

28. Immunomodulator therapy: Monoclonal antibodies, fusion proteins, cytokines, and immunoglobulins

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The immune system consists of a diverse array of immunocompetent cells and inflammatory mediators that exist in complex networks. These components interact through cascades and feedback circuits, maintaining physiologic inflammation (eg, tissue repair) and immunosurveillance. In various autoimmune and allergic diseases, a foreign antigen or autoantigen might upset this fine balance, leading to dysregulated immunity, persistent inflammation, and ultimately pathologic sequelae. In recent years, there has been tremendous progress delineating the specific components of the immune system that contribute to various aspects of normal immunity and specific disease states. With this greater understanding of pathogenesis coupled with advances in biotechnology, many immunomodulatory agents commonly called “biologic agents” have been introduced into the clinic for the treatment of various conditions, including immune globulins and cytokines. The 2 most common classes of approved biologic agents are mAbs and fusion proteins with exquisite specificity. These agents have the potential both to optimize outcomes through more thorough modulation of specific parts of the dysregulated immune response and to minimize toxicity compared with less specific methods of immunosuppression. (*J Allergy Clin Immunol* ■■■■;■■■:■■■-■■■.)

Key words: Monoclonal antibodies, fusion proteins, immunoglobulins, cytokines, autoimmunity

Biologic agents can work through several mechanisms. The simplest would be inhibition of the function of a target molecule by binding to it, thereby preventing ligation with its counter-receptor and downstream effects. Potential targets include (1) lineage- or activation status-specific molecules on B cells, T cells, and other immunocompetent cells; (2) soluble inflammatory mediators, such as cytokines, chemokines, complement proteins, enzymes, and immunoglobulin molecules; and (3) surface receptors for these mediators. Biologic agents can alter cell populations by engaging effector functions, including the complement

Abbreviations used

AS:	Ankylosing spondylitis
CHF:	Congestive heart failure
CTLA-4:	Cytotoxic T lymphocyte-associated antigen 4
DMARD:	Disease-modifying antirheumatic drug
FDA:	US Food and Drug Administration
ICAM:	Intercellular adhesion molecule
IL-1Ra:	IL-1 receptor antagonist
IVIG:	Intravenous immunoglobulin
LFA:	Lymphocyte function-associated antigen
MS:	Multiple sclerosis
PML:	Progressive multifocal leukoencephalopathy
PsA:	Psoriatic arthritis
RA:	Rheumatoid arthritis
SCIG:	Subcutaneous immunoglobulin
SLE:	Systemic lupus erythematosus

cascade and antibody-dependent cellular cytotoxicity; of note, many mAbs and fusion proteins possess functional IgG Fc pieces. Cell depletion can also be induced by apoptosis subsequent to ligation of appropriate targets. Small-molecular-weight immunomodulators, such as glucocorticoids, are reviewed in Chapter 16.

MONOCLONAL ANTIBODIES

Monoclonal antibodies to human targets can be generated either in other species, such as mice, or through recombinant engineering (Fig 1). With chimeric mAbs, the variable region of a murine mAb is fused to the Fc piece of a human IgG molecule. The resulting construct is approximately one quarter murine. For humanized mAbs, only the complementarity determining regions from the original murine mAb are retained, resulting in a construct that is approximately 95% human. There are a number of approaches to create human mAbs to human targets, including immunizing human/severe combined immunodeficient murine chimeras, using EBV-transformed human B cells, and repertoire cloning, in which target antigen is used to capture human complementarity determining regions generated from vast human cDNA libraries, with the mAb then generated from there. Proteins such as mAbs can have residues of polyethylene glycol added. This process, called pegylation, enhances the half-life of the native protein by reducing its renal and cellular clearance after administration. Although even fully human proteins can be immunogenic, in general, the more human a construct, the less immunogenic. Pegylation might further reduce antigenicity and immunogenicity of the native protein. Immunogenicity can develop to molecules with amino acid sequences identical to human sequences related to factors such as differences in patterns of glycosylation. In addition, immunogenicity to mAbs can be anti-idiotypic. Other factors affecting immunogenicity include route of administration (intravenous vs

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Disclosure of potential conflict of interest: A. Kavanaugh has received research support from Amgen, UCB, Abbott, Centocor, Roche, BMS, Genentech, and Biogen Idec. S. J. Lee and J. Chinen have declared that they have no conflict of interest.

Received for publication June 3, 2009; revised July 31, 2009; accepted for publication August 3, 2009.

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0091-6749/\$36.00

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doi:10.1016/j.jaci.2009.08.018

TNF Inhibitors

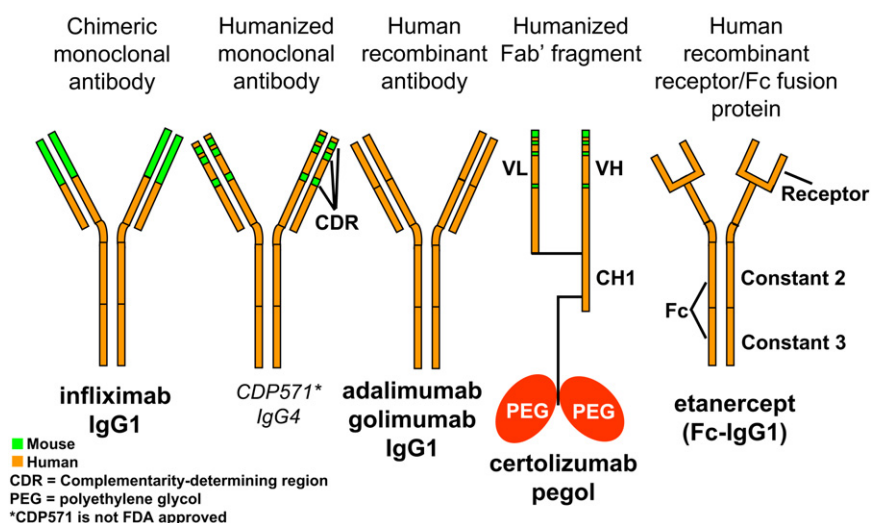


FIG 1. Structure and nomenclature of TNF inhibitors.

subcutaneous), treatment paradigm (continuous vs intermittent), and concurrent use of immunosuppressive therapy.

