Alterations in immune function with biologic therapies for autoimmune disease

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Autoimmune disorders, including rheumatoid arthritis, inflammatory bowel disease, psoriasis, and others, are characterized by dysregulation of various aspects of normal immunity and inflammation. Biologic agents targeting key components of the dysregulated immune response have dramatically improved patient outcomes and transformed treatment paradigms for a number of systemic inflammatory autoimmune diseases. Despite their excellent efficacy, because they do affect normal immune responsiveness, biologic agents can potentially be associated with a variety of adverse effects. Important potential adverse effects related to the use of biologic agents include immunosuppression, which might result in outcomes such as infection, and autoimmunity, that could result in paradoxical inflammation or even autoimmune disease. In this article the current clinical evidence and immunologic mechanisms of the adverse effects related to biologic agents are discussed. (J Allergy Clin Immunol 2016;137:19-27.)

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Biologic agents have revolutionized the treatment of a number of systemic inflammatory autoimmune diseases, including rheumatoid arthritis (RA), inflammatory bowel disease (IBD), psoriasis, psoriatic arthritis, ankylosing spondylitis (AS), and others. Agents targeting specific immune cells (eg, B and T cells) or secreted mediators, such as proinflammatory cytokines (eg, TNF, IL-1, IL-6, IL-17, IL-12, and IL-23), have been developed and brought to the clinic. Specific biologic agents approved for several autoimmune diseases include a soluble TNF receptor IgG Fc fusion protein (etanercept), several anti–TNF-α mAbs (infliximab, adalimumab, and golimumab), and a pegylated antibody fragment (certolizumab pegol), an anti–IL-6 receptor mAb (tocilizumab), an IL-1 receptor antagonist (anakinra), an anti–IL-17A mAb (secukinumab), and an anti–IL-12/IL-23 mAb (ustekinumab, Table I and Fig 1).[1] The anti-CD20 chimeric mAb rituximab is a B-cell–targeting agent initially developed to treat lymphoma that subsequently showed efficacy in patients with autoimmune diseases, including RA, systemic lupus erythematosus (SLE), and Wegener granulomatosis. Another B cell–targeting agent (targeting B cell–activating factor; ie, belimumab) and a T cell–targeting agent (abatacept) have been shown to be efficacious in the treatment of SLE and RA, respectively.[2] Success with available biologic agents has driven research interest in identifying novel biologic agents targeting other pathways.

Abbreviations used
ANA: Antinuclear antibody
AS: Ankylosing spondylitis
DMARD: Disease-modifying antirheumatic drug
IBD: Inflammatory bowel disease
ILD: Interstitial lung disease
NTM: Nontuberculous mycobacteria
RA: Rheumatoid arthritis
SLE: Systemic lupus erythematosus
TNFi: TNF inhibitor

All of these agents target cytokines or cells dysregulated in patients with autoimmune diseases. However, these targets are also key components of normal immune homeostasis and involved in an array of normal physiologic responses. Therefore blocking particular cytokines or cells might result in adverse events. A mechanistic classification of adverse effects potentially related to the use of biologic agents has been proposed: α, high cytokine levels and cytokine release syndrome (or cytokine storm); β, hypersensitivity, acute infusion reaction, inject-site reaction, or anti-drug antibodies; γ, immune imbalance syndrome (immune deviation), impaired immune function (immunodeficiency and immunosuppression), autoimmunity, or allergic/atopic disorder; δ, cross-reactivity; and ε, nonimmunologic function.[3,4]

Because biologic agents are large protein molecules, they can be intrinsically immunogenic and might be expected to lead to immunologic side effects.[4] However, the immune deviation phenomenon of biologic agents is more target related than agent related.[5] Infection is perhaps the prototypical manifestation of immunodeficiency, and paradoxical inflammation or the presence of autoantibodies is most typical of autoimmunity.

In this article the clinical manifestations and underlying immunologic mechanisms of biologic agents' side effects, particularly immune deviation, will be reviewed. Because TNF

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TABLE I. Biologic agents for RA and other rheumatic diseases

Target	Agent	Structure	FDA approval
Cytokine			
TNF-α	Etanercept	Soluble TNF receptor IgG Fc fusion protein	AS, JIA, PsA, PsO, RA
	Infliximab	Chimeric anti–TNF-α mAb	AS, CD, PsA, PsO, RA, UC
	Adalimumab	Fully human anti–TNF-α mAb	AS,CD,JIA, PsA, PsO, RA, UC
	Golimumab	Fully human anti–TNF α mAb	AS, PsA, RA, UC
	Certolizumab pegol	Humanized Fab′ fragment linked to pegylated molecules	AS, CD, PsA, RA
IL-1 receptor	Anakinra	Recombinant IL-1 receptor antagonist	CAPS, RA,
IL-6 receptor	Tocilizumab	Humanized anti–IL-6 receptor mAb	JIA, RA
IL-12/IL-23	Ustekinumab	Fully human anti–IL-12/IL-23 mAb	PsA, PsO
IL-17	Secukinumab	Fully human anti–IL-17A mAb	PsO
Lymphocyte			
T cell			
CD28	Abatacept	CTLA-4:Ig G Fc fusion protein	RA, JIA
B cell			
CD20	Rituximab	Chimeric anti-CD20 mAb	CLL, NHL, RA, GPA, MPA
BAFF	Belimumab	Fully human mAb for soluble BAFF	SLE

