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Biologic Response Modifiers: Indications, Implications and Insights

Benjamin P. Davis, M.D., Ph.D., Zuhair K. Ballas, M.D.

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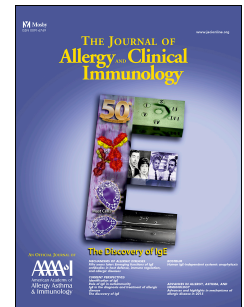
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Corresponding author: Benjamin P Davis, M.D., Ph.D.¹

First Author: Benjamin P Davis, M.D., Ph.D.¹

Order of authors: Benjamin Davis, M.D., Ph.D., Zuhair K Ballas, M.D.²

Affiliations:

¹University of Iowa Hospitals and Clinics, Department of Internal Medicine, Division of Immunology, 200 Hawkins Drive, Iowa City IA 52246, Tel. 319-356-4899, Fax. 319-353-6290, ben-davis@uiowa.edu

²University of Iowa and the Iowa City Veterans Administration, Department of Internal Medicine, Division of Immunology, 200 Hawkins Drive, Iowa City IA 52246, Tel. 319-356-3697, Fax. 319-353-6290, zuhair-ballas@uiowa.edu

Abstract

The field of biologic immune-modulators is currently mushrooming at a dizzying pace. While most of these biologics are tested and approved for one or a few indications, their un-anticipated side effects and their off-label use have contributed significantly to our understanding of basic immune mechanisms, of the involvement of cytokines in several apparently non-immunologic diseases, and of the importance of compartmentalized immune responses. In this review, we attempt to give a bird's-eye view of the major biologics and to highlight insights and implications derived from their secondary effects and adverse reactions.

25

26 **Introduction**

27 There have been several milestones in the field of immunology over the past decade.

28 Taking the bird's-eye view, one can divide these developments in two categories:

29 understanding the genetic and molecular basis of many immune-related diseases and

30 the development of therapeutics aimed at manipulating specific molecules in the

31 immune pathways. Both venues have challenged some long held assumptions about

32 the immune system. While most models and paradigms of the immune response are, by

33 necessity, portrayed as a linear sequence of events, there is a need for a multi-

34 dimensional model showing the multiple layers of interactions of seemingly separate

35 systems. For example, until recently, the innate and adaptive immune systems were

36 considered to be independent of each other. Clearly, this is not the case since now it is

37 obvious that there is constant interaction between the two systems. This gets even

38 more multi-dimensional when one adds the interaction of these two systems with innate

39 lymphoid cells and their products (for recent review, see reference 1 and 2).^{1,2} This

40 understanding is mirrored, or confirmed, by some of the un-anticipated consequences of

41 biological response modifiers (BRM). Another concept gaining recent traction is the

42 compartmentalization of the immune response; this is also mirrored by the apparent

43 paradoxical effects of BRM on, for example, skin vs joints.³ Finally, the literature is

44 replete with examples of paradoxical responses to any given biologic; for example,

45 tissue necrosis factor (TNF) antagonists have been reported to help certain autoimmune

46 diseases while exacerbating others. Even more astonishingly, a TNF antagonist may be

beneficial in inflammatory bowel disease (IBD) but might exacerbate the disease in those patients who have spondyloarthropathy.⁴

In order to put the adverse effects of biologics in perspective, one can turn to experiments of nature. It is now well established that mutations along the IL-12/IFN- γ pathway result in increased susceptibility to atypical mycobacterial infections. Holland et al. found that autoantibodies directed along the IL-12/IFN- γ pathway can mimic the naturally occurring disease resulting in significant susceptibility to mycobacterial infections.⁵ Hence, one wonders whether a biologic directed against IL-12 or IL-12 receptor might result in a similar clinical picture. Indeed, the overlap of autoimmunity and immunodeficiency is now well established;¹ as we shall see below, the biologics used for treatment of autoimmune disease can also significantly disrupt immune homeostasis. This review is designed to summarize the adverse effects, both anticipated and un-anticipated, of commonly used biological response modifiers and to highlight some of the insights into the immune system functioning that were gained by these reactions.

Adverse effects to biologics can be divided in three main categories:

