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Unintended Immunological Consequences of Biologic Therapy

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Abstract

Recent advances in the understanding of immune dysregulation in autoimmune diseases have enabled the development of new monoclonal antibody based drugs called biologics. Biologics have been used to target aberrant immune responses in many diseases, but patients with rheumatologic and other autoimmune diseases have benefited the most and improvements in outcomes have been significant. The use of biologics is not without hazard; however, as these agents block immune pathways adapted to protect the host. This has been borne out by increased rates of infections as well as induction of new autoimmune and hematologic adverse effects. As new drugs for the treatment of autoimmune conditions are entering the pipeline, it is incumbent on the practicing immunologist to understand the mechanism of these biologics and the implications of clinical use.

Keywords

Autoimmune disease; biologics; monoclonal antibody; primary immunodeficiency; secondary immunodeficiency; biologic safety

Introduction

Our understanding of immune function has made great progress over the last few decades. This progress has led to the development of monoclonal antibodies (mAbs, biologics) that have revolutionized the treatment of rheumatologic/autoimmune diseases [1]. Small molecules inhibitors such as the Janus kinase (JAK) inhibitors are also important drugs in treatment of autoimmune disease, but will not be addressed in this review. Biologics provide therapy that target specific aspects of the immune system in order to combat autoimmune

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Compliance with Ethics Guidelines

Conflict of Interest

Drs. Henrickson, Ruffner, and Kwan declare no conflicts of interest.

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responses. Now there are effective therapies for chronic systemic inflammatory conditions that previously had high rates of morbidity and mortality. Although biologics are tremendously successful in treating chronic inflammatory diseases, there are significant risks as specific components of immunological function are suppressed by these drugs [2]. As some of these biologics may mimic known immunodeficiencies, this is an important topic for immunologists to understand. In this review, we present currently available therapies for autoimmune/inflammatory conditions (Table 1), the immune mechanisms that they target and known and possible adverse outcomes based on their targets.

Innate Immunity

Complement

The complement system targets pathogens using three key mechanisms: bacterial cytolysis, pathogen opsonization allowing targeting by phagocytes, and stimulating inflammation via release of anaphylatoxins. The importance of the complement system is emphasized by known deficiencies in complement components such as C5 which results in invasive *Neisseria* infections [3]. Recent data also indicates that complement is involved in other pathways and is key in immune downregulation and homeostasis. Indeed, derangements in complement activation (e.g. atypical hemolytic uremic syndrome (aHUS)) or regulation (e.g. paroxysmal nocturnal hemoglobinuria (PNH)) may lead to inflammatory disease [4].

Eculizumab is currently the only biologic targeting the complement pathway that is approved and is indicated for treatment of PNH [5, 6] and aHUS [5] Eculizumab is a humanized anti-C5 mAb that selectively blocks activation of C5, release of C5a, and initiation of the membrane attack complex [5, 6]. PNH is a rare disorder resulting from an acquired somatic mutation in phosphatidylinositol glycan class A (*PIGA*) gene in hematopoietic stem cells leading to loss of glycophosphatidylinositol (GPI) anchor synthesis and expression of GPI anchored proteins such as decay accelerating factor (DAF or CD55) and CD59, which are key in prevention of complement activation on host cells. PNH patients suffer from hemolytic anemia, thrombosis, and cytopenias at significant morbidity and mortality with limited options for treatment until the advent of eculizumab. Eculizumab was approved for PNH in 2 small randomized clinical trials that showed significant improvement in outcomes for hemolysis and thrombosis. However, a significant subset of patients were refractory to treatment likely due to C3b deposition on red cells causing clearance in the spleen. Based on this observation, drugs targeting C3 are currently in the pipeline for the treatment of PNH [5, 6].

