Adverse Effects of Immunosuppression: Infections

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Contents

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1 Introduction

Immunosuppressive therapies are currently indicated for a wide range of diseases. As new agents emerge and indications evolve the landscape grows increasingly complex. Therapies can target pathologic immune system over-activation in rheumatologic or autoimmune disease, or conditioning and graft versus host disease (GVHD) prophylactic regimens may eliminate or inhibit host immune function to improve graft survival and risk of complication in solid organ transplantation (SOT) or hematopoietic stem cell transplantation (HSCT). With immunosuppressive therapy, infections occur. Complex disease states, host factors, and concomitant therapies contribute to a "net state" of immunosuppression that must be considered and may confound perceived increased infection risks in patients receiving treatment (Roberts and Fishman 2020).

Agents that broadly act across the immune system in dose-dependent fashion, such as corticosteroids, non-myeloablative and myeloablative chemotherapy, predispose patients to a host of bacterial, viral, and fungal infections including opportunistic infections such as *Pneumocystis jirovecii pneumonia* (PJP), tuberculosis or hepatitis B reactivation. Risk factors, mechanisms of immunosuppression, and epidemiology among these broad agents are extensively reviewed elsewhere and will not be covered here. Targeted therapies, both biologic and non-biologic, selectively inhibit the immune system and carry specific individual risks which we aim to describe.

A collection of targeted therapies utilized for patients with inflammatory bowel disease (IBD), multiple sclerosis (MS), rheumatologic diseases, HSCT and SOT are presented, but this chapter is by no means comprehensive. New therapies continue to be developed, and current ones are too numerous to be collected here. These patient

populations are preemptively screened and treated (or receive prophylaxis) for opportunistic infections such as tuberculosis, hepatitis B reactivation, cytomegalovirus (CMV), or toxoplasmosis. This may mitigate infectious risks of therapeutic agents, as pathogens are identified and treated before clinical disease develops. Screening and prevention measures (including immunizations and prophylaxis regimens) as suggested by consensus or local guidelines are assumed and may continue to change as new evidence emerges. A table of hepatitis B reactivation risks and general reactivation risks with monitoring and prevention recommendations based on societal and expert guidance is included at the end of this chapter. Data from published trials, expert opinions, and longitudinal safety monitoring regarding infectious risks associated with therapeutic agents are presented and may be incorporated at the bedside with standards of practice for each individual patient.

2 Non-Biologic Disease-Modifying Therapies and Disease-Modifying Antirheumatic Drugs

2.1 Methotrexate

Methotrexate is employed in rheumatologic, oncologic, and inflammatory bowel diseases (IBD) often as a backbone therapy. It inhibits folic acid metabolism and cytokine production, increases extracellular adenosine, induces peripheral T-cell apoptosis, suppresses IL-1β and IL-6, and broadly inhibits leukocyte activity (Gerards et al. 2003; Walling 2006). Myelosuppression commonly follows and predisposes to infection though inconclusively at lower dosages (Cronstein 1996). Infection risk is highest shortly after initiation and sporadic cases of opportunistic infection have been reported (Kaneko et al. 2006). Tuberculosis reactivation may occur but studies showing a definitive link are lacking (Sadovici et al. 2013). Screening is reasonable, particularly in high prevalence areas or with expectation of future therapies (Sadovici et al. 2013). Studies demonstrating increased infection risk are mixed. A large meta-analysis of placebo-controlled trials in rheumatoid arthritis (RA) showed a small but significant increased infection risk not seen in non-RA populations (Ibrahim et al. 2018).

2.2 Aminosalicylates

Sulfasalazine and its component metabolite 5-aminosalicyclic acid (5-ASA) are utilized in IBD. Multiple formulations of 5-ASA are available with differing delivery sites. Mechanisms of action are not clearly defined, but could include inhibition of prostaglandins, cytokines, lymphocyte DNA synthesis, IL-2 production, or lymphocyte adhesion and function (Rousseaux et al. 2005). Specific infectious risks are not defined. Agranulocytosis and leukopenia occur with sulfasalazine and could predispose patients to infection (Jick et al. 1995). This does not extend to 5-ASA

formulations. Scattered cases of hypersensitivity reactions to sulfasalazine with detectable herpes viruses exist; however, these are limited and without causal proof (Komatsuda et al. 2008; Tohyama et al. 1998). One study reported reductions in surgical site infections in rheumatoid arthritis patients on sulfasalazine compared to other therapies which they proposed may be due to bacterial folic acid synthesis inhibition (den Broeder et al. 2007). No definitive evidence of infectious risk to opportunistic infections is established but risks of agranulocytosis and leukopenia should be considered.

2.3 Pyrimidine Synthesis Inhibitors

Pyrimidine synthesis inhibitors include leflunomide, and its active metabolite teriflunomide. They prevent T-cell activation by antigen presenting cells (Zeyda et al. 2005). They are prescribed in rheumatologic disease and MS but have been used in IBD (O'Connor et al. 2011; Prajapati et al. 2003). Randomized control trials for teriflunomide in MS did not show increased rates of infection compared to placebo and reported only 1 case of intestinal tuberculosis (O'Connor et al. 2011; Confavreux et al. 2014). Two cases of CMV were reported, but leflunomide is active against CMV by theoretical viral capsid formation inhibition (Ariza-Heredia et al. 2014). Active tuberculosis occurs in patients receiving leflunomide though is limited to case reports (Grover et al. 2006). Viral hepatitis screening should be performed before starting therapy due to potential drug hepatotoxicity and possible enhancement of hepatitis B replication (Hoppe-Seyler et al. 2012).