BAFF, B-cell activating factor; *CAPS*, cryopyrin-associated periodic syndrome; *CD*, Crohn disease; *CLL*, chronic lymphocytic leukemia; *CTLA*, cytotoxic T lymphocyte antigen; *Fab′*, antigen biding prime; *FDA*, US Food and Drug Administration; *GPA*, granulomatosis with polyangiitis (Wegener granulomatosis); *JIA*, juvenile idiopathic arthritis; *MPA*, microscopic polyangiitis; *NHL*, non-Hodgkin lymphoma; *PsO*, psoriasis; *PsA*, psoriatic arthritis; *UC*, ulcerative colitis.

inhibitors (TNFis) are the most widely used biologic agents, with millions of patients with various autoimmune diseases having been treated worldwide since their clinical introduction in 1998, and given the wealth of data from many clinical trials and post-marketing surveys on TNFis, these agents have been a focus, and adverse effects potentially related to their use will be reviewed in detail.

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Infection

Immunity against microorganisms depends on various components of the innate and adaptive immune responses.[6] Because biologic agents act on this network in various ways, it is not unexpected that infection is one of the more common side effects observed with the use of these agents. However, autoimmune diseases themselves increase affected patients' susceptibility to infection, an observation most clear among those patients with the most active ongoing inflammatory disease activity. Although use of biologic agents in patients with autoimmune disease might enhance this susceptibility, it could also be reasoned that by controlling disease activity, biologic agents could obviate some of the disease-related infectious proclivity.

Some proinflammatory cytokines, particularly TNF-α, play important roles in host immunity and inflammatory responses. An increased incidence of bacterial infections, particularly pulmonary and soft tissue infections, are seen among patients treated with TNFis.[7,8] Interestingly, the association of TNFis with serious infections requiring hospitalization has not been consistently observed. In some studies the use of biologic agents results in no increased risk,[9-11] whereas others have reported an increased risk.[12,13] In an analysis of data from 4 large US administrative databases (the Safety Assessment of Biologic Therapy project), TNFi use was not more commonly associated with hospitalization than use of conventional disease-modifying antirheumatic drugs (DMARDs) in patients with various autoimmune disease, such as RA, AS, IBD, and psoriasis.[11] In a meta-analysis of 44 randomized controlled trials involving 11,700 subjects receiving TNFis and 5,901 subjects receiving placebo or traditional DMARDs, patients with RA receiving anti-TNF mAbs other than etanercept (adalimumab, certolizumab pegol, and infliximab) experienced a higher risk of serious infection than those receiving placebo or traditional DMARDs.[12] In another meta-analysis of 42,330 patients with RA from 106 randomized trials, a standard or higher dose of biological drugs (pooled analysis of etanercept, adalimumab, infliximab, golimumab, certolizumab pegol, anakinra, tocilizumab, abatacept, and rituximab) was associated with an increase in serious infections compared with use of traditional DMARDs in patients with RA, although low-dose biological drug treatment was not associated.[13] Age of greater than 60 years; the presence of comorbidities, such as chronic kidney disease or impaired lung function; concomitant glucocorticoid use; and a previous serious infection were noted to be key factors increasing the risk of serious infection across many clinical trials.[6,11,14]

Questions regarding the difference in the risk of infection among different TNFi treatments have been raised. In Dutch[15] and Italian[16] registries, mAbs (infliximab or adalimumab) were associated with a higher infection rate than etanercept, but these results were not consistent with analysis of a British registry.[17] In several analyses the increased risk of infection associated with use of a biologic agent was greatest during the initial 6 months of treatment and then decreased over time.[17] This suggests that persons inherently at risk of infection related to specific biologic agents tend to express that risk early, and the apparent attenuation of such risk over time has been attributed to this "depletion of susceptibles" effect.[18,19]

Importantly, safety issues, such as infection, appear to correlate with the systemic inflammatory burden of the underlying disease, as well as comorbid diseases and concomitant medication. Thus in a longer-term analysis of data from adalimumab studies in patients with various autoimmune conditions, serious opportunistic infections and the discontinuation rate for adalimumab because of serious infectious events tended to be higher in patients with IBD and RA compared with those with psoriasis or AS.[20]

An important consideration is that the use of combinations of biologic agents, such as TNFis and IL-1 inhibitor (etanercept