As eculizumab blocks C5, there have been concerns about susceptibility to invasive meningococcal infection. Patients were given meningococcal vaccine during clinical trials, but 2 patients developed meningococcal serotype B infections that resolved with antibiotic therapy. As there have been cases of serotype B infections on eculizumab, it is now recommended that patients receive meningococcal vaccination and prophylactic antibiotics [3, 5]. With the introduction of Bexsero, a meningococcal serotype B vaccine, consideration for use of this vaccine with eculizumab treatment is likely. As the clinical trials and the post marketing data are sparse, the use of this drug should be done with the utmost of caution due to susceptibility to *N. meningitides*. Additionally, caution will be needed as therapeutics

targeting C3 are in development, and C3 deficiency engenders a broader range of susceptibility to infectious pyogenic bacteria such as pneumococcus.

Cytokines

TNF-α, IL-1, and IL-6 are innate pro-inflammatory cytokines that are induced by infection. TNF-α is the primary cytokine that induces the inflammatory cascade as it is able to induce both IL-1 and IL-6. IL-1 is also able to induce IL-6 directly. In concert, this cascade promotes leukocyte recruitment, the activation of T cells, and the elaboration of other pro-inflammatory molecules such as serum amyloid A and C-reactive protein [7]. These cytokines have crucial disease inducing roles in autoimmune diseases (e.g. rheumatoid arthritis (RA), inflammatory bowel disease (IBD)) and autoinflammatory diseases (e.g. cryopyrin associated periodic syndromes (CAPS)) and are thus important therapeutic targets [8].

TNF-α is induced by microbial products during the initiation of an infection and in turn initiates the inflammatory cascade. This makes TNF an important druggable target, but as it is at the apex of the pathway, blocking this cytokine also leaves patients susceptible to infection due to its broad effects in immunity. TNF inhibitors (TNFis) were the initial biologics that were approved for use in RA. Their immunological adverse effects are reviewed in detail in Her *et al* [1]. Suffice it to say that this class of drugs has a high rate of serious infections, including tuberculosis, that were not anticipated in the clinical trials and careful screening for Mtb worldwide and fungal infections (such as *Histoplasma*) is critical in endemic regions Autoimmune conditions and paradoxical inflammation have also been induced by TNFis, which necessitates discontinuation of treatment [1].

IL-1

IL-1 is a prototypic pro-inflammatory cytokine that shares many properties with TNF-α and consists of 2 forms, IL-1α and IL-1β, the main biologically active form being IL-1β. Secretion of IL-1β is tightly regulated and released upon inflammasome activation in monocyte/macrophages during infection and inflammation. IL-1 serves to enhance the effector functions of innate immune cells and also facilitates the action of B cells and CD4+ Th cells [9]. As IL-1 is a key inflammatory cytokine driving innate and adaptive responses, it is an important contributor to autoimmune (e.g. RA) [9] and autoinflammatory (e.g. CAPS) [8]conditions leading to chronic systemic inflammation and symptomatology. Due to the critical role of IL-1 in inflammatory diseases, the application of IL-1 blockade for therapeutic treatment has become an important aspect of biologic development for a multitude of conditions with anakinra, canakinumab, and rilonacept currently approved [9, 10, 8].

Although IL-1 is important in induction of inflammatory responses to pathogens, the use of IL-1 antagonists has been quite safe with mainly increases in common bacterial and viral infections. Unlike other classes of biologics, such as TNFis, there is no increase in opportunistic infections with the use of anakinra such as *M. tuberculosis* (Mtb) reactivation [8] although with longer acting canakinumab (anti-IL-1β) there was a somewhat higher rate of infections (e.g. nasopharyngitis, urinary tract infection) [10][11]. Indeed, use of anakinra

in patients with inflammatory disease during active infections (e.g. hidradenitis suppurativa) or with treatment of autoimmune manifestations in immunodeficient patients (i.e. IBD in chronic granulomatous disease) controls inflammation without causing exacerbation or onset of infection. There are reported cases of neutropenia IL-1 blockade, but there have only been rare cases of neutrophil counts less than 500 cells/mL (all without significant infections) and neutropenia corrects with cessation of therapy [8].