2.4 Thiopurines

Use is declining but azathioprine and mercaptopurine are utilized in IBD, cancer, and certain autoimmune processes. They inhibit nucleic acid metabolism which can result in leukopenia early after initiation and at higher dosages, increasing risk of bacterial infection (Present et al. 1989). Cases of CMV infection are reported in patients with IBD, but leukopenia and the disease itself may be significant risk factors (Present et al. 1989; Hookey et al. 2003). Varicella zoster virus (VZV) reactivations may be more common but risk of specific opportunistic infections is unclear (Gupta et al. 2006).

2.5 Sphingosine Analog

Fingolimod, and newer agents siponimod and ozanimod, function as a sphingosine 1-phosphate analogs causing lymphatic sequestration of lymphocytes (Chun and Hartung 2010). Two, 24-month placebo controlled trials in MS did not demonstrate increased infection rates (though over half reported upper respiratory tract infections), but reported increased mucocutaneous herpes simplex (HSV) and

VZV infections in treatment arms (Calabresi et al. 2014; Kappos et al. 2010). Tuberculosis was reported in only one patient in either trial and reported a home exposure; viral hepatitis was not reported (Calabresi et al. 2014). Sporadic cryptococcus infections, including meningoencephalitis, have occurred (Achtnichts et al. 2015). A trial comparing fingolimod to interferon therapy found more cases of herpesvirus infections in the 1.25 mg arm including fatal cases of disseminated primary VZV and HSV encephalitis (Cohen et al. 2010). No cases of HBV reactivation were reported and standardized screening was not performed. At least nine rare cases of progressive multifocal leukoencephalopathy (PML) have occurred including one patient without a history of natalizumab administration (Berger 2017). Additional studies document severe VZV infection with fingolimod solidifying the association (Gross et al. 2012; Ratchford et al. 2012). Trials of siponimod report increased VZV infections (Kappos et al. 2018). Trials of ozanimod, a selective inhibitor of sphingosine 1-phosphate receptor subtypes 1 and 5, compared to interferon β1a did not show increased rates of VZV infection, but patients were screened for VZV serology or VZV vaccination history prior to enrollment (Comi et al. 2019). Varicella zoster serostatus evaluation and vaccination should be performed prior to therapy (Arvin et al. 2015).

2.6 Dimethyl Fumarate

Dimethyl fumarate activates nuclear 1 factor-like 2 enhancing antioxidant response and altering dendritic cell differentiation in MS (Gold et al. 2012). Randomized, placebo-controlled trials report infections in a majority of patients, typically upper respiratory infections (URI) and urinary tract infections (UTI), but rates did not differ among treatment groups (Gold et al. 2012; Fox et al. 2012). No opportunistic infections were reported at 2 years in either trial and latent TB screening was not standardized. Longitudinal infectious risk is unclear, but there are sporadic case reports. PML has been documented, and at least 1 patient only received dimethyl fumarate (Sweetser et al. 2013). One case of severe disseminated VZV with neurologic deficits has occurred (Ma et al. 2016). Dimethyl fumarate has a favorable infection profile compared to placebo, though rare cases of PML warrant further study.

3 Janus Kinase (JAK) Inhibitors

Janus Kinase (JAK) inhibitors include tofacitinib, baricitinib, and upadacitinib. They are utilized in RA and IBD. Most experience is with tofacitinib. JAK inhibitors prevent lymphocyte activation through inhibition of inflammatory cytokines (Meyer et al. 2010). Large, placebo-controlled trials found increased rates of neutropenia and serious infections including cellulitis or abscesses though patients were often screened for HBV, hepatitis C (HCV), and TB (Fleischmann et al. 2012; Kremer et al. 2013; van der Heijde et al. 2013; van Vollenhoven et al. 2012). Trials also

report cases of tuberculosis (Fleischmann et al. 2012; Kremer et al. 2013; van der Heijde et al. 2013; van Vollenhoven et al. 2012). Opportunistic infections reported include PJP, cryptococcus infection, disseminated VZV, CMV sialadenitis, and esophageal candidiasis (van der Heijde et al. 2013; Lee et al. 2014). Longitudinal safety studies confirm an increased risk of VZV infection associated with tofacitinib (Winthrop et al. 2014). A trial of tofacitinib in IBD reported higher infection and VZV rates compared to placebo, highlighting the risk across multiple populations (Sandborn et al. 2017). A longitudinal safety study over eight years revealed no new opportunistic infection risk, but many patients with the potential for HBV reactivation were screened out of clinical trials (Cohen et al. 2017). Case reports of reactivation exist (Chen et al. 2018).

Trials of baricitinib report infections at similar rates compared to placebo (Dougados et al. 2017; Keystone et al. 2015; Tanaka et al. 2016). While two trials reported no opportunistic infections, Dougados et al. reported cases of TB and VZV in baricitinib groups (Dougados et al. 2017; Keystone et al. 2015; Tanaka et al. 2016). Trials for upadacitinib, a more selective JAK-1 inhibitor, continue but this agent appears to carry lower infectious risk compared to methotrexate (Smolen et al. 2019). Herpes zoster infection occurred more often with upadacitinib.