- Immune stimulation
- Immune suppression
- Disruption of immune homeostasis

Immune Stimulation

Cytokine Release

Temporally, the earliest type of reaction that may occur with biologics, especially on the first administration, is an "immediate" reaction. Some of these reactions may be anaphylactic/anaphylactoid or due to immune complex formation. A subset of such reactions may be due to massive cytokine release. Commonly reported symptoms include skin rashes, fatigue, fever, chills, myalgia, headaches, nausea and diarrhea. This is associated with release of pro-inflammatory cytokines including interleukin (IL)-1 β , TNF- α , interferon (IFN)- β , IFN- γ , IL-6 and IL-8.⁶ This is the consequence of activation of various immune cells including macrophages, monocytes, lymphocytes and natural killer (NK) cells.⁷ The mechanism of action may include direct activation through receptor stimulation, antibody-dependent cell-mediated cytotoxicity (ADCC), complement-mediated cytotoxicity, or apoptosis. One such reaction is associated with Muromonab which is used for acute transplant rejection. Muromonab is directed against cluster of differentiation (CD)-3, which is part of the signaling complex associated with the T-cell receptor. Muromonab leads to activation of T cells and release of cytokines into the circulation.⁸ Rituximab, a monoclonal antibody against CD20 which is expressed on B cells mediates antibody-dependent cell mediated cytotoxicity (ADCC) of B cells resulting in cytokine release⁹ confirming basic studies suggesting that B cells, like T cells, can be a major source of cytokines.^{10,11} For some mAbs there may be a "first exposure effect" in which the reaction wanes with subsequent exposure due to a desensitizing or depleting consequence of the first therapy.¹² An extreme example of cytokine release was seen in the use of TGN1412, a mAb directed against CD28 with the idea that neutralization of the "second T cell activation signal" might result in T cell anergy as was demonstrated in primate pre-clinical experiments. When used in humans, it turned out to be a T cell activation agonist. The first trial on six patients caused massive activation of

lymphocytes, resulting in a cytokine “storm” and multi-organ dysfunction requiring transfer to the intensive care unit.^{13,14} This incident is a stark example of the perils of translating animal data, including primates, to humans.

Prolonged survival of activated lymphocytes

Ipilimumab is an anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) mAb that blocks binding of CTLA-4 to CD80/86 thus blocking inhibitory signals to exhausted T cells¹⁵ resulting in sustained T cell activation which, in this case, is the explicit rationale behind its use. Ipilimumab is approved for the treatment of metastatic melanoma.^{16,17} The idea of using such an antibody originally came from mutant mice but was probably re-enforced by the identification of the clinical phenotype of CTLA-4 haploinsufficiency in humans. Such patients have massive lymphadenopathy due to the sustained proliferation of activated T cells. Variants in this gene have been associated with insulin-dependent diabetes mellitus, Graves' disease, Hashimoto's thyroiditis, celiac disease, systemic lupus erythematosus, thyroid-associated orbitopathy, primary biliary cirrhosis and other autoimmune diseases. Given these associated diseases in CTLA-4 haploinsufficiency, it is not surprising that autoimmune diseases were seen in patients given ipilimumab including skin rashes, inflammatory colitis, hypophysitis, elevated LFTs, and myocarditis.^{16,18-20} Autoimmunity as a side effect of biologics is very well illustrated by the recent introduction of other checkpoint blockade therapy for malignancies. Pembrolizumab and nivolumab bind to programmed cell death protein 1 (PD-1) thus inhibiting apoptosis of T cells, including T regulatory cells, and were introduced to enhance immune responses against tumors.²⁰ Early results indicate that

Pembrolizumab and nivolumab are effective against some tumors. However, by virtue of sustaining T cell activation, similar to ipilimumab, they seem to be associated with the induction or exacerbation of several autoimmune diseases. In the case of ipilimumab, Pembrolizumab, and nivolumab the autoimmune disease activation was expected and confirmed the pre-clinical understanding of the role of T regulatory cells and re-enforced the importance of the "turning off" of any given immune response at the appropriate timepoint.²¹⁻²³ Another biologic that has been shown to target Tregs, mogamulizumab,²⁴ also carries similar autoimmune side effects including Stevens-Johnsons syndrome²⁵ and graft versus host disease²⁴. Together, these findings emphasize that peripheral tolerance is an ongoing process even in adults.

Immune Suppression

Unlike the biologics mentioned above that activate the immune system, whether by design or accident, most of the biologics currently available are directed against turning off an immune response in diseases such as rheumatoid arthritis or psoriasis which are clearly associated with an overactive autoimmune response. As one would expect, while turning off an immune response is beneficial in autoimmunity it might increase susceptibility to infections. This indeed has turned out to be the case. It is almost impossible to list all the infections that have been reported with each biologic, but we have attempted to highlight the most commonly reported infections in Table I. These data reflect reports from clinical trials, post-marketing data, as well as case reports. By necessity, this table is far from complete and should be treated as an overall summary. Although common infections occur with many of these biologics, some biologics may be

most frequently associated with a specific infection suggesting that there may be a dominant immune pathway involved in the defense against each microorganism. This may not be too surprising given that certain primary immunodeficiencies are associated with selective susceptibility to distinct microorganisms. One example is that patients with deficiencies along the IL-12/IFN-gamma axis are susceptible to recurrent atypical mycobacterial infections and salmonella but seem to be able to handle most other microorganisms.²⁶ Lessons learned from patients with primary immunodeficiency also implicate that a certain deficiency might be associated with a certain infection but only in one anatomical compartment. An example is that mutations in TLR3 or UNC93B1 are associated with herpes simplex encephalitis as the dominant infection with little or no peripheral viremia.²⁷