IL-6

IL-6 is a pleiotropic cytokine induced by TNF-α and IL-1 and functions in T cell expansion and activation, B cell differentiation, and activation of acute phase responses. This cytokine affects immune function and metabolic pathways including lipid metabolism, vasculopathies, and endocrine disease. Although downstream from TNF-α and IL-1, IL-6 is critical to immunity as proven by individuals with Hyper IgE syndrome (HIES) who demonstrate decreased IL-6 and IL-17 activity allowing recurrent infections particularly with Gram-negative bacteria and fungi. Although uncommon, children who develop inhibitory IL-6 autoantibodies are susceptible to cutaneous staphylococcal infections [12]. Although IL-6 was thought to be a biomarker of inflammatory disease, it is clear that IL-6 is involved in disease induction in autoimmune disease (e.g. RA, IBD)[13]. Tocilizumab is an IL-6 receptor (IL-6R) blocking humanized mAb approved for treatment of RA [13] and polyarticular and systemic juvenile idiopathic arthritis (PJIA and SJIA)[13, 14]. Tocilizumab, as well as other IL-6R and IL-6 inhibiting biologics, are currently in clinical trials to treat other autoimmune/inflammatory conditions including systemic sclerosis and adult Still's disease [14].

Blocking IL-6 therapeutically is difficult as this cytokine is crucial in multiple immune pathways including Th17 induction and acute phase responses [14, 12]. As such, it would be predicted that biologics targeting this cytokine would increase infections and impact other aspects of immune function. In clinical trials, tocilizumab has had an increased rate of infections with respiratory tract infections being most common, but increased cutaneous infections were also noted [15, 16]. Mtb reactivation has also been reported although at a lower rate than with TNFis and screening for tuberculosis is recommended [1, 16]. Other adverse immune effects observed with tocilizumab include some cases of neutropenia that were not associated with serious infections [10, 17, 16] Finally, in trials for SJIA, there were reports of episodes of macrophage activation syndrome (MAS) upon withdrawal of drug, although SJIA patients have an overall increased rate of MAS [17]. There are a significant number of biologics targeting IL-6 currently in trials (Table 2) and based on the mechanism of action of this cytokine, other possible immunological derangements include a spectrum of infections similar to deficiencies that result in Th17 defects as each biologic will likely have differing off target effects.

Adaptive Immunity

IL-17

IL-17A is an IL-17 family member and has proinflammatory functions linked to secretion of TNF, IL-6, IL-1 and GM-CSF. IL-17A is fundamental to eradication of extracellular bacteria

and fungal infections, but is also associated with autoimmune diseases including RA, psoriasis and multiple sclerosis (MS)[18]. Therefore, while IL-17 blockade could improve immune dysregulation in selected autoimmune conditions , it potentially increases fungal and extracellular bacterial infection. In humans, IL-17 pathway deficiencies lead to chronic mucocutaneous candidiasis [19]. Additionally, Th17 cells are important in combating mycobacterial infections making Mtb reactivation a concern [20]. Secukinumab, an anti-IL-17A mAb, is approved for plaque psoriasis [21–24], ankylosing spondylitis (AS) [25] and psoriatic arthritis (PsA)[26, 27]. Studies and trials have demonstrated an overall increase in infections with secukinumab versus placebo, including the expected increase in candida infections (mostly mild to moderate oral or genital infections whose incidence was dose dependent)[23, 28, 27] [29] oral herpes infections [30], as well as tinea pedia and two cases of perianal dermatophytosis [28]. In addition, neutropenia , and Crohn's disease (CD) were noted to be increased versus placebo in some studies[21, 22, 24–26]. There was no Mtb reactivation or invasive fungal infections noted [30], but it is recommended to screen for TB prior to initiating therapy and to use caution if considering use in a patient with active CD