Ruxolitinib selectively inhibits JAK1 and JAK2 and is used to treat chronic GVHD after HSCT and myelofibrosis. Placebo-controlled trials in myelofibrosis reported cases of bacterial infection but differences between arms were not evaluated (Verstovsek et al. 2012). While no opportunistic infections were reported, case reports of cryptococcal infection, HBV reactivation, TB, CMV retinitis, and PML exist, but this may reflect the net state of immunosuppression rather than drug effect (Caocci et al. 2014; Colomba et al. 2012; von Hofsten et al. 2016; Wathes et al. 2013; Wysham et al. 2013). Increased cryptococcal infection risk exists and should be considered in differential diagnosis of fungemia, meningoencephalitis, or pneumonia in this population, but cases remain limited (Harvey et al. 2019). Future longitudinal studies may reveal risks. Vaccination for VZV and screening for opportunistic infections including TB and viral hepatitis should be performed prior to starting JAK inhibitors.

4 Integrin Antibodies and Adhesion-Molecule Inhibitors

4.1 Natalizumab

Selective adhesion-molecule inhibitors are prescribed for MS. Natalizumab functions as an α4β1 integrin antibody (Epstein et al. 2018). An initial randomized, double-blind trial showed no difference in rates of infection between natalizumab and placebo groups (Miller et al. 2003). However, post-marketing studies and real-world experience have reported potential pathogens. Sporadic HSV or VZV cases including meningoencephalitis have been reported, suggesting a temporal relationship to drug therapy but studies demonstrating a link are lacking (Fine et al. 2013). Initial trials did not report latent TB reactivation, but similar integrins are involved in

immune response against pulmonary *Mycobacterium tuberculosis* infection (Polman et al. 2006; Rudick et al. 2006). Longitudinal studies have not found an increased risk of active TB (Mulero et al. 2012). Latent tuberculosis screening prior to natalizumab therapy is reasonable. At least one case of acute liver failure and death from HBV reactivation has been reported in a patient on natalizumab, but major trials did not report cases (Miller et al. 2003; Polman et al. 2006; Rudick et al. 2006; Hillen et al. 2015).

The most well-described infectious complication associated with natalizumab is PML. Studies have shown incidences from 2.13 to 20.7 per 1,000 treated patients (Schwab et al. 2017; Vennegoor et al. 2015). JC virus (JCV), the viral pathogen responsible for PML, seroprevalence stands at 50–90% of the adult population and clinical disease in immunocompetent hosts rarely occurs (Brew et al. 2010). In patients treated with natalizumab, prior immunosuppression, prolonged duration of treatment and JCV specific antibodies are risk factors for PML (Schwab et al. 2017). An expert panel recommends JCV serologic screening at baseline, 12 months after initiation, and every 6 months thereafter (McGuigan et al. 2016). After an anti-JCV antibody index level of 1.5, additional screening is not needed. Imaging, with MRI, should occur annually, with increasing frequency as anti-JCV antibody index increases, as findings may precede clinical disease (McGuigan et al. 2016). Once PML develops, outcomes are poor and neurologic sequelae are common (Brew et al. 2010). No therapies, other than cessation of natalizumab, have demonstrated significant treatment benefit though rare cases utilizing JC virus specific donor lymphocytes have shown potential promise for future study (Berzero et al. 2021). Trials have evaluated natalizumab in Crohn's disease but longitudinal studies are less robust (Ford et al. 2011).

4.2 Vedolizumab

Vedolizumab is a humanized monoclonal α4β7 integrin antibody which selectively inhibits lymphocyte gastrointestinal tract migration and is utilized in the treatment of Crohn's disease and ulcerative colitis (Soler et al. 2009). Clinical trials in IBD reported no increases in infectious complications (Feagan et al. 2013; Parikh et al. 2012; Sandborn et al. 2013). Longitudinal reviews from these and other trials demonstrated a reduced infection rate overall with vedolizumab compared to placebo but higher rates of gastroenteritis (Colombel et al. 2017). Risk factors included prior anti-TNF failure, corticosteroid use, and narcotic analgesics. Tuberculosis was reported at a rate of 0.1 events per 100 patient years and 3 of the 4 recorded cases had negative latent tuberculosis screening testing at initiation. Hepatitis B reactivation was not reported, and although a clear risk has not been demonstrated with vedolizumab therapy, it is considered to carry a moderate risk of reactivation (Loomba and Liang 2017). Patients on vedolizumab have non-inferior immunologic responses to hepatitis B vaccination so it should be administered if indicated (Harrington et al. 2020). Notably 10% of reviewed patients reported unexplained neurologic symptoms but none were diagnosed with PML in a 2-year follow-up

period (Colombel et al. 2017). The authors concluded that at a similar rate of JCV seropositivity, 6–7 cases would be expected if vedolizumab had a similar PML risk as natalizumab.