Infections associated with specific biologics

IL-1 has two forms, IL-1 α and IL-1 β , and its activity is normally regulated by the IL-1R antagonist (IL-1Ra). IL-1 production is regulated via inflammasome formation in innate immune cells such as macrophages and neutrophils during infection; it can enhance effector functions of innate immune cells, B cells, and CD4⁺ cells.²⁸ It is a critical player in both autoimmune and autoinflammatory conditions, such as RA and the periodic fever syndromes, respectively. There are currently three approved anti-IL-1 biologics: Anakinra, Canakinumab, and Rilonacept.²⁸⁻³⁰ Anakinra is a recombinant human IL-1Ra, which blocks the activity of IL 1 α and β by competitively binding to the IL-1RI. Canakinumab is human anti-IL-1 β monoclonal antibody (IgG1). It neutralizes IL-1 by competing for binding to IL-1RI. Rilonacept is a human dimeric fusion protein, which

contains the extracellular domain of both IL-1 receptor components: IL-1RI and IL-1RAcP and has a much higher affinity for IL-1 β compared to IL-1 α . Despite its significant position in the immune response, anti-IL-1 therapy has been relatively safe. The most prevalent infection events are common bacterial and viral infections and there is little or no increased risk of opportunistic infections with the use of Anakinra.³⁰ Canakinumab, which has a longer half-life compared to Anakinra, is associated with a slightly higher rate of common infections.^{29,31} Interestingly, Anakinra, seems to help control hyperinflammation without worsening active infections in patients with hidradenitis suppurativa, IBD, or chronic granulomatous disease.³⁰ These findings suggest that IL-1 activated pathways may be more important in the homeostasis of inflammation as compared to infection control. Indeed, Anakinra has been used extensively in a wide spectrum of diseases (most of which are off-label uses). As summarized in Table 2, the beneficial effects of Anakinra in these diseases sheds light on the role of immune-mediated inflammation in diseases that hitherto may not have been thought to be related to immune dysfunction.³⁰

IL-12 is part of a heterodimeric cytokine family and consists of two chains: IL-12p35 and IL-12p40. IL-12p40 is a target of ustekinumab which is approved for treatment of psoriasis and severe inflammatory bowel disease.³²⁻³⁴ IL-12p40 is a subunit for both IL-12 and IL-23. As mentioned above, Mendelian susceptibility to mycobacterial disease (MSMD) is a primary immunodeficiency associated with IL12B and IL12RB1 mutations among other mutations.³⁵ Although there were higher rates of common upper respiratory tract infections and nasopharyngitis in Ustekinumab trials, there was not an

increased susceptibility to the infections that are associated with MSMD.^{36,37} This is probably because the IL-12 inhibition by Ustekinumab is not complete and the IFN- γ pathway is still intact.

Abatacept is a fusion of the extracellular domain of CTLA-4 to an IgG1 Fc region. It binds to CD80/CD86 with higher affinity than CD28 thus nullifying the “second signal” needed for T cell activation and resulting in T cell anergy. Types of infections associated with abatacept include sinusitis, nasopharyngitis, bronchitis, urinary tract infection (UTI), gastroenteritis, pneumonia, cellulitis, pyelonephritis, and diverticulitis.³⁸⁻⁴⁰ Specific associated infections include Candida, mycobacteria, herpes simplex, influenza, herpes zoster, aspergillus, and histoplasma.^{39,41} However, meta-analysis of abatacept trials showed no significant increase in serious and total infections.^{39,42} Belatacept, a fusion molecule similar to abatacept but with higher CD80/CD86 avidity, is approved for EBV seropositive kidney transplant rejection.⁴³⁻⁴⁵ Adverse reactions reported include nasopharyngitis, cytomegalovirus (CMV), mycobacteria, fungi, progressive multifocal leukoencephalopathy (PML), and polyoma nephropathy.⁴³⁻⁴⁶ The different affinity of CD28 and CTLA-4 to CD80/CD86 and the use of Belatacept because of its higher avidity brings to life basic immunology principles that have been theoretical until the dawn of the era of biologics.

Alemtuzumab is a humanized IgG1 mAb that binds the CD52 antigen expressed by most human mononuclear cell subsets and is approved for chronic lymphocytic leukemia and multiple sclerosis. Because of the expression of the target molecule on

lymphocytes, monocytes, dendritic cells and the male genital tract, Alemtuzumab can cause significant cellular immunodeficiency. Severe and lethal infections including tuberculosis reactivation, systemic viral infections, and invasive systemic fungal infections have been reported. Infections occur in 30–97% of patients.⁴⁷

B cells play a major role in autoimmune conditions. In addition to producing antibodies, B cells also secrete cytokines and act as antigen presenting cells.⁴⁸ As such, B cells have been targeted for therapy of autoimmune disorders. Rituximab, the anti-CD20 therapy mentioned above, has shown transient hypogammaglobulinemia with average B cell recovery up to 9 months following initial dosing.^{49,50} With ongoing treatment there does appear to be a risk of delayed recovery of B cells associated with significant hypogammaglobulinemia and infectious risk.^{51–54} Atacicept, a fusion protein of the TACI receptor and IgG Fc, binds Blys (aka. BAFF) and APRIL (which is still in clinical trials). It is associated with increased susceptibility to *Haemophilus influenza*, *Legionella*, and *Klebsiella* infections, some of which were fatal.^{55,56}