IL-12/IL-23

IL-23 is a member of the IL-12 family, which also includes IL-27 and IL-35. This complex family of heterodimeric cytokines share cytokine subunits, but have divergent, sometimes orthogonal, functions. For example, although IL-12 and IL-23 share IL-12p40, IL-12 induces Th1 differentiation while IL-23 plays a role in Th17 differentiation/maintenance [31]. As discussed previously, immunodeficiency patients with Th17 pathway mutations have susceptibility to mucocutaneous candidiasis, mycobacteria, salmonella and *S. aureus* induced cold abscesses, but these infections were not seen in ustekinumab trials [18]. Given that this cytokine subunit is shared with IL-12, it is important to consider that effect as well. Mendelian susceptibility to mycobacterial disease (MSMD) is a broad set of diseases (such as IL12B, IL12RB1 mutations), which impact production and response to IFN-γ and are characterized by susceptibility to infections including Mycobacteria (i.e. BCG vaccine strains, MTb, etc), as well as *Candida* and Salmonella, among others [32]. IL-12Rβ1 defects are the most common cause of MSMD, with multiple mutations and broad clinical phenotype with susceptibility to mycobacteria (non BCG), invasive salmonellosis, and *Candida*, in addition to less frequent infections with bacteria (*Klebsiella*, *S. pneumoniae*, *Nocardia*) and other fungi [32]. Patients with IL-12p40 deficiency lack IL-12 and IL-23, and are characterized by BCG-osis after vaccination, salmonellosis and infections similar to IL-12Rβ1 deficiency [32]. Ustekinumab is a human IgG1 anti-IL-12p40 mAb. It is approved for treatment of severe plaque psoriasis and PsA [33–35]. There was no mention of systemic candidal infections in trials [36, 37] although there were higher rates of infection more broadly, most commonly including upper respiratory tract infections/nasopharyngitis [38, 39], but also reported a case of asymptomatic Mtb reactivation [38, 40], herpes zoster [34, 37] and cellulitis [39, 34]. It is recommended to screen for TB prior to initiating therapy and not to treat patients with active TB and to treat latent TB in patients prior to initiating therapy. Malignancy was also reported with non-melanoma skin cancer being most common [37]. Finally, one case of reversible posterior leukencephalopathy syndrome was reported

IL-2Rα (CD25)

IL-2Rα, one chain of the high affinity IL-2 receptor (IL-2R), is found on activated T cells and regulatory T (Treg) cells. Daclizumab, blocks the IL-2 binding site on IL-2R, has been approved for treatment of organ transplant rejection, and in a phase III trial of daclizumab showed superiority in relapsing remitting MS versus IFN β-1-α[41]. With regards to adverse events, when daclizumab was compared to IFN β-1-a for relapsing-remitting MS, there was a similar rate of herpes infection, upper respiratory tract infections and urinary tract infections and no episodes of PML [41]. If note, one study reported higher rates of aspergillus colonization in lung transplantation [42]. There were higher rates of elevated liver function tests and cutaneous reactions in the daclizumab group. In prior studies, higher infection rates, including cellulitis and wound infections, cutaneous reactions and LFT elevations were also noted [43, 44].

Basiliximab, a chimeric monoclonal antibody IL-2Rα antagonist, is approved for use in induction of tolerance and transplant rejection in kidney transplant and did not have a clear pattern of increased infection. In trials, there was concern with regards to possible increase in infections [45–49]. It carries a black box warning with regards to being administered by physicians familiar with immunosuppression and transplant.

T cell

CTLA-4

T cells require two signals for activation, TCR activation via cognate peptide-MHC complex and costimulation [50]. The prototypic costimulatory signal is transduced by CD28 on T cells binding to CD80/86 on antigen presenting cells. As T cell activation progresses, CTLA-4 is upregulated and transduces negative signals as it binds with higher affinity to CD80/86 blocking further interaction with CD28. CTLA-4 is also constitutively expressed on regulatory T cells and acts to preserve peripheral tolerance.

