Targeted Immunomodulatory Therapy: An Overview

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ABSTRACT

Monoclonal antibodies and other biologic response modifiers have allowed for targeted drug therapy in managing various autoimmune diseases. A number of immune pathways have been exploited in the development of targeted immunomodulatory therapies, including cytokine-directed therapies such as tumor necrosis factor-alpha and interleukins, integrins, B-cells, and co-stimulation modulators. With new targeted therapies in the pipeline, more options are becoming available for treatment of autoimmune diseases.

KEYWORDS: monoclonal antibodies, biologic response modifiers, immunomodulatory therapy

INTRODUCTION

With major advances in genetic sequencing and biomedical research, targeted therapy with monoclonal antibodies (mABs) has emerged as a successful strategy for managing autoimmune diseases. Treatment with mABs has the advantage of modifying specific immune pathways as opposed to other non-specific therapies. The first mAB (muromonab CD3) was developed from mice and approved in 1986 to prevent rejection of a kidney transplant.[1] However, this first generation of mABs was not well-tolerated due to foreign recognition of the murine components by the patient's immune system.[2]

Since then, different approaches to producing chimeric (part mouse, part human) and fully humanized mABs have been discovered, rendering mABs less immunogenic. One such approach to producing mABs is from hybridomas, formed from the fusion of B-lymphocytes and immortal myeloma cells.[1] The B-lymphocytes are obtained from the spleens of mice after they have been immunized against a specific antigenic determinant, or epitope.[1] The hybridomas are cultured, leading to the generation of polyclonal antibodies. The polyclonal culture is screened for the desired antibody activity and then cloned.[1]

The World Health Organization has policies for nomenclature of mABs.[3] The structure is composed of four parts: the prefix, substem-A, substem-B, and suffix. Substem-A indicates the nature of the target of the mAB, such as tumor or cardiovascular. Substem-B indicates the originating species of the mAB (i.e. human, mouse, chimeric, etc.). The suffix "-mab" is common to most mABs.3

CYTOKINE-DIRECTED THERAPIES

TNFα Inhibitors

Tumor necrosis factor-alpha (TNFα) is a cell-signaling protein, or cytokine, that induces cell proliferation and differentiation through its interaction with TNF receptors on cell surfaces. TNFα plays a role early in many inflammatory immune processes. It is produced primarily by macrophages, but also by monocytes, B-cells, and other tissues. Activation of TNFα also leads to the secretion of interleukin (IL)-1 and IL-6, both proinflammatory cytokines. Dysregulation of TNFα can lead to the development of various autoimmune diseases such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), ankylosing spondilitis, and psoriasis.[4] For instance, in IBD, TNFα secretion leads to the stimulation of endothelial cells to express adhesion molecules, facilitating migration of various white blood cells into inflamed tissue.[5]

TNFα inhibitor therapies are recombinant IgG mABs that essentially serve as decoy TNF receptors. They bind to TNFα molecules and prevent their interaction with TNF receptors, ultimately leading to suppression of the immune system and inflammatory responses. Examples of TNFα inhibitors are adalimumab and etanercept, with the latter possessing a longer half-life due to its dimeric nature. The goal of treatment with TNFα inhibitor therapy is to reduce inflammation and severity of symptoms, with the hope of achieving improved quality of life.

Interleukins

Interleukins are a large class of cytokines responsible for various immune responses, including inflammatory response mediation, lymphocyte growth and differentiation, and immune cell chemotaxis, which can be implicated in autoimmune diseases. Interleukin-17A (IL-17A), produced largely by T-helper 17 cells (Th17), acts directly on keratinocytes to stimulate various pro-inflammatory processes in plaque psoriasis.[6] Interleukin-12 (IL-12) and interleukin-23 (IL-23) have been implicated in the production and development of Th17 cells, leading to psoriatic plaques and joint inflammation in psoriatic arthritis.[7] In RA, IL-6 is released directly by synovial cells and macrophages into the synovium causing inflammation and destruction.[8]

Monoclonal antibodies targeting interleukins are directed at cytokines involved in the production of interleukin, the interleukin itself, or receptors at which interleukin exerts its effect. Ustekinumab was developed against the p40 subunit of both IL-12 and -23, both important in differentiation of naïve T-cells to Th17 cells that produce IL-17A. Ustekinumab binds the p40 subunit of IL-12 and -23, resulting in reduced levels of Th17 cells.[9] Secukinumab, an anti-IL-17A mAB, has been approved for treatment of plaque psoriasis. Inhibition of IL-17A prevents triggering of signaling and recruitment of numerous innate immune cells such as mast cells, neutrophils, and macrophages to psoriatic plaques.[10] Tocilizumab, an anti-IL-6 receptor (IL-6R) recombinant mAB, blocks IL-6 signal transduction by binding to IL-6R embedded in the cell membrane and floating in soluble form in the blood. It also can dissociate already formed IL-6/IL-6R complexes, thereby effectively halting downstream signal transduction pathways that lead to joint inflammation and destruction in RA.[11]

SELECTIVE ADHESION MOLECULE INHIBITORS/ INTEGRIN RECEPTOR ANTAGONISTS

Integrin molecules are conducive to lymphocyte trafficking by facilitating adhesion and migration from the vasculature into inflamed tissue. Integrin molecules are expressed on the surface of activated lymphocytes. Integrins interact with their receptors, which are the cell-adhesion molecules (CAMs) present on vascular endothelium. This interaction enables lymphocytes to migrate across the endothelium into tissues such as the brain and gut.[12] Integrins α4β1 and α4β7 are implicated in multiple sclerosis and IBD, respectively.