TNF- α is induced by pathogen associated molecular patterns (PAMPs) and is part of the inflammatory cascade. Although it was known that TNF- α is important in the defense against mycobacterial infection (resulting in the *development* of granulomas), it was not until TNF antagonists were used in human subjects that it became clear that TNF- α plays a pivotal role in the *maintenance* of a granuloma.^{57,58} The reactivation of tuberculosis by TNF antagonists was an unanticipated finding. In addition to mycobacterial infections (*Mtb*), other infections are associated with anti- TNF- α therapy

including *Pneumocystis jiroveci*, *Listeria*, *Legionella*, *Coccidioidomycosis*, *Candida*,
Histoplasma, *Aspergillus*, and reactivation of hepatitis B.⁵⁹⁻⁶¹ Increased incidence of
certain infections, especially fungi, is dependent on the prevalent organism in the
geographic residence of the patient.⁶² Along with IL-1 and TNF- α , IL-6 is considered to
be an early innate signaling cytokine. Tocilizumab, an anti-IL-6 receptor mAb, is
approved for rheumatoid arthritis and systemic onset juvenile arthritis. Similar to anti-
TNF- α therapy, tocilizumab has been associated with *Mtb* reactivation.^{63,64}
Interestingly, blockade of IL-6 by tocilizumab, similar to anti-IL-1 therapy, seems to be
beneficial in the treatment of hyperinflammation disease and cytokine storm.⁶⁵

Deficiencies in the terminal components of complement (C5-C9) are associated with
recurrent, invasive *Neisseria* infections.⁶⁶ Eculizumab is a mAb that binds with high
affinity to complement protein C5, inhibiting its cleavage to C5a and C5b and preventing
the generation of the terminal complement complex C5b-9.^{67,68} Eculizumab is approved
for treatment of paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic
uremic syndrome (aHUS).^{67,68} A theoretical concern, therefore, is an increased
susceptibility to *Neisseria* infections. Although patients were given meningococcal
vaccine prior to the antibody therapy, during clinical trials, two patients developed
Neisseria meningitis thus reproducing the natural deficiencies of terminal complement
components.⁶⁹

IL-17A is important to the immune response to both extracellular bacterial and fungal
infections. At least two primary immunodeficiency disease are associated with

deficiencies in IL-17: Chronic mucocutaneous candidiasis and hyper IgE syndrome. Rheumatoid arthritis (RA), Psoriasis and multiple sclerosis are associated with increased levels of IL-17. Secukinumab is an anti-IL-17A mAb that is approved for psoriasis and ankylosing spondylitis (AS).⁷⁰⁻⁷² As expected, Secukinumab is associated with an increase in candida infections, herpes virus, tinea pedis, and perianal dermatophytosis.⁷³⁻⁷⁵

Cancer

Multiple biologics have been associated with an increased risk of cancer. Ustekinumab, has been associated with non-melanoma skin cancer.⁷⁶ Belatacept, discussed above, is associated with non-melanoma skin cancer and lymphoproliferative disease.^{43,44} There are multiple lines of clinical data on the risk of lymphoma, leukemia, and solid malignancies, with the use of TNF inhibitors.⁷⁷ But the true association is controversial as co-variants including the underlying disease process and other concomitant immunosuppressive therapy obscure the data.⁷⁷

Disruption of immune homeostasis

Autoimmunity

TNF inhibitor therapy has been associated with cutaneous vasculitis and lupus-like syndromes which resolve upon discontinuation of the inhibitor therapy.⁷⁸ Other autoimmune phenomena associated with TNF inhibitors include cutaneous psoriasis, sarcoidosis, antiphospholipid syndrome, uveitis, interstitial lung disease (ILD),

dermatomyositis (DM), polymyositis (PM), demyelinating disease, peripheral neuropathies, and autoimmune hepatitis.⁷⁹⁻⁸⁶ These complications occurred with both anti-TNF mAbs and the TNF receptor fusion protein, etanercept, indicating that these reactions represent a drug class effect of TNF blockers. Additionally, Atacicept is a recombinant fusion protein containing the extracellular TACI receptor and IgG1 Fc. Atacicept targets Blys and APRIL inhibiting their activities. In trials for MS, Atacicept was associated with an unexpected worsening of CNS lesions.⁸⁷ And finally, Secukinumab, an anti-IL-17A mAb, was associated with Crohn's disease.⁷¹

Hypersensitivity

Hypersensitivity is an expected risk of BRMs as these molecules can serve as antigens even if they are fully humanized given the development of anti-idiotypic antibodies. To stay consistent with the theme of this review we will not cover typical anaphylactic or anaphylactoid reactions to biologics as these have been covered extensively recently.⁸⁸ But, rather, here we will focus on two unique hypersensitivity reactions that have occurred with BRMs that have further informed our understanding of hypersensitivity reactions.