Abatacept, a fusion of the extracellular domain of CTLA-4 to an altered Fc segment of IgG1, was developed to block T cell costimulation by binding to CD80 and CD86, thus preventing T cell activation. It has been approved for RA and JIA [51–62]. By preventing proper activation of T cells, concern for opportunistic infection is appropriate. Prior to initiating abatacept, screening for latent TB is recommended and treatment for latent TB should be completed prior to abatacept initiation. In addition, screening for hepatitis infection is also recommendation given concern for reactivation. Common infections included upper respiratory tract infections, [54, 55, 58–60, 62, 63], nasopharyngitis [63, 52, 54, 58, 59, 62], bronchitis [55, 62], UTI [63, 52, 60, 62] and sinusitis [56]. A small increase in herpes simplex was noted versus placebo [53], as well as influenza and gastroenteritis [64]. Serious infections included pneumonia [63, 52, 55, 58, 59, 62], bronchitis [55], cellulitis [65, 60] and urinary tract infections [63, 62, 52], pyelonephritis and diverticulitis. Infections with *Candida* [53, 66], TB [53][67],noted to be in patients from endemic areas, herpes zoster [66] , ABPA[53], histoplasmosis [66], malignancies, which were generally consistent with placebo other than increases in lymphoma and lung malignancy which were argued to be consistent with the RA population [53, 52, 51], and autoimmunity (generally

psoriasis, with a few episodes of development of ANA or anti-dsDNA antibodies[64]) were also reported [63, 66, 55] though some of the studies were not placebo controlled.Overall, meta-analyses of abatacept studies demonstrated no significant increase in serious [68] or overall infections [53, 51]. Of note, abatacept in combination with TNF antagonists was shown to increase infections without increasing efficacy and is not recommended. Interestingly, patients with LRBA deficiency (CTLA-4 deficiency based on defective CTLA-4 recycling) have shown improvement with abatacept administration, and has been shown recently to be effective in CTLA-4 haploinsufficient patients [69][70].

Belatacept, CTLA-4Ig with higher avidity, has been approved for kidney transplant rejection in EBV seropositive patients, given the black box concern for development of PTLD, with a higher risk in the EBV seronegative population, as well as in CMV seronegative patients or those who have received T cell therapies [71–73]. Adverse reactions included nasopharyngitis and serious infections including increased CMV [71]. There was increased malignancy (especially non-melanoma skin cancer) and fungal and viral infections at similar rates compared with use of cyclosporine alone [74, 73]. There was an increase in TB infections with belatacept versus cyclosporine, which was noted to generally be in endemic regions, and they recommend screening for and treating latent TB prior to initation[73]. Post-transplant lymphoproliferative disorder was also reported [72], more often in the CNS [73], and is a black box warning for this therapy [75]. Of note, PML has also been reported [73] as well as polyoma virus nephropathy (often with BK virus). They recommend prophylaxis for CMV and PCP for three months after transplant. Patients who are undergoing liver transplant are not recommended to receive belatacept given worse outcomes.

In the setting of cancer, much like chronic infection, adaptive immunity can become hampered in its ability to combat a chronic antigen. Specifically, T cells become exhausted [76], with inhibitory signals outweighing the effect of activating signals. In this setting, therapeutic activation is desired. When predicting possible adverse events, CTLA-4 knock out mice were noted to have rampant autoimmunity and eventual fatality [77]. In humans, CTLA-4 haploinsufficiency mutations yield a clinical phenotype consistent with common variable immune deficiency in addition to dysfunctional Tregs and autoimmunity [78]. Ipilimumab is a mAb that prevents CTLA-4 interaction with CD80/86 allowing reactivation of exhausted T cells by halting inhibitory signals [76]. Ipilimumab is approved for the treatment of metastatic melanoma and is in trials for non-small cell and small cell lung carcinoma, renal cell carcinoma, and prostate cancer [79–81]. Ipilimumab carries a black box warning for immune related adverse events (irAE), which include skin rash, inflammatory colitis, hypophysitis, elevated LFTs and other inflammatory conditions [82, 79, 83]. Interestingly, treatment guidelines for many irAEs have been developed with good acute improvement, though some serious irAEs require cessation of therapy and high dose corticosteroids, and other therapies depending on the severity and affected organ [84, 82].

