Biologic response modifiers: Indications, implications, and insights

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The field of biologic immune modulators is currently mushrooming at a dizzying pace. Although most of these biologics are tested and approved for one or a few indications, their unanticipated side effects and off-label use have contributed significantly to our understanding of basic immune mechanisms, the involvement of cytokines in several apparently nonimmunologic diseases, and 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. (J Allergy Clin Immunol 2017;139:1445-56.)

Key words: *Biologics, biologic response modifiers, immune dysfunction, infection, autoimmunity, immunodeficiency*

Abbreviations used
BRM: Biological response modifier
CNS: Central nervous system
CTLA-4: Cytotoxic T lymphocyte–associated protein 4
IBD: Inflammatory bowel disease
PML: Progressive multifocal leukoencephalopathy
RA: Rheumatoid arthritis
Treg: Regulatory T

There have been several milestones in the field of immunology over the past decade. Taking the bird's-eye view, one can divide these developments into 2 categories: understanding the genetic and molecular basis of many immune-related diseases and the development of therapeutics aimed at manipulating specific molecules in the immune pathways. Both venues have challenged some long-held assumptions about the immune system. Although most models and paradigms of the immune response are portrayed by necessity as a linear sequence of events, there is a need for a multidimensional model showing the multiple layers of interactions of seemingly separate systems. For example, until recently, the innate and adaptive immune systems were considered independent of each other. Clearly, this is not the case because now it is obvious that there is constant interaction between the 2 systems. This becomes even more multidimensional when one adds the interaction of these 2 systems with innate lymphoid cells and their products.[1,2] This understanding is mirrored or confirmed by some of the unanticipated consequences of biological response modifiers (BRMs). Another concept gaining recent traction is compartmentalization of the immune response; this is also mirrored by the apparent paradoxical effects of BRMs on, for example, skin versus joints.[3] Finally, the literature is replete with examples of paradoxical responses to any given biologic; for example, TNF antagonists have been reported to help certain autoimmune diseases while exacerbating others. Even more astonishingly, a TNF antagonist might be beneficial in patients with inflammatory bowel disease (IBD) but might exacerbate the disease in those with spondyloarthropathy.[4]

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. Browne and Holland[5] found that autoantibodies directed along the IL-12/IFN-γ pathway can mimic the naturally occurring disease, resulting in significant susceptibility to mycobacterial infections. 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 unanticipated, of commonly used BRMs 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 into 3 main categories: immune stimulation, immune suppression, and disruption of immune homeostasis.

IMMUNE STIMULATION

Cytokine release

Temporally, the earliest type of reaction that can occur with biologics, especially on first administration, is an "immediate" reaction. Some of these reactions can be anaphylactic/anaphylactoid or caused by immune complex formation. A subset of such reactions might be due to massive cytokine release. Commonly reported symptoms include skin rashes, fatigue, fever, chills, myalgia, headaches, nausea, and diarrhea. These are associated with release of proinflammatory cytokines, including IL-1β, TNF-α, IFN-β, IFN-γ, IL-6, and IL-8.[6] This is the consequence of activation of various immune cells, including

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macrophages, monocytes, lymphocytes, and natural killer cells.[7] The mechanism of action can include direct activation through receptor stimulation, antibody-dependent cell-mediated cytotoxicity, complement-mediated cytotoxicity, or apoptosis. One such reaction is associated with muromonab, which is used for acute transplant rejection. Muromonab is directed against CD3, 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, an mAb against CD20 that is expressed on B cells, mediates antibody-dependent cell-mediated cytotoxicity of B cells, resulting in cytokine release,[9] confirming basic studies suggesting that B cells, like T cells, can be a major source of cytokines.[10,11]

For some mAbs there might be a "first-exposure effect" in which the reaction wanes with subsequent exposure because of a desensitizing or depleting consequence of the first therapy.[12] An extreme example of cytokine release was seen in the use of TGN1412, an mAb directed against CD28 with the idea that neutralization of the "second T-cell activation signal" can result in T-cell anergy, as demonstrated in primate preclinical experiments. When used in human subjects, it turned out to be a T-cell activation agonist. The first trial on 6 patients caused massive activation of lymphocytes, resulting in a cytokine "storm" and multiorgan dysfunction requiring transfer to the intensive care unit.[13,14] This incident is a stark example of the perils of translating animal data, including data from primates, to human subjects.

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/CD86, thus blocking inhibitory signals to exhausted T cells[15] and resulting in sustained T-cell activation that 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 identification of the clinical phenotype of CTLA-4 haploinsufficiency in human subjects. Such patients have massive lymphadenopathy caused by the sustained proliferation of activated T cells. Variants in this gene have been associated with insulin-dependent diabetes mellitus, Graves disease, Hashimoto 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, increased liver function tests, 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 regulatory T (Treg) 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 preclinical understanding of the role of Treg cells and re-enforced the importance of "turning off" any given immune response at the appropriate timepoint.[21-23] Another biologic that has been shown to target Treg cells, mogamulizumab,[24] also carries similar autoimmune side effects, including Stevens-Johnsons syndrome[25] and graft-versus-host disease.[24] 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 patients with diseases such as rheumatoid arthritis (RA) or psoriasis, which are clearly associated with an overactive autoimmune response. As one would expect, although turning off an immune response is beneficial in patients with autoimmunity, it might increase susceptibility to infections. Indeed, this 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.[5,8,9,13,16,18-20,22,23,26-72] These data reflect reports from clinical trials, postmarketing data, and 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 might be most frequently associated with a specific infection, suggesting that there could be a dominant immune pathway involved in the defense against each microorganism. This might 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-γ 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 anatomic compartment. An example is that mutations in Toll-like receptor 3 *(TLR3)* or *UNC93B1* are associated with herpes simplex encephalitis as the dominant infection with little or no peripheral viremia.[73]

Infections associated with specific biologics

IL-1 has 2 forms, IL-1α and IL-1β, and its activity is normally regulated by the IL-1 receptor antagonist (IL-1RA). IL-1 production is regulated through 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.[74] It is a critical player in both autoimmune and autoinflammatory conditions, such as RA and the periodic fever syndromes, respectively.

There are currently 3 approved anti–IL-1 biologics: anakinra, canakinumab, and rilonacept.[27,74,75] Anakinra is a recombinant human IL-1 receptor antagonist that blocks IL-1α and IL-1β activity by competitively binding to the IL-1 receptor type I. Canakinumab is a human anti–IL-1β mAb (IgG_1). 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-1 receptor