5 Tumor Necrosis Factor (TNF)-Alpha Inhibitors

TNF-alpha inhibitors led to breakthrough advances in IBD and rheumatologic disease but carry infectious risks. Class drugs include monoclonal antibodies against TNF-alpha (adalimumab, golimumab, and infliximab), pegylated fragment of a humanized anti-TNF-alpha antibody (certolizumab), and soluble TNF-alpha receptor (etancercept). They inhibit neutrophil and macrophage function, granuloma formation and stability, increasing risks for granulomatous and intracellular infections (Harris et al. 2008). Extensive randomized trials show mixed rates of bacterial, fungal, and viral infections, but a large meta-analysis of 106 trials in rheumatologic patients showed increased risks of serious infection with standard dosing (Singh et al. 2015). Infectious risks may be highest early in therapy (Galloway et al. 2011). Higher TB risk exists for all agents, though etanercept may be lower, and screening should be standard (Dixon et al. 2010). Risk of non-tuberculous mycobacterial infections is also increased (Winthrop et al. 2013). Longitudinal studies demonstrate higher rates of granulomatous infection with infliximab than etancercept, and cases of coccidioidomycosis, histoplasmosis, nocardiosis, cryptococcus, listeriosis, and candidiasis along with tuberculosis have been described (Wallis et al. 2004). Endemic mycoses infections occur earlier after therapy initiation and at higher rates compared to alternative agents (Bergstrom et al. 2004). Invasive fungal infection with aspergillus, zygomycetes, and PJP may occur (Wallis et al. 2004; Tsiodras et al. 2008). Most evidence presented covers studies of adalimumab, infliximab, or etancercept, but similar risks likely occur with certolizumab and golimumab for which additional longitudinal investigation is required (Keystone et al. 2009; Smolen et al. 2009).

Herpes zoster infection rates are higher after adalimumab and infliximab use (Strangfeld et al. 2009). Hepatitis B reactivation, including cases of fulminant hepatitis, has been documented (Zingarelli et al. 2009). Antiviral therapy has been utilized successfully while on anti-TNF-alpha therapy. Screening, including surface antigen and both core and surface antibodies, should be performed prior to initiation of therapy. Vaccination or antiviral prophylaxis should be given if indicated and anti-TNF-alpha treatment is needed (Table 1) (Singh et al. 2016; Di Bisceglie et al. 2015). Evidence indicating worsening of hepatitis C in chronic quiescent disease due to treatment is lacking, but screening should be performed. The American College of Rheumatology recommends etancercept as the drug of choice in patients with active hepatitis C if needed (Singh et al. 2016).

Infliximab may be also used for steroid-refractory GVHD after HSCT. While these patients have increased risks of fungal infection or CMV disease, infliximab carries an additional risk compared to other agents, particularly for invasive fungal infection and some experts recommend mold prophylaxis if infliximab is needed

(Couriel et al. 2004). Screening for latent mycobacterial infection, viral hepatitis, and fungal infections in high-risk areas is recommended and should be performed before initiation of anti-TNF-alpha therapy. Active infection with these or other bacterial, viral, or fungal infections may preclude use. Prophylaxis could be considered with recurrent herpesvirus infection, chronic hepatitis B infection, or molds colonization and infection in HSCT patients.

6 T-Cell Costimulatory Blockers

6.1 Abatacept

Abatacept, the first T-cell costimulatory blocking agent developed, is a CTLA-4 IgG1 fusion protein which blocks CD28 binding and disrupts T-cell activation (Judge et al. 1996). Abatacept may be used to treat RA, psoriatic arthritis, and juvenile idiopathic arthritis. Infectious complications of abatacept are rare but bronchopulmonary infections have been most commonly observed. A 2009 meta-analysis found no differences in infection rates when comparing patients receiving abatacept to those receiving placebo (Salliot et al. 2009). Further, when compared to patients receiving TNF-alpha inhibitors and rituximab, patients receiving abatacept had a significantly lower risk of infections requiring hospitalization (Yun et al. 2016).

6.2 Belatacept

Belatacept, a daughter protein of abatacept and more potent T-cell inhibitor, selectively blocks costimulatory pathway for T-cell activation and is used as de novo or conversion from calcineurin inhibitor (CNI) maintenance immunosuppression after kidney transplantation (Perez et al. 2018). Data in liver and thoracic transplantation is limited though emerging. In the BENEFIT and BENEFIT-EXT trials urinary tract and CMV infections were most common but no differences were seen between intensive belatacept, less intensive belatacept, and cyclosporine treatment groups (Durrbach et al. 2016). Additionally, there were no differences in rates of serious infections between groups. A large, single-center, retrospective study found significantly higher rates of low level CMV viremia when belatacept was used without tacrolimus (Adams et al. 2017). This increased CMV rate was thought to be due to higher rates of rejection in this group which was treated with thymoglobulin and steroids. More recently, a single-center retrospective study of CMV seronegative kidney transplant recipients found a higher incidence of CMV viremia, higher rates of first-line antiviral failure, and longer time to virus clearance in CMV high-risk patients treated with de novo belatacept-based maintenance regimens when compared to those treated with tacrolimus (Karadkhele et al. 2021).

Early belatacept studies found increased rates of post-transplant lymphoproliferative disease (PTLD) in recipients who were initially Epstein Barr

virus (EBV)-seronegative resulting in an FDA boxed warning for belatacept use in these patients (Grinyo et al. 2010). Though belatacept should be avoided in EBV-seronegative recipients, a 2014 Cochrane systematic review found PTLD risk was similar in recipients receiving belatacept when compared to those receiving calcineurin inhibitors (CNI (Masson et al. 2014). Further, no differences in PTLD risk were seen between EBV seropositive and seronegative groups or between patients receiving high- or low-dose belatacept.

