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 2010;125:S314-23.)

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

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

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 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 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,

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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

doi:10.1016/j.jaci.2009.08.018

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 κB 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% 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