One interesting story of hypersensitivity to BRMs unfolded with cetuximab, an anti-epidermal growth factor receptor (EGFR) monoclonal antibody. Anaphylactic reaction to cetuximab occurred during the first infusion in about 5% of patients. This was determined to be due to pre-formed antibodies against the galactose- α -1,3-galactose.^{89,90} This sugar moiety occurs as a posttranslational modification of

302 cetuximab. This sugar moiety is expressed in all tissues of mammals except humans
303 and old world monkeys. Sensitization appears to be linked to a bite by the lone star tick
304 .⁹¹ Hypersensitivity reactions to radio-contrast media have been associated with
305 recombinant IL-2 therapy in cancer patients.⁹² These reactions occurred in 28% of
306 patients that had previously received IL-2 together with radio-contrast media. The
307 hypersensitivity reactions occurred on subsequent exposures to radio-contrast media. It
308 is likely this phenomena is occurring through an adjuvant like mechanism.

312 **Compartmentalization**

313 An important concept for immune system function is the idea of compartmentalization.
314 Perhaps this is not a novel idea since it has been known for quite sometime that certain
315 organs are “immune privileged”. More recently, however, this concept has been
316 modified to suggest that the local microenvironment of any given organ might modify the
317 quality and/or quantity of an immune response. For example, immune response to
318 mucosal exposure might be different than the response to parenteral administration.
319 The concept of immune compartmentalization is evident in differential organ
320 responsiveness to certain biologics. For example, the response to rituximab in some
321 autoimmune diseases (immune thrombocytopenic purpura, Graves’ disease, and
322 pemphigus vulgaris) correlated with the decrease in the autoantibody titer. In other
323 diseases (e.g., systemic lupus erythematosus and rheumatoid arthritis), however, a
324 significant clinical response did not necessarily correlate with the decrease in the

autoantibody titer, suggesting that B cells contribute to the disease by mechanisms other than (or in addition to) autoantibody production or that rituximab might have hitherto unidentified immune effects other than its binding to CD20. It is possible that localized effects, such as cell to cell communication, may be more important than the diffuse effects of antibody production. In an open-label pilot study,⁹³ rituximab was used for atopic eczema. Using the eczema area and severity index, all patients had a significant reduction in skin symptoms. Allergen-specific IgE levels, however, were not significantly decreased, but cutaneous B cells were reduced by 50%. Similar to the results with rheumatologic diseases, it appears that local B cells might play a significant role in atopic dermatitis apart from IgE.

TNF- α antagonists

Although TNF inhibitors are indicated for psoriatic arthritis, they have been associated with exacerbation of numerous skin disorders including cutaneous psoriasis as well as cutaneous lupus, cutaneous vasculitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, eosinophilic fasciitis and atopic dermatitis.^{3,94,95} Although there is general agreement that TNF- α is an inflammatory mediator, these paradoxical effects of TNF antagonists suggest that TNF might be detrimental in the joints but protective in the skin.

Interleukin-6

Tocilizumab, which targets IL-6 receptor, seems to have a predilection to hepatic toxicity. Elevated levels of liver enzymes as well as elevated plasma lipid levels are

relatively common side effects.⁹⁶ While, the exact mechanism for the induction of transaminitis is not known as of yet, IL-6 is important for hepatocyte homeostasis and has been linked to both hepatic regeneration and metabolic function. On the other hand, IL-6 is believed to be important in promoting multiple myeloma⁹⁷ as well as liver tumors.⁹⁸

Integrins

Anti-integrin therapy has also underscored the important role of integrins in tissue specific responses. $\alpha_4\beta_7$ integrin is expressed on gut-associated lymphoid tissues (GALT) and binds mucosal addressin cell-adhesion molecule-1 (MadCAM-1). Vedolizumab, an anti- $\alpha_4\beta_7$ integrin mAb that targets intestinal-homing lymphocytes, is approved for treatment of IBD.^{99,100} Secondary to this selectivity, there were minor increases in gastrointestinal infections.¹⁰⁰ Natalizumab, an anti- α_4 integrin antibody approved for the treatment of MS and Crohn's disease is associated with progressive multifocal leukoencephalopathy (PML) suggesting there is a role of adhesion molecules in the control of the JC polyomavirus infection.¹⁰¹ Natalizumab has also been associated with varicella zoster and herpes simplex infections of the central nervous system.¹⁰² Efalizumab, a recombinant anti- $\alpha_L\beta_2$ (LFA-1) antibody, was withdrawn from the market in 2009 due to three fatal cases of PML.¹⁰³ It is assumed that the blocking effect of these integrin antibodies leads to impaired trafficking of immune cells into the CNS leading to the increased risk of infection. These were all unexpected findings as it was thought that the blood brain barrier blocks the migration of lymphocytes to the brain.

These side effects suggest that peripheral lymphocytes might use adhesion molecules to enter the CNS where they keep JC polyoma viruses, if not other viruses as well, at bay.