7 Selective B-Cell Depletion and Inhibition

7.1 Anti-CD 20 Monoclonal Antibodies

7.1.1 Rituximab

Rituximab, an anti-CD20-directed monoclonal antibody causes rapid depletion of B cells, interferes with B- and T-cell interactions, can lead to hypogammaglobulinemia, and may have prolonged immune effects lasting 6–-12 months or longer (Thiel et al. 2017). Hypogammaglobulinemia may predispose patients to recurrent sinopulmonary infections and may also require routine administration of intravenous immunoglobulin (Barmettler et al. 2018; Casulo et al. 2013). Late onset neutropenia has also been described and can occur an average 5 months after drug cessation and up to nearly 1 year and in certain high-risk patients, antibacterial prophylaxis has been used during prolonged periods of neutropenia (Breuer et al. 2014). Rituximab can be used for a range of B-cell malignancies, immune disorders such as refractory RA, and for desensitization of highly sensitized or ABO-incompatible transplant recipients, as well as antibody-mediated rejection. Fatal cases of HBV reactivation led to an FDA boxed warning for rituximab use in patients with HBV infection (Martin et al. 2014). All patients should be screened for HBV prior to initiation of rituximab and all other anti-CD20 agents and AASLD guidance for screening is described in Table 1. These agents should be discontinued in patients with HBV reactivations.

The varied and composite immune defects induced by rituximab use increases infectious risk in certain patients. Though trials of rituximab for RA have not demonstrated increased infectious risks, overall it is difficult to assess and estimate specific risks given the broad range of infectious risk in published studies, limited controlled trials, and heterogeneity of concomitant immunosuppressive agents (Grim et al. 2007; Kamar et al. 2010; Kelesidis et al. 2011; Shi et al. 2019). Other opportunistic infections such as PML caused by JC virus reactivation have been described and newer anti-CD20 agents may also increase risk (Focosi et al. 2019; Molloy and Calabrese 2012). Additionally, rates of PJP infection may be higher in patients receiving rituximab when compared to those on TNF-alpha inhibitors (Rutherford et al. 2018).

7.1.2 Obinutuzumab, Ofatumumab, Ocrelizumab

Obinutuzumab, a newer anti-CD20 monoclonal antibody with high in vitro potency, used for CLL and follicular lymphoma can increase the risk for severe respiratory tract infections and VZV reactivations, and invasive fungal infections after monotherapy have been reported (Mikulska et al. 2018; Tse et al. 2015). In a study of the anti-CD20 agent, ofatumumab, used for refractory B-cell CLL, half of the patients developed mild to moderate infections (Coiffier et al. 2008). Additionally, in a trial of ofatumumab for relapsing MS, the most common infections reported were upper respiratory tract infections (39%) and urinary tract infections (10%) (KESIMPTA 2020). Similarly, in studies of ocrelizumab, used for relapsing or primary progressive MS, patients have experienced upper and lower respiratory tract infections, skin infections, as well as HSV and VZV reactivations though serious infections are uncommon (Hauser et al. 2020; Montalban et al. 2017). PML after ocrelizumab monotherapy is rare and limited to case reports (Focosi et al. 2019).

7.2 Other Anti-B-Cell Agents

Inotuzumab ozogamicin, an anti-CD22 antibody-drug conjugate, binds to CD22 resulting in internalization and release of ozogamicin which leads to apoptosis. In an open-label phase 3 trial of inotuzumab ozogamicin vs standard intensive chemotherapy for relapsed or refractory B-cell ALL, febrile neutropenia was more common in the inotuzumab ozogamicin group but the incidence of sepsis and pneumonia was similar between groups (Kantarjian et al. 2016). Finally, belimumab is a monoclonal antibody blocking B-lymphocyte stimulator (BlyS) used for SLE. In a long-term safety study cellulitis and pneumonia were found to be the most common infectious complication (Merrill et al. 2012). Serious infections of the urinary tract, CMV, and PML have been reported (Merrill et al. 2012; Raisch et al. 2016).

7.3 Lymphocyte Depleting Agents

7.3.1 Alemtuzumab

Alemtuzumab is an anti-CD52 monoclonal antibody which causes profound and prolonged (up to 1 year) T- and B-cell depletion as well as neutropenia (Hillmen et al. 2007). It is used to treat MS, CLL, Hodgkin's and non-Hodgkin's lymphomas and is used after SOT to prevent (induction therapy) and treat graft rejection, and after alloHSCT to prevent and treat GVHD (Hillmen et al. 2007; Skoetz et al. 2012; Watson et al. 2005). Increased rates of CMV, HSV, and VZV have been seen in patients treated for NHL and MS and herpetic antiviral prophylaxis is typically used in HSCT and SOT recipients treated with alemtuzumab. During periods of alemtuzumab induced profound CD4 depletion, PJP risk is increased and anti-PJP prophylaxis is recommended. Interestingly, though infectious risk is perceived to be significant, and studies have reported this increased risk, similar rates of infections

have been seen when alemtuzumab has been compared to other induction regimens after kidney transplantation (Morgan et al. 2012). Alternatively, a single-center study found increased rates of opportunistic infections when alemtuzumab was used as rejection therapy when compared to induction therapy (Peleg et al. 2007).