Standard nomenclature for mAbs identifies their source with the last 4 or 5 letters: -omab, murine; -ximab, chimeric; -zumab, humanized; and -umab, human (Fig 1). The middle part of the name reflects the disease indication for which the mAb was initially intended: -lim- for immune and inflammatory diseases, -cir- for cardiovascular disorders, and -tu- for tumors or neoplastic conditions. The first 3 or 4 letters can be chosen by the sponsor/developer. A number of mAbs have been approved for human use; this chapter will focus on several key mAbs used in the treatment of autoimmune conditions.

FUSION RECEPTORS

Fusion proteins are typically composed of the extracellular domains of native transmembrane proteins, such as cell-surface receptors, linked to another molecule. In most cases the linker that has been used has been the Fc portion of human immunoglobulin, which enhances the pharmacokinetic properties of the construct. The Fc portion of the fusion receptor can be engineered to be functional or not. As their primary mechanism of action, fusion receptors competitively inhibit the binding of a ligand to its specific counterreceptor and thereby prevent downstream effects.

AGENTS THAT INHIBIT PROINFLAMMATORY CYTOKINES

In patients with autoimmune diseases, imbalances in the cytokine cascade can help the initiation and propagation of the immune driven inflammation. In several inflammatory arthritides, including rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS), the proinflammatory cytokine TNF- α has been shown to play a central role in inflammatory reactions and has proved to be an especially attractive target for biologic agents. Among its sundry activities, TNF- α activates various cell types, promotes accumulation of immunocompetent cells at sites of inflammation by means of activation of the vascular endothelium and upregulation of adhesion molecules, and stimulates

synthesis of other proinflammatory cytokines (eg, IL-1, IL-6, and GM-CSF), chemokines (eg, IL-8), and other mediators. IL-1 also stimulates production of other proinflammatory cytokines, angiogenic factors, and endothelial adhesion molecules. Both TNF- α and IL-1 mediate bone and cartilage destruction through activation of osteoclasts (eg, receptor activator for nuclear factor κ B ligand and macrophage colony-stimulating factor) and macrophages to release destructive mediators (eg matrix metalloproteinases, collagenase, and prostaglandins). IL-6 is a regulatory cytokine involved in T- and B-cell activation, osteoclast differentiation/activation, and other activities relevant to the pathogenesis of RA. Other immunomodulatory cytokines considered of significance in the treatment of infectious diseases and malignancies include interferon type I (α and β), IFN- γ , IL-2, and IL-7.

TNF inhibitors: Therapeutic uses

There are 5 currently available TNF inhibitors: infliximab, a chimeric anti-TNF- α mAb initially approved in 1998; etanercept, a recombinant soluble p75 TNF receptor (CD120b)-IgG Fc fusion protein initially approved in 1998; adalimumab, a human anti-TNF- α mAb initially approved in 2002; certolizumab pegol, a pegylated Fab' fragment of a human anti-TNF- α antibody initially approved in 2008; and golimumab, a human anti-TNF- α mAb initially approved in 2009 (Table I). Although not all 5 TNF inhibitors are approved for the following conditions, TNF inhibitors are most commonly used for the treatment of RA, PsA, AS, Crohn disease, juvenile idiopathic arthritis, and psoriasis.

All 5 TNF inhibitors have been shown to substantially improve the signs and symptoms of disease, functional status, and quality of life and slow radiographic progression in patients with established RA.¹⁻⁸ Several studies have demonstrated an even greater clinical and radiographic response and the probability of disease remission among patients with early RA.⁹⁻¹¹ Interestingly, the inhibition of radiographic progression of disease seemed to be dissociated from clinical efficacy, as measured with the typically used composite scoring measures, such as the American College of Rheumatology 20% improvement criteria. Thus some patients who did not achieve an American College of Rheumatology 20%

TABLE I. Characteristics of biologic agents: Dosing, half-life, and indications

Agent	Typical adult dosing	Mode of delivery	Half-life
Cytokine inhibitors			
Etanercept	25 mg biweekly or 50 mg every week	SQ	4-5 d
Infliximab	3-10 mg/kg q4-8 wk	IV	8-9.5 d
Adalimumab	40 mg every other week	SQ	12-14 d
Golimumab	50 mg every month	SQ	19-27 d
Certolizumab	200-400 mg every 2-4 wk	SQ	12-14 d
Anakinra	100 mg every day	SQ	4-6 h
Rilonacept	320 mg then 160 mg every week	SQ	6-8 d
Tocilizumab	4-8 mg/kg every 4 weeks	IV	12 d
T-cell modulators			
Abatacept	RA: 10 mg/kg every 4 weeks	IV	14.7 d
Alefacept	15 mg IM every week × 12 wk	IM	270 h
B-cell modulators			
Rituximab	1,000 mg every 2 wk × 2 doses	IV	60-170 h
Adhesion cell modulators			
Natalizumab	300 mg every 4 wk	IV	11 d

SQ, Subcutaneous; IV, intravenous; IM, intramuscular.

improvement criteria response still experienced inhibition of radiographic damage.^{2,12} Although they can be administered as monotherapy, all TNF inhibitors appeared to be more effective when used in combination with disease-modifying antirheumatic drugs (DMARDs), commonly methotrexate. Combination therapy with methotrexate has beneficial pharmacokinetic effects for some TNF inhibitors in addition to clinical synergy for the treatment of RA.