Interleukin-2

Recombinant IL-2 (rIL-2) used in cancer therapy has multiple immunostimulatory effects, including effects on T-cells, NK-cells, monocytes and B cells. Many of its reported toxicities stem from capillary leak-associated changes.^{104,105} Indeed high dose IL-2 is associated with capillary leak syndrome which differs from the idiopathic capillary leak syndrome (Clarkson syndrome) in that pulmonary edema is not a feature of Clarkson syndrome. It appears that IL-2 increases endothelial cell permeability in most organs while the mechanisms inducing Clarkson syndrome (which are still unknown) spare pulmonary endothelial cells.¹⁰⁶ Additional toxicities of high dose IL-2 include flu-like illness, nausea, diarrhea, skin rashes, hypothyroidism, altered mental status, cytopenias, coagulopathy, hyperbilirubinemia, elevated transaminase levels, hypoalbuminemia, and acid/base and electrolyte imbalances.¹⁰⁷ IL-12 administered to patients in a phase II trial resulted in serious adverse events that involved elevated transaminases, hyperbilirubinemia, cytopenias, severe fatigue, dyspnea, and stomatitis.^{108,109} These wide ranging effects suggest that organ specificity, at least for cytokine effects, might be dose dependent and may not be different from the multi-organ disease seen in certain gain-of-function mutations.^{110,111} It is worth noting that the generalized toxicities of IL-2 are dose-dependent. Indeed, low dose IL-2 therapy has been tried with the aim of targeting T regulatory (Treg) cells. Treg constitutively express the IL-2

receptor alpha chain (CD25) on their surface. It is thought that low dose IL-2 therapy might result in preferential activation of T regulatory cells which might be beneficial in autoimmune diseases. It remains to be seen whether this strategy will be effective.¹¹²

Clarifying Spectrum of Disease

Asthma

The use of biologics is also prompting rethinking the spectrum of disease subsets (endotypes) based on molecular markers.¹¹³ Studies using TNF antagonists in asthma¹¹⁴ did not reveal a major therapeutic benefit and most clinical trials with TNF antagonists are currently on hold. This might be premature because, as indicated by Brightling et al,¹¹⁵ there could be a subset of asthmatic patients that might benefit from TNF neutralization, including Th17 high or neutrophilic asthma. There is a need for measuring various cytokines in blood, sputum, and broncho-alveolar lavage with the hope of targeting biologic therapy to the dominant cytokine. One predicts that the future of biologics will involve custom tailoring biologic therapy depending on the spectrum of biomarkers identified in subsets of a given disease. The need for this is best illustrated by anti-IL-5 therapy in asthma. Currently, two anti-IL-5 biologics, mepolizumab and reslizumab, are approved for use in severe and uncontrolled asthma. Initial studies of mepolizumab in asthma did not show a significant effect.¹¹⁶ It wasn't until patients were endotyped based on their eosinophil status that subsequent studies showed that this medication could have a very significant effect in treating appropriately selected asthma patients.¹¹⁷⁻¹¹⁹

Rheumatoid Arthritis

Several patient variables have been associated with differing responses to the array of biologic therapies in RA. Some variables are modifiable such as obesity and smoking. Whereas, others are more inherent to the patient including disease activity, quality of life scores, serotype, genetics, and cytokine levels.¹²⁰

Psoriasis and Ankylosing Spondylitis

Studies in psoriasis and ankylosing spondylitis demonstrate that additional disease states predict response to particular biologics. For instance, in cases of severe arthritis, severe cutaneous involvement, or the co-morbidities of anterior uveitis or inflammatory bowel disease anti-TNF α therapy is the preferred choice.¹²¹

Inflammatory Bowel Disease

A number of patient variables have been associated with response to biologics in both ulcerative colitis (UC) and Crohn's disease and include inflammatory markers, disease duration, smoking status, isolated ileitis, isolated colitis, age, previous exposure to biologic agents and immunosuppressant drugs.¹²² Additionally, a number of genetic polymorphisms have been associated with response to anti-TNF therapy in both UC and Crohn's disease.¹²³

Chronic Rhinosinusitis

Multiple biologics have been studied in chronic rhinosinusitis. Most of these have targeted chronic rhinosinusitis with nasal polyposis, as this subtype is highly associated

with Th2 type inflammation. Multiple studies have shown effectiveness for anti-IL5 (mepolizumab and reslizumab), anti-IgE (omalizumab), and anti-IL-4/IL-13 (dupilumab) in the polyposis subtype.¹²⁴ Of note, the anti-IL-5 therapies did correlate with biomarker response including serum IL-5Ra, eosinophil cationic protein, and peripheral eosinophil levels.¹²⁴

Conclusion

We are well beyond the dawn of the age of biologics. The approval of numerous biologic therapies for use in immune disorders is approaching a dizzying rate. Not only does this new reality provide opportunity to further our knowledge of the human immune system, but it illustrates the need for a clinical immunologist who can navigate the non-linear interactions of various arms of the immune system. Indeed, many biologics are used by non-immunological disciplines; this might result in a delayed recognition of unintended consequences. This review demonstrates that biologics have reinforced some basic immunology learned in *in vitro* and animal studies and negated others. Through immune stimulatory effects of these therapies we have witnessed adverse events of cytokine release and induction of autoimmunity. Their use has also reinforced the knowledge of immune suppressed states regarding immunodeficiency in both human disease and animal models and further delineated parts of the immune system that help protect against particular infections or cancer. Additionally, the observed effects of biologics indicate that induced immune imbalance, or disruption of immune homeostasis, may lead to “hypersensitivity” to self or foreign antigens. Certain immune molecules appear to play more of a role in particular tissues thus emphasizing the

importance of immune system compartmentalization. The use of biologics is also helping uncover endotypes of disease. A schematic overview of various biologics discussed and their site of action is depicted in Figure 1. We hope this review provides overview of the lessons already learned from the use of clinical biologics and a glimpse of the type of insights that may lie ahead.