Adhesion Molecules

Leukocyte trafficking from the vasculature into the peripheral tissues involves three critical steps: rolling, firm adhesion and transendothelial migration. Selectins mediate initial

tethering and subsequent rolling of leukocytes along the endothelium [85, 86]. Leukocyte rolling permits further cell-cell interactions between integrins and endothelial adressins required for firm adhesion [85, 86]. Integrins are composed of α and β subunits that initiate intracellular signaling activating leukocytes when bound to their cognate addressin[85, 86], ultimately allowing for transendothelial migration. Genetic defects in cell adhesion have been identified resulting in Leukocyte Adhesion Deficiency (LAD) syndromes [85]. Starting in childhood, LAD patients have significant defects in antibacterial and antifungal defense resulting in characteristic non-purulent infections (oomphalitis and periodontitis) as well as invasive infections of other sites [85].

Natalizumab is a recombinant humanized IgG4 mAb that targets α_4 integrin blocking the binding of both gut-specific $\alpha_4\beta_7$ as well as $\alpha_4\beta_1$ integrin (binds VCAM-1 on the blood brain barrier)[87]. Natalizumab is currently approved as monotherapy for relapsing forms of MS and as a second line agent for refractory IBD. A surprising outcome of natalizumab post-market surveillance was occurrence of progressive multifocal leukoencephalopathy (PML), a severe demyelinating disease associated with activation of latent JC virus infection in immunocompromised hosts [88, 89]. Efalizumab, a recombinant humanized neutralizing antibody to $\alpha_L\beta_2$ (LFA-1) had been approved for the treatment of severe psoriasis, but was withdrawn from the market in 2009 due to occurrence of three fatal cases of PML[90]. It is thought that due to impaired trafficking of lymphocytes into the CNS, there is a loss of lymphocyte-mediated CNS immunosurveillance which leads to the development of PML. Although not as well-known, there have been reports of increased rates of varicella zoster and herpes simplex central nervous system opportunistic infections in patients on natalizumab [91].

Lymphocytes bearing $\alpha_4\beta_7$ integrin home to the gut where they bind mucosal adressin cell-adhesion molecule-1 (MadCAM-1) expressed specifically on gut-associated lymphoid tissues (GALT). Vedolizumab, a recombinant humanized IgG1 antibody, is selective for gut tissue and binds only the $\alpha_4\beta_7$ complex [86, 89]. Due to this selectivity, vedolizumab has a more limited infectious risk profile. No known cases of PML have been associated with vedolizumab. Not surprisingly, there were slight increases in gastroenteritis and enteric abscesses compared to placebo given that vedolizumab inhibits lymphocyte transmigration into the gut [89]. Although there are case reports raising concerns that decreased immunosurveillance of nasopharyngeal mucosa were causing systemic infections [89, 92], this was not statistically significant [89]. Vedolizumab is approved as second-line treatment of moderate to severe IBD TNFi non-responders.

B Cells

B cells have been implicated in numerous autoimmune conditions, particular those where prognosis or response to therapy can be associated with autoantibody status, e.g. systemic lupus erythematosus (SLE), or ANCA vasculitis. In addition to secreting harmful autoantibodies, B cells also release pro-inflammatory cytokines (lymphotoxin, TNFα and IL-6) and present antigen to autoreactive T cells [93–95]. Therefore, there has been considerable interest in development of B-cell targeted therapies for the treatment of autoimmune conditions.

CD20 is a glycosylated phospholipid expressed on circulating B cells, but not B-cell hematopoietic precursors, plasmablasts or plasma cells [96]. Rituximab is a chimeric anti-CD20 mAb which induces transient depletion of circulating peripheral B cells. Rituximab is approved for the treatment of refractory, indolent non-Hodgkins' lymphoma, with methotrexate for TNFi-refractory RA, and for granulomatous polyangiitis. Of note, rituximab monotherapy in systemic lupus erythematosus (SLE) was not successful as many patients experienced worsening lupus flares with B cell reconstitution, which may in part be secondary to B-cell activation factor (BAFF) driven repopulation of autoreactive B cells following rituximab [97].