7.3.2 Antithymocyte Globulin

Antithymocyte globulin (ATG) is a polyclonal immunoglobulin that depletes peripheral blood T-cells, B cells with immune effects persisting beyond 1 year. ATG is used to prevent (induction therapy) and treat graft rejection after SOT, certain hematologic disorders, and prevent and treat GVHD in allogeneic HSCT recipients. In the setting of long-lasting lymphopenia, herpesvirus infections, CMV, EBV, and EBV driven PTLD, BK virus, and PJP infections have been described (Arai et al. 2017; Charpentier et al. 2003; Issa and Fishman 2009). After SOT, CMV is common in the setting of ATG use without CMV antiviral prophylaxis (von Muller et al. 2006). An early trial of ATG compared to basiliximab found higher rates of UTIs and non-CMV herpesvirus infections but lower rates of CMV disease (Brennan et al. 2006). A recent meta-analysis found no difference in 1-year infection rate between patients receiving basiliximab when compared to ATG (Wang et al. 2018). Further, a recent single-center study of elderly patients found the use of ATG increased rates of infectious complications (UTIs and CMV) when compared to basiliximab (Pham et al. 2020). The infectious risk of ATG appears to be dose dependent (Issa and Fishman 2009; Kang et al. 2021).

7.3.3 Brentuximab Vedotin

Brentuximab vedotin is an anti-CD30 monoclonal antibody-drug conjugate that causes apoptosis by disrupting the microtubule network and is used for the treatment of relapsed and refractory Hodgkin lymphoma and anaplastic large T-cell lymphoma. Studies in patients after HSCT have provided prophylaxis for herpes viruses and PJP (Moskowitz et al. 2015). Though rare, PML after brentuximab vedotin use has been described (Carson et al. 2014). CMV reactivations, PJP, aspergillus, and pseudomonal pneumonias have been observed in patients receiving brentuximab (Gopal et al. 2012).

8 Interleukin Inhibitors

8.1 IL-1 Inhibitors

Interleukin-1 inhibitors include anakinra, canakinumab, and rilonacept. Clinical use is limited mainly to rheumatologic disease and cyclic fever syndromes. Downstream effects of IL-1 involve both innate and adaptive immunity (Mantovani et al. 2019).

Anakinra is a recombinant human IL-1 receptor antagonist with the most longitudinal data. Large, randomized, controlled trials report either a trend toward increased infections or no difference between groups without notable increased risk of opportunistic infections (Cohen et al. 2004; Fleischmann et al. 2003). It

should be noted that patients in both treatment and control arms received corticosteroids and other DMARDs. While sinusitis and URIs were most common, Fleischmann et al. noted that 74% of patients developing serious infection were able to resume anakinra without additional problem (Fleischmann et al. 2003). An open-label follow-up of several of these patients did find one case each of atypical mycobacterial infection, histoplasmosis and candida esophagitis though two of the patients were on prednisone and/or methotrexate (Fleischmann et al. 2006). Subsequent meta-analyses have suggested this increased infection risk may only be at higher doses and also do not report cases of opportunistic infection (Salliot et al. 2009).

Rilonacept is a human dimeric fusion protein composed of an extracellular component of IL-1 receptor and the Fc portion of IgG1 which binds IL-1 subunits to inhibit activity. Higher rates of infection were shown in one early study but not found in another (Hoffman et al. 2008). Opportunistic infection was not reported in this study, but at least one case of *Mycobacterium avium* complex was documented and screening for tuberculosis is still recommended (Koo et al. 2011; Salvana and Salata 2009). Studies of canakinumab, an IL-1β antibody, have shown higher rates of infection compared to placebo but no difference in rates of tuberculosis or reported cases of other opportunistic infections (De Benedetti et al. 2018; Ridker et al. 2017). Infection rates with IL-1 inhibitors may be increased overall predominantly with respiratory tract infections, but studies demonstrating increased risks of opportunistic infection are lacking.

8.2 IL-2 Inhibitors

Basiliximab is the primary humanized IL-2 receptor antibody utilized in clinical practice. Daclizumab was previously used, but withdrawn from the market for safety concerns, though much of the known literature is from patients receiving daclizumab. IL-2 inhibitors have been employed as conditioning regimens in SOT recipients including heart, liver, and kidney allografts and may reduce need for calcineurin inhibitors, steroids or serve as an alternative to antithymocyte globulin (Brennan et al. 2006; Ansari et al. 2015; Emre et al. 2001; Liu et al. 2004). Some studies have found no increased rates of death due to infection with IL-2 inhibitor use but did not report specific episodes (Morris et al. 2005). A Cochrane review did find IL-2 inhibitor receptor inhibitor treated patients had a trend toward less CMV infection at 3 and 6 months which reached statistical significance at 12 months but this is confounded by prophylaxis versus preemptive strategies (Webster et al. 2010). Additionally no difference was noted in CMV infection rate compared to other biologics including muromonab-CD3 or alemtuzumab. In a study of liver transplant patients receiving basiliximab, overall reported infections were lower compared to patients receiving steroids and no opportunistic infections were reported (Liu et al. 2004). Most patients had chronic hepatitis B and received lamivudine. A study of renal transplant patients at least 65 years old demonstrated a decreased incidence of bacterial infection, the majority of which were urinary tract infection, and CMV