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846 **TABLE 1: Overview of Selected Biological Response Modifiers (BRMs)**

Class	FDA Approved Indications	EMA Approved Indications	Immune Side Effects	General Infectious Issues	Specific Infectious Risk
Tumor Necrosis Factor-Alpha antagonist (infliximab, etanercept, adalimumab, certolizumab, golimumab) Ref: 62,78-83,85,86,94,95	- RA* - UC* (adult and pediatric) - Crohn's disease (adult and pediatric) - psoriasis (arthritis and plaque) - AS* - PJIA* - hidradenitis suppurativa - uveitis	same as FDA but not including hidradenitis suppurativa, uveitis	- cutaneous psoriasis cutaneous neoplasms Anti-dsDNA cutaneous/discoid lupus demyelinating disease - IBD among spondyloarthritis cytopenias - anti-phospholipid syndrome - sarcoidosis - dermatomyositis - polymyositis - autoimmune hepatitis	- granuloma breakdown mycobacteria fungus intracellular bacteria viral parasitic	histoplasma PJP* listeria legionella coccidioides candida aspergillus TB* HSV* HBV* blastomycetes
CD3 agonist (muromonab) Ref: 8	allogeneic renal, heart and liver transplants. (no longer available)	no longer available	cytokine storm	- viral - fungal - protozoa	CMV* HSV VZV* EBV* .
Anti-CD20 (rituximab, ofatumumab) Ref: 9,51-54	- NHL* - CLL* - GPA* - RA	same as FDA, but not including GPA	cytokine release hypogammaglobulinemia cytopenias	viral bacterial fungal - osteomyelitis - otitis - conjunctivitis - enteritis - URI* - PNA/bronchitis - cellulitis	PML* pseudomonas CMV HSV VZV H. flu* - strep. pneumo - klebsiella - aspergillus - candida - staph aureus - campylobacter west nile virus HBV and HCV* parvovirus b19
CD28 agonist (TGN1412) Ref: 13	not approved	not approved	cytokine storm		

Class	FDA Approved Indications	EMA Approved Indications	Immune Side Effects	General Infectious Issues	Specific Infectious Risk
CD80/86 antagonist (abatacept, belatacept) Ref: 40,41,43-46,125,126	- RA - kidney transplant rejection in EBV sero-positive patients. - PJIA	same as FDA	PTLD* in EBV sero-negative patients	- sinusitis - nasopharyngitis - bronchitis - urinary tract infection - gastroenteritis - pneumonia - cellulitis - pyelonephritis - diverticulitis sepsis bacterial viral fungal	- candida - TB HSV influenza - VZV - aspergillus - histoplasma CMV PML polyoma nephropathy
Anti-CD52 (alemtuzumab) Ref: 47	- chronic B cell lymphocytic leukemia - MS	MS	ITP* Hemolytic anemia Neutropenia Pancytopenia	systemic viral infections systemic fungal infections bacterial protozoa	TB reactivation - mucor - VZV - HSV CMV EBV PJP - candida - aspergillus - cryptococcus
CTLA-4 antagonist (ipilimumab) Ref: 16,18-20,22,23	metastatic melanoma	same as FDA	inflammatory colitis hypophysitis transaminitis myocarditis - vitiligo hypopituitarism	?	?
PD-1 antagonist (pembrolizumab, nivolumab) Ref: 22,23	- melanoma - NSCLC* - HNSCC*	- melanoma - NSCLC - RCC* - HL*	- myocarditis - vitiligo hypophysitis hypothyroidism - hepatitis - colitis - nephritis - pneumonitis T1DM	?	?
Blys, APRIL, TACI antagonist (atacept, belimumab) Ref: 55,56	SLE*	in clinical trials	worsening of CNS multiple sclerosis	URI UTI Bronchitis PNA	H. flu - legionella - klebsiella influenza PML

