas.³ Also, after looking at long-term follow-up data on patients who developed TB after taking TNF- α inhibitors, it seems that biological therapy can be safely resumed after treatment of TB.^{42,43} The risk for reactivation of latent TB with abatacept and TCZ seems to be low; however, there are fewer clinical trials that used these drugs and included a population with TB exposure or had TB screening as a part of their studies.⁴¹

The risk of patients developing reactivation TB can be mitigated by appropriate screening for, and treatment of, latent TB infection when starting patients on anti-TNF therapy.³ Tuberculin skin test, interferon gamma release assay, chest radiograph, and sputum examination are all useful screening tools to supplement the exposure history and physical examination findings in decreasing the incidence of reactivation TB in immunocompromised patients on TNF- α inhibitors.

Biologic therapy is also believed to increase the risk of atypical mycobacterial infections, *Legionella*, *Listeria*, and *Salmonella*, as well as viral and fungal infections. Histoplasmosis is the most common fungal infection associated with TNF inhibitors.³ CNS involvement and disseminated disease is more likely in patients with histoplasmosis on TNF- α inhibitors. However, in a retrospective study of 98 patients treated with TNF- α inhibitors who developed histoplasmosis, only 2% developed CNS involvement.³ Other patients with possible endemic mycoses on TNF- α inhibitors are increasingly susceptible to coccidiomycosis and blastomycosis. Herpesvirus and *Listeria* and *Nocardia* meningitis are rare but reported infections associated with TNF- α inhibitor use.³

Children are especially vulnerable to bacterial infections because of the immaturity of their immune system. In a study examining children with JIA who used TNF- α inhibitors, the risk of serious bacterial infections requiring hospitalization was 2.7 times greater than children with JIA who were treated with DMARDs.⁵ Although DMARDs and TNF- α inhibitors are often used together, the risk of infection is also associated with TNF- α inhibitors being used as a monotherapy in children with JIA.⁵

Although it is evident that biologics result in secondary immune deficiency, the significant benefits of these medications need to be considered as well. TNF- α inhibitors are used in the treatment of children with moderately to severely active polyarticular JIA, which causes arthritis involving more than 4 joints within the first 6 months in patients younger than 16 years. These patients generally have a refractory course and are therefore more likely to have joint damage, which negatively affects their functioning and quality of life. With the advent of biologic agents, the disease course and prognosis has dramatically changed for those affected.⁴⁴ TNF- α inhibitors have been shown to decrease disease remission. Starting TNF- α inhibitors earlier in the disease course of RA and JIA has been shown to improve outcome in clinical studies.^{45,46}

There are measures that providers can take to reduce the risks of infection. Reducing the dose of glucocorticoids, alternate-day dosing, and concurrent use of other immunosuppressive medications can decrease associated risks.⁴⁷ The US FDA and the European Medicines Agency have developed parameters for

Table 1
List of biologics and their infection risk

Biologic	Brand Name	Mechanism of Action	Approved Uses	Infection Risk
Certolizumab	Cimzia	TNF- α inhibitor; binds to human TNF- α with a K_D of 90 pM	Crohn disease, RA, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis	Increased risk of opportunistic infections. Cases of reactive TB or new TB have occurred. Most common adverse reactions >7% (upper respiratory tract infection, rash, and urinary tract infection). New infection risk 0.91 per patient-year in RA patients. ⁴⁸
Adalimumab	Humira	TNF- α inhibitor; binds to human TNF- α	RA, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis	Increased risk of serious infection. Cases of reactive TB or new TB have occurred. ⁴⁹
Infliximab	Remicade	TNF- α inhibitor; chimeric human and mouse peptide sequence monoclonal antibody	RA, Crohn disease, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, ulcerative colitis	Most common adverse reactions (>10%), infections. Treated serious infections reported in 36% patients. Most common, sinusitis, pharyngitis, bronchitis, and urinary tract infections. Serious infections included pneumonia, cellulitis, abscess, skin ulceration, sepsis, and bacterial infection. Cases of reactivation of TB or new TB infections have been observed. ⁵⁰
Golimumab	Simponi	TNF- α inhibitor	RA, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis	Serious infections have been reported in 1.4% of treated patients. Serious infections include sepsis, pneumonia, cellulitis, abscess, TB, invasive fungal infections, and hepatitis B infection. Cases of reactivation of TB or new TB infections have been observed. ⁵¹
Rituximab	Rituxan	B cell inhibitor	RA, Wegener's granulomatosis, pemphigus vulgaris, non-Hodgkin lymphoma, chronic lymphocytic leukemia	Serious infections have been reported in patients with prolonged hypogammaglobulinemia. Most common infections, nasopharyngitis, upper respiratory tract infections, urinary tract infections, bronchitis, and sinusitis. ⁵²

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Table 1
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Biologic	Brand Name	Mechanism of Action	Approved Uses	Infection Risk
Anakinra	Kineret	IL-1 Inhibitor	RA	Incidence of infection was 40% in Kineret-treated patients, vs 35% in placebo-treated patients. Incidence of serious infections, 1.8% in Kineret-treated patients vs 0.6% in placebo. Most common infections, cellulitis, pneumonia, and bone and joint infections. Patients with asthma were at higher risk of developing infection (5%) vs placebo (<1%). ⁵³
Sarilumab	Kevzara	IL-6 inhibitor	RA	Serious infections have been reported. Most frequent pneumonia and cellulitis. Rate of overall infection 0.6%–0.8% in the treatment group compared with 0.5% in the placebo group. Rate of serious infection in events per 100 patient-years was 3.0 (150 mg) and 4.3 (200 mg) in the Kevzara treatment groups compared with 3.1 in the placebo group. Cases of TB have been reported. ⁵⁴
Tocilizumab	Actemra	IL-6 Inhibitor	RA, giant cell arteritis, polyarticular JIA, systemic JIA, cytokine release syndrome	Rate of overall infections, 119 events per 100 patient-years, similar to the MTX group. Serious infections, 3.6 per 100 patient-years, 1.5 per patient-years in the MTX group. Most common infections, upper respiratory tract infections and nasopharyngitis. Most common serious infections, pneumonia, urinary tract infection (UTI), cellulitis, herpes zoster. Cases of TB have been reported. ⁵⁵
Abatacept	Orencia	CTLA4 co-stimulator inhibitor	RA	Infections reported in 54% patients in the treatment group, 48% in the placebo group. Most common infections, upper respiratory tract infections, nasopharyngitis, sinusitis, UTI, influenza, bronchitis. Serious infections, 3% in the treatment group, 1.9% patients in the placebo group. ⁴⁰

Note: Approved uses are in the United States indicated by the FDA.

administering biologics for adult patients.⁵ However, there needs to be guidelines for the screening of children being treated with TNF- α inhibitors (**Table 1**).

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