Etanercept and adalimumab have been approved for the treatment of juvenile idiopathic arthritis.^{13,14} Children who received TNF inhibitors either with or without methotrexate had better clinical outcomes, as measured by using the American College of Rheumatology Pediatric 30% (ACR Pedi 30) response, which represents a 30% or greater improvement in the signs and symptoms of juvenile idiopathic arthritis.

PsA is characterized by the association of inflammatory arthritis with skin psoriasis. The treatment of patients with PsA requires consideration of peripheral arthritis, axial arthritis, skin and nail involvement, dactylitis, and enthesitis. TNF- α levels are notably increased in biopsy samples of skin and synovial tissues from patients with PsA, providing a rationale for the use of TNF inhibitors in the treatment of PsA and psoriasis. TNF inhibitors have been shown to be highly effective in improving the signs and symptoms of arthritis and increasing functional status and quality of life among patients with PsA. Similar to the effect seen in patients with RA, TNF inhibitors also attenuated the progression of radiographic joint damage.¹⁵⁻¹⁸ Moreover, dramatic improvements in the symptoms of skin psoriasis were achieved, as were improvements in the extra-articular involvement characteristics of PsA, such as dactylitis and enthesitis. Improvement in skin psoriasis with TNF inhibitor therapy has likewise been noted in patients without arthritis. Although improvements in joints and skin often occur in parallel, there might be discordance between dermatologic and articular outcomes in individual patients, suggesting potential heterogeneity to pathophysiologic mechanisms underlying different clinical manifestations.

Until the advent of TNF inhibitors, nonsteroidal anti-inflammatory drugs were the only agents shown to alleviate axial symptoms related to AS. In recent years, TNF inhibitors have demonstrated their ability to substantially decrease signs and symptoms of spinal inflammation.¹⁹⁻²³ Paralleling data from

patients with RA, TNF inhibitors provided rapid clinical improvement, often as early as 2 weeks. Patients with increased acute-phase reactants at study entry or with evidence for spinal inflammation on magnetic resonance imaging tended to respond more favorably to TNF inhibitors. Because methotrexate is not an effective therapy for spinal inflammation in patients with AS, it has not been used in studies of the TNF inhibitors. A goal in treating AS would be to stop the progression of spinal ankylosis. Despite their ability to attenuate spinal inflammation on a sensitive imaging modality, such as magnetic resonance imaging, TNF inhibitors have not seemed to be able to affect radiographic progression when compared with historical control of TNF inhibitor-naïve patients with AS.²⁴

Levels of TNF- α are increased in the mucosa of inflamed intestines and thought to exert deleterious effects relevant to the pathophysiology of inflammatory bowel disease (Crohn disease and ulcerative colitis). Treatments with TNF inhibitor mAbs have shown improvement in both clinical and endoscopic luminal fistulas and bowel mucosal inflammation associated with Crohn disease.²⁵⁻³⁰ To date, etanercept has not been shown to be effective in inflammatory bowel disease.²⁹ Initially, treatment of Crohn disease with TNF inhibitors was reserved for the most severe, refractory fistulizing disease as a single course. After the success in this group of patients, repeated treatments and more chronic dosing regimens are being used. Intermittent use of infliximab, which is commonly used in the treatment of Crohn disease, has been associated with a greater propensity for the development of antibodies to infliximab and can be attenuated by the concomitant use of immunosuppressive agents, such as corticosteroids, azathioprine, methotrexate, and 6-mercaptopurine.³¹ The use of infliximab in combination with immunosuppressive agents (eg, methotrexate and azathioprine) has been shown to enhance efficacy and decrease immunogenicity.²⁷ TNF inhibitor mAbs are also being studied and used in the treatment of ulcerative colitis.

Several studies, mostly anecdotal and in patients with RA, have demonstrated that switching from one TNF inhibitor to another can be effective and restore clinical response in patients who have lost therapeutic efficacy with the first.³² Although the success of TNF inhibitors in these autoimmune conditions has been remarkable, it is worth noting that almost uniformly, treatment failed to induce long-term treatment-free remission or immunologic

tolerance. Thus maintenance of clinical response required continuous therapy. Also, TNF inhibitors have not proved effective in other conditions, including several wherein there was pathophysiologic evidence for a role for this cytokine in the disease process. Among autoimmune conditions, TNF inhibitor therapy has been notably ineffective to date in patients with Sjögren syndrome and several forms of vasculitis, including Wegener granulomatosis and polymyalgia rheumatica/temporal arteritis. With regard to congestive heart failure (CHF), data from animal models of ischemic cardiomyopathy implicated TNF as a key mediator of deteriorating cardiac function and hence an attractive target. However, TNF inhibitors have failed to improve symptoms in patients with CHF in clinical trials and sometimes resulted in worsened clinical outcome. Although limited, there were studies on TNF inhibitors that showed negative results in patients with multiple sclerosis (MS), along with anecdotal reports of the development or worsening of demyelinating symptoms among patients with RA treated with these agents. TNF inhibitors are still being actively investigated in a variety of other diseases.

TNF inhibitors: Safety considerations

In general, TNF inhibitors have been well tolerated in clinical trials. *In vitro* studies suggested that TNF inhibitors selectively decrease proinflammatory cytokine levels while preserving both the humoral and cell-mediated arms of the immune response. However, a number of relevant safety issues regarding the use of TNF inhibitors have emerged in postmarketing pharmacovigilance assessments.^{33,34} Adverse events associated with TNF inhibitors can be broadly classified as target/class related or agent related. Target-related adverse events include those potentially attributable to the immunosuppression inherent in blocking a key component of the immune system, such as an inflammatory cytokine; this would include increased susceptibility to infections and malignancies. In addition, specific inhibition of TNF might predispose patients to increased susceptibility to tuberculosis, autoantibody production, hepatotoxicity, demyelinating disease, and clinical worsening of CHF. Agent-related adverse events, such as allergic reactions and antigenicity, are idiosyncratic reactions that relate to the particular agent used.