Class	FDA Approved Indications	EMA Approved Indications	Immune Side Effects	General Infectious Issues	Specific Infectious Risk
IL-1 antagonist (anakinra, canakinumab, rilonacept) Ref: ³⁰	- RA - periodic fever syndromes - SJIA*	- RA - periodic fever syndromes - SJIA - Gout	- pneumonitis - colitis - hepatitis - endocrinopathies - nephritis - dermatitis - encephalitis - psoriasis - vitiligo neutropenia	common bacterial and viral infections	
IL-2 (aldesleukin) Ref: ^{92,104,105,107}	- metastatic renal cell carcinoma - melanoma	not approved	hypersensitivity to radio-contrast media New-onset or exacerbation of autoimmune disease - transaminitis - cytopenias - skin rashes flu-like illness (dose-dependent) tissue eosinophilia capillary leak syndrome	Not well documented as most patients on chemotherapy.	
IL-6R antagonist (tocilizumab) Ref: ^{63,96}	- RA - SJIA - PJIA	same as FDA	- transaminitis - lipidemia	mycobacterial reactivation pneumonia UTI cellulitis gastroenteritis diverticulitis sepsis bacterial arthritis	TB VZV cryptococcus aspergillus candida pneumocystis
IL-12/IL-23 (p40 subunit) antagonist (ustekinumab) Ref: ^{36,37,76,108,109}	- psoriasis (plaque and arthritis) - Crohn's disease	- psoriasis - Crohn's disease	- transaminitis - cytopenias - stomatitis - nonmelanoma skin cancer	common upper respiratory infections diverticulitis, cellulitis pneumonia apendicitis cholecystitis sepsis osteomyelitis gastroenteritis bronchitis UTI	
IL-12/IFN- γ (autoantibody)				atypical mycobacteria	

Class	FDA Approved Indications	EMA Approved Indications	Immune Side Effects	General Infectious Issues	Specific Infectious Risk
Ref: ^{5,26}					
IL-17A antagonist (secukinumab) Ref: ^{71,73,74}	- psoriasis (plaque and arthritis) - AS	Psoriasis (plaque and arthritis)	Crohn's disease	- tinea pedis - perianal dermatophytosis URI	candida - HSV
C5 antagonist (eculizumab) Ref: ⁶⁹	- PNH* - aHUS*	PNH			neisseria
α 4 β 7 antagonist (vedolizumab) Ref: ¹⁰⁰	- Crohn's - Ulcerative Colitis	- Crohn's - Ulcerative Colitis	transaminitis	- gastrointestinal infections URI - bronchitis	PML
α 4 antagonist (natalizumab) Ref: ^{101,102}	- MS - Crohn's disease	MS	hepatotoxicity	UTI gastroenteritis vaginitis tonsillitis tooth abscess	PML CNS VZV CNS HSV
α L β 2 (efalizumab) Ref: ¹⁰³	not approved	not approved		bacterial viral fungal pneumonia sepsis meningitis encephalitis bronchitis gastroenteritis	PML CMV blastomycosis cryptococcus TB HSV

*abbreviations: hsv, herpes simplex virus; tb, tuberculosis; cmv, cytomegalovirus; vzv, 36varicella zoster virus; ebv, 36epstein-barr virus; hbv and c, hepatitis virus b and c; uri, upper respiratory infection; pna, pneumonia; pml, progressive multifocal leukoencephalopathy; ptld, post-transplant lymphoproliferative disease; uti, urinary tract infection; ra, rheumatoid arthritis; uc, ulcerative colitis; as, ankylosing spondylarthritis; nhl, non-hodgkins lymphoma; cl, chronic lymphocytic leukemia; gpa, granulomatosis with polyangitis; ms, multiple sclerosis; pjp, pneumocystis jiroveci pneumonia; nscl, non-small cell lung cancer; sjia, systemic juvenile idiopathic arthritis; PJIA, polyarticular juvenile idiopathic arthritis; PNH, p36aroximal nocturnal hemoglobinuria; aHUS, Atypical hemolytic-uremic syndrome; CNS, central nervous system; ITP, immune thrombocytopenia; HNSCC, head & neck squamous cell carcinoma; HL, Hodgkin's lymphoma; T1DM, type I diabetes mellitus; RCC, renal cell carcinoma; SLE, systemic lupus erythematosus; H. flu: hemophilus influenza; . #Bolded items are issues listed as warning or precautions in the product inserts.

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860 Table 2

Some Diseases in which IL-1 blockade may be beneficial
Adult onset Still's Disease
Macrophage Activation Syndrome
Hereditary Autoinflammatory Diseases
Behcet's disease
Schnitzler's Syndrome
Recurrent idiopathic pericarditis
Neutrophilic dermatosis
Neutrophilic Panniculitis
Multicentric Castleman Disease
Erdheim-Chester Disease
SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteomyelitis)
PFAPA (Periodic fever with aphthous stomatitis, pharyngitis and adenitis)
Hidradenitis Suppurativa
Gout and Pseudo gout
Multiple Myeloma

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Figure 1. Summary of immune biologic-target interactions. Targets include specific cell surface molecules on antigen-presenting cells, B-cells, T-cells, endothelium, migrating inflammatory cells as well as cytokines. TACI, Transmembrane activator and CAML interactor; BAFF, B-cell activating factor ; BCMA, B-cell maturation antigen; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; IL-1, interleukin-1; IL-2R, interleukin-2 receptor; IL-6, interleukin-6; IL-12, interleukin-12; IL-17, interleukin-17; IL-23, interleukin-23; $\alpha 4$, $\alpha 4$ integrin; $\alpha b 2$, $\alpha b 2$ integrin; $\alpha 4 b 7$, $\alpha 4 b 7$ integrin; VCAM-1, Vascular cell adhesion protein 1 ; ICAM-1, Intercellular Adhesion Molecule 1; MAdCAM-1, mucosal vascular addressin cell adhesion molecule 1; APC, antigen presenting cell.