In initial clinical trials, transient hypogammaglobulinemia was seen in 14% of patients and average B cell recovery was 6-9 months following rituximab treatment [98, 99]. However, there have since been numerous reports of delayed reconstitution of memory B cells with hypogammaglobulinemia and recurrent infections in a subset of patients treated with rituximab [100–103]. Of note, several newer anti-CD20 mAbs have been developed, including ocrelizumab, ofatumumab, and veltuzumab. Ofatumumab was approved in a multi-drug regimen for treatment of chronic lymphocytic leukemia. Multiple clinical trials are ongoing with these biologics for both oncologic and rheumatologic conditions.

Depletion of B cells with anti-CD20 antibodies may also result in disruption of combined immune function. Both rituximab and oftatumumab bear black-box warnings regarding risk of PML and hepatitis B reactivation, deriving from post-market rituximab use. PML has been reported following rituximab use in malignancy as well as SLE, RA, and autoimmune cytopenias [104, 105]. Hepatitis B reactivation has mainly been seen with combined chemotherapy regimens for hematologic malignancy with fatalities reported [105]. *Pneumocystis jiroveci* infections have also been seen with combination regimens for malignancy and with rituximab monotherapy for autoimmune conditions, illustrating the importance of B cells in induction of specific T-cell immunity[105]. This is analogous to X-linked agammaglobulinemia, or CD40-ligand deficiency, where defective B cell antigen presentation results in combined immunodeficiency. As only a small number of patients were affected by opportunistic infections following rituximab, there may be additional patient specific factors contributing to infectious adverse events.

As noted previously, it is thought that in some SLE patients BAFF drives rapid reconstitution of autoreactive B cells following rituximab monotherapy [97]. BAFF is a TNF-superfamily member secreted by multiple cell types (T follicular helper cells, monocytes, and dendritic cells) that is critical for maintaining B cell homeostasis [106–108, 97]. Elevated plasma BAFF levels have been correlated with increased disease activity in SLE and return of anti-dsDNA antibodies following rituximab treatment [106, 97]. Belimumab, a human recombinant IgG targeting soluble BAFF only, is approved for the treatment of SLE. Data from trials demonstrated unchanged memory B cell populations, decreased naïve B cells, and decreased activated plasma cells. Retrospective analysis of a small cohort showed unchanged titers to tetanus, diphtheria, and pneumococcus, but perhaps decreased response to *de novo* antigen challenge (seasonal influenza vaccination)[109, 110]. Investigation into the immune consequences of BAFF inhibitor use in autoimmune disease is ongoing and include studies examining vaccine responses while on belimumab [111]. Long term follow

up data of SLE patients over four years of belimumab use (approximately half on concomitant steroid or mycophenolate) has been reassuring as rates of infection with belimumab were similar to those using systemic immunosuppressant alone (i.e. corticosteroids, antimalarial agents, azathioprine, mycophenolate mofetil, methotrexate, or leflunomide alone or in combination) [112]. Trials investigating combination therapy with rituximab followed by belimumab for prevention of B cell reconstitution in SLE and lupus nephritis are ongoing [97]. However, it remains unclear if combined anti-B cell therapy may create synergistic immunosuppressive effects such as prolonged hypogammaglobulinemia, increased incidence of PML, or other unexpected immunosuppression. Tabalumab and blisibimod (fusion peptide antagonist), two additional biologics that target soluble and membrane-bound BAFF, were examined in initial clinical trials for efficacy in SLE [108]. Despite initial positive data, further development of tabalumab was halted by its manufacturer due to perceived low therapeutic window compared to placebo. Blisibimod is currently in trials for SLE [113].