Safety data from clinical trials and registries have shown a small but consistent increase in infections among TNF inhibitor-treated patients compared with those treated with DMARDs, most commonly methotrexate. Generally, the risk of serious infections was not substantially greater, with relative risks ranging from 0 to 2. The risk of infection with TNF inhibitors increased significantly when combined with other biologic agents. For example, combination therapy with the TNF inhibitor etanercept and the IL-1 receptor antagonist (IL-1Ra) anakinra resulted in a higher rate of serious infections in patients with RA, despite the failure to achieve any additive clinical benefit. Data, particularly from pharmacovigilance, have noted a number of opportunistic infections (eg, listeriosis, histoplasmosis, and coccidioidomycosis) among those patients treated with TNF inhibitors. Because of the increased baseline risk of infection among patients with RA, without a control group, it is difficult to ascertain the excess infection risk specifically attributable to TNF inhibitors in these patients. Another potential sequela of immunosuppression is malignancy. With a few notable exceptions, the bulk of the data to date do not support an increased risk of solid tumors related to TNF inhibitor therapy. However, greater numbers of hematologic

malignancies, particularly non-Hodgkin lymphoma, have been observed in some registries. Complicating the assessment of the risk attributable to therapy is the increased baseline risk of lymphoma among patients with RA, especially among those with higher disease activity. This introduces bias toward observing cases among patients treated with TNF inhibitors as the most severe, and patients with active RA are often the most common type of patients treated. The relative effect of dose and duration of therapy and host factors, such as comorbidities, relevant genetic polymorphisms, and concomitant medications, on the risk of infections and malignancy remains incompletely defined. Because of potential immunosuppression, vaccination with live vaccines is not recommended while patients are receiving TNF inhibitors.

In addition, inhibition of TNF might predispose patients to a variety of untoward effects that seem to be specific to inhibition of the TNF molecule. There are a fair amount of animal and *ex vivo* data supporting the important role played by TNF in controlling tuberculosis. In contrast to typical presentation of acute tuberculosis as pneumonia, about half of the cases of tuberculosis related to TNF inhibitors presented as extrapulmonary or disseminated tuberculosis. The majority of these tuberculosis cases appear to be reactivation of latent tuberculosis, with infection occurring within the first few months of therapy; however, newly acquired cases have been well described. The incidence of cases might be greater with the mAb TNF inhibitors than with the fusion protein inhibitor. Fortunately, screening for latent tuberculosis before initiating TNF inhibitor therapy has been an effective strategy, with a reduction in incidence of new tuberculosis cases by approximately 85%. Latent tuberculosis can be screened by using either a tuberculin skin test with purified protein derivative or *ex vivo* tests that quantify IFN- γ release from sensitized lymphocytes in blood incubated with tuberculosis antigens. Treatment with TNF inhibitors has also been associated with development of autoantibodies. Although the mechanism of this is unknown, it does not appear to result from inhibition of TNF itself, perhaps through induction of apoptosis. The autoantibodies typically generated include the antinuclear antibody (which develops in about half of patients with RA treated with TNF inhibitors), antibodies to double-stranded DNA (which develop in approximately 10% to 15% of patients treated with TNF inhibitors), and anticardiolipin antibodies. Although rare, progression to a lupus-like illness can occur in patients treated with TNF inhibitors. Also, mild-to-moderate increases in liver function test results (generally <3 times the upper limit of normal) have been observed with TNF inhibitors. Many of these cases were confounded by concomitant use of potentially hepatotoxic drugs and underlying medical conditions. However, in light of the occurrence of liver failure of unidentified cause in several cases, clinicians should be aware of these rare events and consider monitoring liver function tests. Lastly, several cases of MS and other demyelinating conditions have been identified among patients treated with TNF inhibitors, although the true effect of TNF inhibitors on the development of MS remains undefined.

Despite their shared ability to inhibit TNF, there are some notable differences between the 5 approved TNF inhibitors. Infliximab, adalimumab, golimumab, and certolizumab are IgG1 mAbs that are specific for TNF- α ; etanercept is a fusion protein of the type II TNF receptor and binds both TNF- α and lymphotoxin α (also known as TNF- β). The clinical relevance of this distinction is unknown. In addition, the binding characteristics of the

mAbs and the fusion protein differ slightly. Although all agents bind soluble TNF with high affinity, the mAbs have slightly higher affinity for membrane-bound TNF, presumably related to the physical constraints of the binding domains of the soluble TNF receptor, compared with that of mAbs. Whether these differences might account for the variability in efficacy and safety remains to be seen. The successful introduction of certolizumab pegol would suggest that the ultimate mechanism of action of TNF inhibitors does not appear to require Fc fragment-related activities.

IL-1 inhibitors: Anakinra and rilonacept

IL-1 is synthesized as an inactive precursor. On cleavage by IL-1 β -converting enzyme, it activates a variety of cells that can then release mediators destructive to bone and cartilage. In the RA synovium, although there is an increase in the naturally occurring IL-1Ra that prevents the binding of IL-1 to its receptor, the levels are apparently insufficient to counteract the effects of IL-1.