infection in patients receiving basiliximab compared to thymoglobulin (Pham et al. 2020). One fungal infection was reported, but not further described. In a placebo controlled trial of cardiac transplant patients all receiving cyclosporine, prednisone, and MMF, patients receiving daclizumab had no significant difference in infections reported though there was one case of cryptococcal meningitis in the daclizumab group (Hershberger et al. 2005). Basiliximab has also been used for steroid-refractory GVHD after allogeneic HSCT with some reported cases of bacterial and fungal infections in addition to herpes virus reactivation, though these are not controlled studies and may be due to cumulative and concomitant immunosuppression rather than basiliximab therapy (Massenkeil et al. 2002; Tang et al. 2020). IL-2 inhibitors have been utilized in sporadic studies for IBD with mixed results and further studies are ongoing (Creed et al. 2003; Sands et al. 2012). There do not seem to be specific infectious complications in patients related to basiliximab therapy beyond those seen with other conditioning or treatment regimens.

8.3 IL-6 Inhibitors

The primary IL-6 inhibitors commercially available are tocilizumab, sarilumab, siltuximab, and satralizumab. Most studies include patients receiving tocilizumab. Fewer cases of infection may occur in patients receiving siltuximab, but only tocilizumab will be covered here due to published studies of clinical experience (van Rhee et al. 2015). Whether similar infection risks exist with such agents requires further investigation.

8.4 Tocilizumab

Tocilizumab, a humanized IL-6 receptor antibody, has been used as primary or adjunctive therapy for a variety of rheumatologic disorders, steroid-refractory GVHD after allogeneic HSCT, chronic antibody-mediation allograft rejection in SOT recipients, and the COVID-19 pandemic (Burmester et al. 2014; Choi et al. 2017; Drobyski et al. 2011; Pettit et al. 2021). In patients with Crohn's disease it has shown improved clinical response in patients with refractory disease though there was a non-statistically significant increase in rates of gastrointestinal abscesses or infections in the treatment arms (Danese et al. 2019; Ito et al. 2004). Initial studies of patients with RA treated with tocilizumab showed an increased risk of non-serious infections, mainly bacterial skin and subcutaneous infections or bacterial or viral respiratory tract infections, without an increased risk of hepatitis or tuberculosis when compared to other medications (Campbell et al. 2011). The higher end of published studies report rates of serious infections around 9.1 per 100 patient years with pneumonia occurring most frequently (Sakai et al. 2015). Rates of infection may exceed those found in patients receiving placebo treatment but may not exceed those receiving TNF-alpha inhibitors in statistical analysis (Sakai et al. 2015; Iannone et al. 2018). While some trials have reported no increased rates of

opportunistic infections or tuberculosis, a large meta-analysis included cases of tuberculosis, candidiasis, atypical mycobacterial infection, cryptococcal disease, and PJP (Emery et al. 2008; Schiff et al. 2011). Most clinical studies describe tocilizumab use in the setting of rheumatologic disease. In a series of kidney allograft recipients, there were fewer infections in patients receiving tocilizumab compared with IVIG and rituximab though two cases of PJP were reported in patients receiving tocilizumab (Sethi et al. 2021). During the one year follow-up period after completion of therapy, infections occurred at a rate of 46.3 per 100 patient-years and included cases of CMV, BK virus, VZV, and histoplasmosis. Urinary tract infections were most common and most patients received concomitant immunosuppression including agents such as tacrolimus or mycophenolate. Case series of viral hepatitis in patients treated with tocilizumab including HBV reactivation, hepatitis C, acute hepatitis E, CMV and EBV have been documented (Biehl et al. 2021).

8.5 IL-12/23 Inhibitors

Through binding of the p40 subunit common to both interleukins, ustekinumab inhibits both IL-12 and IL-23 and has been utilized in rheumatologic and inflammatory bowel diseases (Kavanaugh et al. 2014; Sandborn et al. 2012). An early trial in Crohn's disease did not report a difference in rates of infection though patients received other immunosuppressants as well (Kavanaugh et al. 2014). In one trial for psoriasis and psoriatic arthritis overall infection rates, mostly URIs, may have been increased at higher dosing but not maintenance dosing and at least one serious cutaneous VZV infection was reported (Leonardi et al. 2008). No cases of active tuberculosis were reported, but some patients were diagnosed with latent tuberculosis prior to trial entry and received isoniazid. Other subsequent trials did not demonstrate this increased infection rate at the 90 mg dosage and did not report opportunistic infections (Kavanaugh et al. 2014; Papp et al. 2008). A study in ulcerative colitis patients found similar infectious complications with the exception of one patient with CMV colitis and one with legionella pneumonia. Similar to other studies, patients received additional immunosuppressive agents (Sands et al. 2019). Ustekinumab demonstrated a non-significant trend toward lower rates of surgical site infection compared to TNF-alpha inhibitors in Crohn's disease patients (Lightner et al. 2018). Overall when used for psoriatic arthritis ustekinumab does not carry an increased risk of infection compared to other therapies (Kalb et al. 2015).

9 Complement Inhibitor

Eculizumab is a monoclonal antibody that inhibits terminal complement activation by binding to complement factor 5 and is used for atypical hemolytic uremic syndrome-associated thrombotic microangiopathy after kidney transplantation, paroxysmal nocturnal hemoglobinuria, refractory myasthenia gravis, neuromyelitis optica. Terminal complement inhibition increases the risk of infections with

encapsulated bacteria. Most notably, *Neisseria* spp. infection risk is significantly increased and vaccination and antimicrobial prophylaxis targeting *N. meningitidis* are recommended (Winthrop et al. 2018).