Atacicept is a human recombinant fusion protein containing the extracellular TACI receptor fused to IgG1 Fc and neutralizes BAFF and A PRoliferation Inducing Ligand (APRIL). APRIL is a TNF superfamily member of cytokines which acts in conjunction with BAFF by binding TACI, B-cell maturation antigen receptors on B cells to promote B cell development and proliferation [108]. Atacicept failed to meet 20% improvement criteria for RA, and in trials for MS, a paradoxical worsening of CNS lesions was seen [114]. During SLE trials, atacicept increased rates of opportunistic infection compared to placebo, including *Haemophilus*, *Legionella*, and *Klebsiella* [115]. Atacicept also significantly decreased IgG levels compared to placebo and this correlated with increased rates of invasive infections, some of which were fatal [115]. These factors led to discontinuation of trials for this biologic.

Conclusions

Biologics have vastly increased the number of effective treatments in autoimmune conditions. This has significantly improved treatment of patients with conditions that were previously difficult to treat or required corticosteroids which itself comes with numerous side effects. However, the success of these therapies must be tempered by the immunosuppressive effects of these agents. There can be predicted adverse outcomes as well as off target effects which have come to light with some biologics. As immunologists, we should be aware of these possible immunological safety issues with biologics as they continue to enter common use. This is particularly important as there is a dizzying array of biologics for not only autoimmune diseases (Table 2.), but also for oncologic and metabolic inflammatory diseases that are currently entering the therapeutic pipeline.

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Table 1

Currently Approved and Discontinued Biologics

Generic Name	Brand Name	Indications
Innate Immunity		
Eculizumab	Soliris	Paroxysmal nocturnal hemoglobinuria
Anakinra	Kineret	Rheumatoid arthritis (RA) Neonatal Onset Multisystem Inflammatory Disease
Canakinumab	Ilaris	Familial cold autoinflammatory syndrome Muckle-Wells syndrome Systemic juvenile idiopathic arthritis (SJIA)
Rilonacept	Arcalyst	Cryopyrin associated periodic syndromes
Tocilizumab	Actemra	RA, SJIA, Polyarticular juvenile idiopathic arthritis
Adaptive Immunity		
Secukinumab	Cosentyx	Plaque psoriasis, Psoriatic arthritis Ankylosing spondylitis
Ustekinumab	Stelara	Plaque psoriasis, Psoriatic arthritis
T cells		
Basiliximab	Simulect	Renal transplant rejection
Abatacept	Orencia	RA, Juvenile idiopathic arthritis (JIA)
Belatacept	Nulojix	Renal transplant rejection
Ipilimumab	Yervoy	Melanoma, unresectable or metastatic; adjuvant
Adhesion Molecules		
Natalizumab	Tysabri	Multiple sclerosis Ankylosing spondylitis Crohn’s disease (CD)
Vedolizumab	Entyvio	Inflammatory bowel disease (CD, ulcerative colitis)
B cells		
Rituximab	Rituxan	RA Granulomatous polyangiitis, Microscopic polyangiitis
Belimumab	Benlysta	Systemic lupus erythematosus
Discontinued		
Daclizumab		Renal transplant rejection
Efalizumab		Plaque psoriasis
Atacicept		Systemic lupus erythematosus

Table 2

Biologics in phase II/III trials

Generic Name	Target	Trial Indications
Gevokizumab	IL-1β	Diabetes, type II
Sifalimumab	IFN-α	Systemic lupus erythematosus
Rontalizumab	IFN-α	Systemic lupus erythematosus
Clazakizumab	IL-6	Rheumatoid arthritis
Sirutumab	IL-6	Rheumatoid arthritis Depression
Mavrilimumab	GM-CSFRα	Rheumatoid arthritis
Ixekizumab	IL-17	Plaque psoriasis
Brodalumab	IL-17R	Plaque psoriasis
Tildrakizumab	IL-23	Plaque psoriasis
Guselkumab	IL-23 p19	Plaque psoriasis
Oteliximab	CD3ε	Diabetes, type I
Teplizumab	CD3	Diabetes, type I
Visilizumab	CD3	Inflammatory bowel disease
Blisibimod	BAFF	Systemic lupus erythematosus
Tabalumab	BAFF	Systemic lupus erythematosus