Anakinra, approved in 2001 for the treatment of RA, is a recombinant IL-1ra that differs from the endogenous IL-1Ra by a single amino acid addition at the amino terminus (Table I). Compared with the TNF inhibitors, the clinical responses achieved by anakinra are generally more modest; this, combined with cost and the need for daily injections, has led to its relatively infrequent use in the treatment of RA. However, it has been gaining renewed interest and has been shown to be effective in the treatment of cryopyrin-associated periodic syndromes, including familial cold autoinflammatory syndrome and Muckle-Wells syndrome.³⁵ These rare autosomal dominant disorders, characterized by a gain-of-function mutation in the cryopyrin gene (CIAS1, NLRP3), are associated with oversecretion of IL-1 β , rash, arthralgia, and fever. Rilonacept (previously known as IL-1-Trap), which was approved in 2008 for the treatment of cryopyrin-associated periodic syndromes, is a fusion protein comprised of the extracellular domain of the IL-1 accessory protein and IL-1 receptor type 1 attached to the Fc portion of IgG1. Rilonacept binds to IL-1 α and IL-1 β with high affinity (Table I) and was generally well tolerated, with injection site responses being the most common adverse events.³⁶ Physicians should remain vigilant about infections with any IL-1 inhibitor. Studies evaluating the role of anakinra and rilonacept in other diseases associated with IL-1 oversecretion, such as chronic gout and adult-onset Still disease, are ongoing, with promising early results.

IL-6 inhibitors: Tocilizumab

Tocilizumab is a humanized anti-IL-6 receptor mAb that binds to both soluble and membrane-bound IL-6 receptor (Table I). Tocilizumab has been shown to improve the signs and symptoms of disease and functional status and slow radiographic progression in patients with RA. The clinical improvement was rapid and evident within the first 2 weeks of treatment.³⁷⁻⁴⁰ Although it can be administered as monotherapy, tocilizumab appears to be more effective when used in combination with methotrexate.

In clinical studies tocilizumab was associated with a slightly higher rate of infections, mainly respiratory and gastrointestinal tract infections. Transient decreases in neutrophil counts, increases in serum lipid levels (total cholesterol, high-density lipoprotein, and low-density lipoprotein), and increases in liver function test results have been observed with tocilizumab. The

potential long-term implications of these laboratory abnormalities have not been fully defined.

CYTOKINES

IFN- α

IFN- α is produced by the cells of the immune system in response to the presence of double-stranded RNA viruses, inducing cell activation of macrophages and natural killer cells and enhancing antigen presentation. Both IFN- α 2a and IFN- α 2b have been used therapeutically with similar results. IFN- α is used in combination with ribavirin in the treatment of hepatitis C viral infection,⁴¹ reducing viremia and providing protection against the development of chronic liver disease and cryoglobulin-associated vasculitis. Side effects can be significant, with up to 68% of patients presenting with psychiatric symptoms, such as depression, irritability, and insomnia. It has also been used to improve survival in patients with advanced renal cancer, although with a modest increase of 2.6 months, achieving a median survival of 11 months.⁴² Other uses are in the management of melanoma, hepatitis B infection, and systemic vasculitis.

IFN- β

IFN- β is produced in fibroblasts and is 45% identical to IFN- α , sharing similar antiviral activity against double-stranded RNA viruses. Clinically, it has been used in the treatment of MS because of its additional anti-inflammatory effect.⁴³ IFN- β slows progression of disease, reducing the percentage of patients with disability from 35% to 22% after 2 years of treatment. Common adverse effects are depression and suicidal ideation, flu-like symptoms, and increase of liver enzyme levels.

IFN- γ

IFN- γ is produced by leukocytes to induce macrophage activation and increase oxidative burst. It is clinically used to enhance immunity in patients with chronic granulomatous disease, in which it has been shown to help by reducing the frequency of infections up to 67% when used in combination with antibacterial and antifungal prophylaxis.⁴⁴ IFN- γ is administered subcutaneously at 50 $\mu\text{g}/\text{m}^2$ 3 times a week. Potential side effects include fever, hypotension, and flu-like symptoms. In patients with congenital osteopetrosis, IFN- γ slows disease progression. It is also used on a trial basis in some patients with the rare occurrence of deficiency of the IFN- γ /IL-12 axis caused by a deficiency of either of these cytokines, expecting that the administration of this cytokine would reduce the patient's susceptibility to severe mycobacterial disease.

IL-2

Recombinant IL-2 has been approved by the US Food and Drug Administration (FDA) for the treatment of metastatic renal cancer⁴² and malignant melanoma.⁴⁵ IL-2 promotes the activation of T cells and natural killer cells, enhancing their antitumor activity. It also induces the differentiation of regulatory T cells, which are of significance to the control of inflammatory responses. The administration of IL-2 to patients with HIV⁴⁶ has resulted in an increase in CD4⁺ T-cell counts and, when used in combination with highly active anti-retroviral treatment drugs, did not increase HIV viremia and reduced the occurrence of AIDS-defining

infections. Side effects are dose related and include hypotension, flu-like symptoms, behavioral changes, and renal impairment.

IL-7

Because of its biologic activity in the homeostasis of T cells, which includes the expansion of naive and memory T cells in the setting of lymphopenia, IL-7 has been suggested as an adjuvant in the treatment of HIV infection and in lymphopenia after chemotherapy. Reports of its administration in HIV-infected patients showed less significant side effects than IL-2 treatment, with sustained dose-dependent expansion of T cells.⁴⁷

AGENTS THAT INHIBIT T CELLS

There is a large body of evidence suggesting autoreactive T cells, especially CD4⁺ T_H1 T cells, serve a key role in orchestrating the immune-driven inflammatory responses in patients with autoimmune diseases, such as RA, Crohn disease, PsA, and psoriasis. Productive CD4⁺ T-cell responses require 2 signals: binding of specific antigen-associated MHC class II molecule to the T-cell receptor complex and a second signal from costimulatory molecules. If T cells do not receive the second signal, then tolerance or ignorance of the antigen ensues, and a productive immune response is not generated. Among the most important costimulatory molecules is CD28, which binds CD80 and CD86. CD28 and its natural inhibitor, cytotoxic T lymphocyte-associated antigen 4 (CTLA-4; CD152), are present on T cells and bind to CD80 and CD86 on antigen-presenting cells. CD28 ligation results in stimulation of T cells, whereas CTLA-4 serves an inhibitory role. CTLA-4, which binds CD80 and CD86 with substantially higher affinity than CD28, inhibits the stimulatory effects of CD28 by competitively binding to CD80 and CD86.