10 Calcineurin Inhibitors

Cyclosporine and tacrolimus potently prohibit T-cell activation and proliferation by inhibiting calcineurin, blocking transcription of early cytokine genes. Though these agents are most commonly used to prevent organ rejection after SOT and GVHD after HSCT they have also been used to treat a variety of refractory autoimmune diseases. Infections with CMV, EBV (and EBV driven PTLD), BK virus, and invasive fungal infections have been described with CNI use (Singh 2005). A recent trial found reduced-dose tacrolimus and everolimus was associated with a lower incidence of CMV infection and disease compared to standard dose tacrolimus and mycophenolate (Tedesco-Silva et al. 2015).

11 Mammalian Target of Rapamycin (mTOR) Inhibitors

Sirolimus and everolimus block B- and T-cell activation by impairing pro-inflammatory cytokine responsiveness and also reduce neutrophil migration. Sirolimus and everolimus are used to prevent organ rejection after SOT and everolimus is approved for the treatment of advanced renal cell carcinoma, breast carcinoma, neuroendocrine tumors, and tuberous sclerosis-associated tumors (Qi et al. 2013). Everolimus use in cancer patients has been associated with increased risk of pneumonia and sepsis and a meta-analysis found higher rates of infection-related deaths when sirolimus was used after kidney transplantation (Qi et al. 2013; Schena et al. 2009). Reactivations of TB, VZV, and HBV have been described in cancer patients and infectious screening should be implemented prior to mTOR inhibitor use (Knoll et al. 2014). Interestingly mTOR inhibitors directly inhibit viral replication. Compared to CNI-based regimen, mTOR inhibitor-based regimen may carry a lower risk of CMV infection after kidney transplant and inhibit BK virus replication (Hirsch et al. 2016; Mallat et al. 2017).

12 Mycophenolic Acids

Mycophenolate mofetil (MMF) is utilized for immunosuppression after SOT or HSCT and for various rheumatologic diseases. It decreases early acute rejection rates in SOT and reduces rates of GVHD (Jorge et al. 2008; Vogelsang and Arai 2001). Through depletion of deoxyguanosine triphosphate or induction of T-cell apoptosis it suppresses B and T lymphocytes (Allison and Eugui 2005). In renal transplants, higher infection rates were observed compared to alternative agents (Pourfarziani et al. 2007). MMF may selectively inhibit pathogens such as

hepatitis C, HSV, HIV, influenza or PJP, but it carries increased risks for BK virus or CMV (Ritter and Pirofski 2009).

In SOT, BK viremia, viuria, and nephropathy occur more frequently with MMF (Mengel et al. 2003; Shi et al. 2007). A dose-dependent correlation between MMF and CMV disease has been shown in kidney transplant patients (Moreso et al. 1998). This occurs at higher doses >3 g/day, and studies report no increase in CMV rates at lower dosage (Ritter and Pirofski 2009). Conversely, some studies have shown increased rates of CMV disease even at 2 g/day dosing (Basic-Jukic et al. 2005). Variable and unreported CMV prophylactic or preemptive management strategies in these studies complicate findings. Studies of MMF in heart, liver, and lung transplant have not demonstrated similar findings (Jain et al. 1998; Palmer et al. 2001). Increased CMV antigenemia occurs in HSCT, but studies demonstrating increased CMV disease are lacking (Hambach et al. 2002). Clinicians should be aware of potential BKV and CMV risk of patients on MMF therapy.

Table 1 Risk of Hepatitis B reactivation, monitoring, and prevention (Di Bisceglie et al. 2015)

Immunosuppression	HBV status[a]	Risk	Monitoring[b]	Antiviral prevention/ therapy[c]
Anti-CD20 or HSCT	sAg +	Very high	Baseline HBV DNA	Yes
	sAg −/ cAb +	Moderate		
High-dose corticosteroids (≥prednisone 20 mg equivalent) Cytokine inhibitors	sAg +	High	Baseline HBV DNA	Yes
	sAg −/ cAb +		HBV DNA monitoring every 1–3 months	If HBV DNA becomes detectable
Cytotoxic chemotherapy Anti-TNF-alpha Anti-rejection therapy (SOT) Anti-integrin JAK inhibitors Interleukin inhibitors	sAg +	Moderate	Baseline HBV DNA	Yes
	sAg −/ cAb +		HBV DNA monitoring every 1–3 months	If HBV DNA becomes detectable
Methotrexate Aminosalicylates Thiopurines Pyrimidine synthesis inhibitors Sphingosine analogs Dimethyl fumarate Mycophenolic acids	sAg +	Low	Baseline HBV DNA	Yes
	sAg −/ cAb +		HBV DNA monitoring every 1–3 months	If HBV DNA becomes detectable

[a]All patients should be screened for HBsAg and HBcAb prior to initiation of immunosuppression
[b]If HBV testing is positive expert consultation (Infectious Diseases or Hepatology) is recommended
[c]Nucleos(t)ide analogs entecavir, tenofovir disoproxil fumarate, tenofovir alafenamide may be used (Buti et al. 2017). Lamivudine may be used when entecavir and tenofovir are not available (Huang et al. 2014; Loomba et al. 2008)

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