Daclizumab and basiliximab

These 2 therapeutic antibodies are directed against CD25, the protein α component of the IL-2 receptor.⁴⁸ Their therapeutic effect is the block of IL-2 binding in T and B cells, inhibiting their activation and the development of an immune response and inducing anergy. They are indicated for the prevention of organ transplant rejection, particularly kidney grafts, and have been suggested for the management of autoimmune disorders. For this purpose, the humanized antibody daclizumab is in phase II trials for the treatment of MS and has been shown to decrease the frequency of relapses. These agents induce a state of immunosuppression, which results in an increased frequency of urinary tract infections and respiratory tract infections; however, opportunistic infections have not been observed. Other side effects are paresthesias, transient increased in liver enzyme and bilirubin levels, and skin rash.

Abatacept

Abatacept, approved in 2005 for the treatment of RA, is a soluble protein consisting of the extracellular domain of CTLA-4 linked to the Fc portion of IgG1 (Table I). Abatacept has been shown to improve the signs and symptoms of disease, functional status, and quality of life and slow radiographic progression in patients with RA.^{49,50} Abatacept was well tolerated in clinical trials, with a slight increase in the incidence of infections, especially among those with underlying chronic obstructive pulmonary

disease. In one study abatacept appeared to have efficacy comparable with that of a TNF inhibitor in patients with RA receiving methotrexate.⁵¹ As with other biologic agents, live vaccines should be avoided when receiving abatacept. A safety study assessing the combination of abatacept and TNF inhibitor therapy observed a higher incidence of serious adverse effects, including infections, at 1-year follow-up compared with that seen in those receiving monotherapy.⁵² Given similar findings of increased infections with TNF inhibitors and IL-1ra combination therapy, combination therapy with abatacept and other biologic agents is also discouraged.

Alefacept

Alefacept, approved in 2003 for the treatment of chronic plaque psoriasis, is a fusion protein of a soluble form of the extracellular domain of lymphocyte function-associated antigen (LFA) 3 attached to the Fc portion of an IgG1 molecule. It binds CD2⁺ T cells and is thought to improve symptoms of psoriasis by inducing memory T-cell apoptosis, inhibiting inflammatory gene expression, and preventing T-cell migration into psoriatic plaques. The interaction of LFA-3 on antigen-presenting cells and CD2 on T cells is thought to be important in T-cell activation and in the development of cells into memory T cells. Alefacept, either as monotherapy or in combination with other psoriasis therapy (eg, methotrexate), has been shown to be effective for skin psoriasis.^{53,54} T-cell depletion related to therapy did not correlate or predict the response rate during treatment or follow-up. Despite its effectiveness in the treatment of psoriasis, alefacept appears to be only modestly effective for PsA.⁵⁵ With the availability and effectiveness of TNF-I in the treatment of PsA, alefacept is therefore rarely used for the treatment of PsA.

Anti-p40 agents

Another approach to modulating the function of T cells in autoimmune and inflammatory diseases targets cytokines relevant to the development of certain T-cell subsets. IL-12, a cytokine central to the development of T_H1 T cells, and IL-23, a cytokine that helps sustain T_H17 T cells, share a common p40 subunit.⁵⁶ Agents that target the p40 subunit, including the human mAb ustekinumab and ABT874, might be expected to attenuate inflammatory processes driven by T_H1 and T_H17 T cells. These therapies are under investigation in a variety of autoimmune diseases, and ustekinumab has received regulatory approval in several countries for the treatment of psoriasis. In patients with psoriasis, ustekinumab therapy induced a substantial improvement, as measured by the psoriasis area and severity index.⁵⁷ The extent of improvement appeared to perhaps even have been larger than that achieved with TNF inhibitors, which are themselves highly effective in patients with psoriasis. The same agent has also been studied in patients with PsA and been found to have some efficacy in that condition.⁵⁸ Interestingly, the duration of clinical benefit after a few injections is prolonged and appears to far exceed the pharmacokinetic profile of the drug.

AGENTS THAT INHIBIT B CELLS

Recent data suggest that B cells might contribute significantly to the initiation and perpetuation of the immune response in various autoimmune diseases, including RA and systemic lupus

erythematosus (SLE). Not only can B cells produce potentially pathologic autoantibodies (eg, rheumatoid factor and antinuclear antibody) and proinflammatory cytokines, but they can also present antigens to T cells and provide costimulatory signals essential for T-cell activation, clonal expansion, and effector function.

CD20 inhibitor: Rituximab

Rituximab is a chimeric IgG1 mAb directed against the B-lymphocyte surface antigen CD20. It was initially approved in 1997 for the treatment of CD20⁺ B-cell non-Hodgkin lymphoma and later for the treatment of RA in 2006. CD20 is a cell-surface molecule restricted to the surface of pre-B through activated mature B cells. Rituximab is thought to induce lysis of CD20⁺ B cells through several mechanisms, including complement activation, antibody-dependent cell-mediated cytotoxicity, and induction of apoptosis. Depletion of B cells can last up to 9 months or longer after a single course of therapy. Rituximab has been shown to improve the signs and symptoms of disease, functional status, and quality of life and slow radiographic progression of disease in patients with RA.^{59,60} Although rituximab can be used alone or in combination with DMARDs, the combination therapy yielded better clinical outcomes. Also, patients who are seropositive for rheumatoid factor had greater clinical response compared with rheumatoid factor–seronegative patients. In smaller studies rituximab has shown promising results in the treatment of other autoimmune diseases, such as SLE, primary Sjögren syndrome, idiopathic thrombocytopenic purpura, chronic inflammatory demyelinating polyneuropathy, and vasculitis. Additional trials are underway that should answer questions regarding dosing, treatment intervals, safety, and tolerability in these conditions.

Despite the potential for immunodeficiency related to depletion of mature B cells, no significant increases in infections, either serious or opportunistic, were reported in patients with RA and non-Hodgkin lymphoma treated with rituximab. The overall levels of serum immunoglobulin generally remain stable during treatment. This could be related to preserved function of plasma cells, which lack CD20 and are therefore not depleted by rituximab. However, if rituximab is used as a recurrent or maintenance therapy for autoimmune conditions, this might become more of a safety concern because plasma cells are not replenished by memory B cells. Thus far, some patients have undergone more than 4 cycles of rituximab without increased risk of adverse events.⁶¹ Other notable adverse effects include rare neutropenia, reactivation of hepatitis B, and progressive multifocal leukoencephalopathy (PML). Three cases of PML in patients receiving rituximab for non-FDA-approved conditions, mainly SLE, have been reported.⁶² The exact role of rituximab in the development of PML remains unknown given its rare occurrence, but it highlights the importance of pharmacovigilance and potential unforeseen long-term adverse effects related to biologic agents. Although treatment has overall been well tolerated, infusions have been associated with hypersensitivity reactions, Stevens-Johnson syndrome, and type III serum sickness–like illness and cytokine release syndrome. The infusion reactions are more common during the first infusion and might occur more in patients with lymphoma than in those with RA.^{33,34} Lastly, given the potential for suboptimal response, vaccinations should be administered before rituximab, if possible.

Anti-IgE antibody: Omalizumab

This antibody was developed to aid in the management of severe asthma with an allergic component. Omalizumab binds IgE with high affinity, considerably reducing levels of free IgE and inhibiting its interaction with the IgE receptor. The clinical improvement correlated well with the measurement of biologic markers.⁶³ Its administration to patients with severe asthma with low to moderately increased serum IgE levels results in a 26% decrease in the asthma exacerbation rate and a 50% decrease in severe exacerbations and emergency department visits, as well as a reduction in systemic corticosteroid use.⁶⁴ It has also been shown to be useful to reduce symptoms in patients with corticosteroid-resistant chronic urticaria.

AGENTS THAT INHIBIT CELL ADHESION, MIGRATION, OR BOTH

Activated T lymphocytes must migrate to sites of inflammation and lymph tissue to exert their diverse effects. The entry of lymphocytes into specific sites occurs through several specific interactions between the adhesion molecules on lymphocytes, including the integrins and their ligands on endothelial cells. Particularly important for lymphocyte migration and homing are LFA-1 and its counterreceptors, intercellular adhesion molecule (ICAM) 1 and ICAM-2, and very late antigen-4 and its counter-receptor, vascular cell adhesion molecule 1.

Integrin inhibitors: Natalizumab

Natalizumab, approved in 2004 for the treatment of MS, is a recombinant humanized IgG4 mAb directed against the α_4 subunit of $\alpha_4\beta_1$; it also binds to and inhibits the function of the $\alpha_4\beta_7$ integrins, the ligand of which is mucosal addressin cell adhesion molecule 1. $\alpha_4\beta_1$ integrin, an adhesion molecule present on leukocytes, has been implicated in the pathogenesis of MS by facilitating migration of lymphocytes into the site of disease. In addition to blocking the migration of lymphocytes into the central nervous system and intestinal parenchyma, natalizumab induces T-cell apoptosis and anergy and prevents T-cell binding to osteopontin and fibronectin, thereby attenuating T cell–mediated inflammation. In 2 large clinical trials, natalizumab, either alone or in combination with IFN- β -1a was associated with significantly lower relapse rates and disability and fewer new MS lesions on magnetic resonance imaging.⁶⁵ However, shortly after FDA approval, natalizumab was temporarily withdrawn from the market after 3 cases of PML were reported. Similar to rituximab, the exact role of natalizumab in the development of PML remains unknown.

CD11a inhibitor: Efalizumab

Efalizumab, approved in 2003 for the treatment of psoriasis, is a humanized IgG1 mAb directed against the cell adhesion molecule CD11a. CD11a is an α subunit of the LFA-1 molecule on T cells that binds to ICAM-1 on antigen-presenting cells and endothelial cells. In addition to inhibiting activation of T cells, efalizumab also blocks trafficking of lymphocytes into the skin by blocking LFA-1/ICAM-1 interaction. Efalizumab has been shown to provide greater improvement in symptoms of skin psoriasis after 3 months of therapy, with a continued increase in response if therapy was continued for another 3-month cycle.⁶⁶ However, the development of PML among several patients treated with efalizumab led to its withdrawal in 2009.

TABLE II. Clinical use of human immunoglobulin preparations

Primary immunodeficiency diseases (that result in defect in antibody responses)
Secondary immunodeficiency conditions (with impaired antibody responses)
HIV infection
B-cell leukemia
Use of chemotherapy or radiotherapy
Autoimmune syndromes
Hematologic: ITP, autoimmune hemolytic anemia
Rheumatologic: RA, vasculitis, Kawasaki disease, uveitis, SLE
Endocrinologic: Autoimmune diabetes mellitus, Graves ophthalmopathy
Neurologic: Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, dermatomyositis
Dermatologic: TEN, Steven-Johnson syndrome
Infectious diseases
CMV
Rotavirus
Parvovirus B19

ITP, Immune thrombocytopenic purpura; *TEN*, toxic epidermal necrolysis; *CMV*, cytomegalovirus.

IMMUNOGLOBULINS

Therapeutic use

Immunoglobulin concentrates derived from human plasma have been used since the 1940s and were used initially in the management of viral diseases, such as hepatitis. Bruton published the first report of the use of immunoglobulins to treat a patient with an immune defect who presented with agammaglobulinemia and frequent infections. This resulted in the increase of the gammaglobulin fraction in the patient's serum and a reduction in the number of infections. Currently, human immunoglobulin preparations are derived from pooled plasma of up to 10,000 individual donors per batch of immunoglobulin products, introducing safety concerns regarding the transmission of blood-borne infectious diseases. This is addressed by means of donor screening for infectious diseases and by introducing in the manufacturing process several steps to remove viral particles. There are 2 forms of administration: subcutaneous immunoglobulin (SCIG) and intravenous immunoglobulin (IVIG).⁶⁷

In addition to its use as antibody replacement, IVIG preparations are indicated as an immunomodulator in many inflammatory conditions, such as idiopathic thrombocytopenic purpura (Table II). Only 6 of these indications are approved by the FDA: the treatment of primary immunodeficiencies, HIV infection, Kawasaki disease, and immune thrombocytopenic purpura and the prevention of infections in B-cell leukemias and in patients undergoing bone marrow transplantation.⁶⁸ The anti-inflammatory properties of immunoglobulins have been attributed to different mechanisms, including those mediated by neutralization of autoantibodies and anti-idiotypic antibodies and neutralization of toxins and T-cell superantigens and those mediated by the modulation of the Fc receptors in the cells of the immune system. More recently, Anthony et al⁶⁹ showed that the anti-inflammatory activity of immune globulins can be explained by the action of Fc fragments containing sialic acid on macrophages inducing the expression of the inhibitory FcγIII receptor. Both human and murine recombinant sialylated Fc proteins were able to suppress inflammation in a murine model of arthritis. This finding might lead to the development of a therapeutic anti-inflammatory agent that is not derived from human plasma and that reduces safety concerns and availability shortages.

Dosage and adverse reactions

In the United States several IVIG preparations and 1 SCIG preparation are commercially available.⁶⁸ They differ in their method of purification, osmolality and IgG concentration, IgA and sodium contents, stabilizer (to prevent IgG aggregation; eg, glycine, sucrose, or maltose), and pH; however, they are administered similarly, except when adverse reactions occur, such as idiosyncratic reactions in a particular patient or if suspected hypersensitivity to IgA leads to the use of those products with undetectable IgA. Patients with diabetes mellitus should avoid products containing sugar molecules as stabilizers. IVIG is used as an anti-inflammatory agent at 1 to 2 g/kg in 1 dose or divided in 2 daily doses. The IVIG dose used for replacement in patients with antibody deficiencies is 400 to 600 mg/kg administered every 3 to 4 weeks to maintain a trough IgG level of at least 500 mg/mL and reduce the frequency of infections. Because of increased immunoglobulin catabolism or protein loss, some patients might require even higher doses, which need to be optimized to each patient, also taking into consideration the clinical assessment. Because of the volume limitations for subcutaneous administration, SCIG is not used for inflammatory disorders and is recommended to be administered weekly for immune deficiencies, with doses that correspond to the IVIG dose mentioned above (approximately 100 mg/kg/wk). No differences of efficacy to prevent infections have been found in clinical trials comparing IVIG and SCIG. The weekly subcutaneous administration of immunoglobulins provides a tighter range of serum IgG levels, which is of advantage for patients who experience side effects associated with peak IgG concentrations. Although side effects associated with SCIG infusions are at the infusion site, IVIG side effects are not common, although they can be severe, including back pain, fever, hypotension, thrombosis, headaches, and skin rashes. Pre-medication with antihistaminic agents, nonsteroidal anti-inflammatory drugs, and corticosteroids and hydration with normal saline are common measures used to prevent these symptoms. Serious adverse effects, such as aseptic meningitis, seizures, anaphylaxis, pulmonary edema, and thrombosis, have been rarely reported. Therefore it is recommended that IVIG be administered with medical monitoring for early detection and management of these possible events.

FUTURE DIRECTIONS

The factors that drove the initial introduction of the biologic agents—a clinical need for better outcomes, greater delineation of pathophysiology allowing definition of various targets, and progress in biotechnology allowing development of agents—will no doubt continue to fuel progress in this area. It can be expected that additional mAbs and fusion receptors, both directed at existing targets and against novel targets, will continue to be developed and brought to the clinic. Along with the number of agents, it is anticipated that the conditions for which these agents are used will also expand. For existing biologic agents, a number of questions remain as to the optimum treatment paradigms (eg, sequence of biologic agents) and most appropriate patient populations for their use; this will be germane for newer agents as well. As always, the balance between achieving higher levels of efficacy, with disease remission being the ultimate goal, need to be balanced against safety considerations. For macromolecules, such as mAbs and soluble receptors, there is the potential for optimizing their characteristics, including ease of use, immunogenicity, and cost. For certain targets, it is possible that small-molecule inhibitors might be developed that can address some of these issues. However, because these molecules can be anticipated to have pharmacokinetic, mechanistic, and other important differences from their macromolecular counterparts, this might translate into variable safety and efficacy. Therefore newer agents of a different class, even those whose putative target is the same as existing therapies, need to be assessed with the same rigor as the currently available agents.

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