Integrin receptor antagonist therapies are mABs that serve as decoys for the CAM receptors. They bind to integrin molecules to prevent interaction with CAMs, ultimately blocking migration of the activated T-lymphocytes into inflamed tissues. Selectivity of adhesion-molecule inhibitors can vary; for instance, natalizumab modulates lymphocyte trafficking in both the central nervous system and gut, while vedolizumab is specific to the gut. Increased specificity is advantageous for targeting desired tissues and limiting adverse effects, such as progressive multifocal leukoencephalopathy, which is a Black Box Warning for natalizumab. The currently available integrin receptor antagonist therapies are humanized mABs. Overall, the goal of integrin receptor antagonist therapy is to reduce migration of activated T-cells and limit progression of chronic inflammation.

B-CELL DEPLETING THERAPIES

B-cells play an important role in numerous autoimmune diseases. In healthy individuals, auto-reactive B-cells are removed from both the bone marrow and peripheral circulation prior to causing significant harm. In autoimmune diseases, a defect causes these auto-reactive B-cells to escape notice and produce antibodies, present "self" antigens, and produce various cytokines implicated in the disease process.

Monoclonal antibodies directed at B-cells are generally focused at B-cell depletion. The primary agent used for B-cell depletion in autoimmune diseases is rituximab, a mAB directed against the CD-20 antigen on B-lymphocytes. CD-20 is present on more than 95% of B-cells and plays a part in B-cell activation and cell-cycle progression. When rituximab binds to CD-20, it activates complement-dependent and antibody-dependent B-cell cytotoxicity, and B-cell apoptosis.[13]

OTHER BIOLOGIC RESPONSE MODIFIERS (BRMS)

Co-stimulation Modulators

T-cells require two signals from antigen-presenting cells (APCs) to undergo activation: antigen presentation by histocompatibility molecules and a co-stimulatory signal provided by molecules on the APCs. In the CD80/86-CD28 co-stimulatory pathway, CD80 or CD86 on APCs binds with CD28 on the surface of T-cells and causes T-cell activation, proliferation, and cytokine production. Co-stimulatory pathways may also be inhibitory, as seen with cytotoxic T-lymphocyte antigen-4 (CTLA-4). CTLA-4 binds to CD80 or CD86, resulting in inhibition of T-cell responses by preventing release of interleukins and blocking cell-cycle progression.[14] This pathway is important in the pathogenesis of RA, where activated T-cells are present in inflamed synovium.

Co-stimulation modulator antibodies target the signals required for co-stimulation of the T-cells to occur. Abatacept, a fusion protein used in the treatment of RA, consists of the extracellular domain of human CTLA-4 protein and the modified Fc region of human IgG1. The CTLA-4 portion of abatacept binds CD80/86 on APCs, thereby blocking the interaction between CD28 and APCs required for T-cell activation. The result of this blockade is a long-lasting attenuation of T-cell response.[15] Belimumab, a human IgG1λ recombinant mAB used in the treatment of systemic lupus erythematosus, targets B-lymphocyte stimulator (BLyS), the co-stimulator for B-cell survival and function. BLyS binds to BLyS receptors and promotes the survival of autoantibody-producing B-cells by preventing their selection and apoptosis. Belimumab binds to soluble BLyS, preventing interaction with BLyS receptors and thereby decreasing B-cell survival and production of autoantibodies.[16]

Interleukin BRMs

IL-1 is a system consisting of two pro-inflammatory ligands and the naturally occurring antagonist IL-1Ra. In RA, levels of IL-1 are elevated in plasma and synovial fluid.[17] Anakinra, a recombinant human IL-1Ra, binds to IL-1 receptors to prevent intracellular signaling leading to cell activation and biological responses.[18]

Table 1. Currently Approved Monoclonal Antibodies and Biologic Response Modifiers

Generic Name	Brand Name	Class	Clinical Uses
Adalimumab	Humira®	TNF inhibitor	Rheumatoid arthritis, Psoriatic arthritis, Plaque psoriasis, Crohn's disease, Ulcerative colitis, Ankylosing spondylitis, Juvenile idiopathic arthritis
Etanercept	Enbrel®		
Certolizumab pegol	Cimzia®		
Golimumab	Simponi®		
Infliximab	Remicade®		
Anakinra	Kineret®	IL-1 antagonist	Rheumatoid arthritis
Canakinumab	Ilaris®	IL-1 inhibitor	Juvenile idiopathic arthritis
Tocilizumab	Actemra®	IL-6 antagonist	Rheumatoid arthritis, Juvenile idiopathic arthritis
Ustekinumab	Stelara®	IL-12 and IL-23 inhibitor	Psoriatic arthritis, Plaque psoriasis
Secukinumab	Cosentyx®	IL-17A receptor antagonist	Plaque psoriasis, Ankylosing spondylitis, Psoriatic arthritis
Ixekizumab	Taltz®	IL-17A receptor antagonist	Plaque psoriasis
Abatacept	Orencia®	Co-stimulation blocker of CD-28	Rheumatoid arthritis, Juvenile idiopathic arthritis
Belimumab	Benlysta®	BLyS inhibitor	Systemic lupus erythematosus
Vedolizumab	Entyvio®	Integrin receptor antagonist	Crohn's disease, Ulcerative colitis
Natalizumab	Tysabri®	Anti-integrin antibody	Crohn's disease, Ulcerative colitis, Multiple sclerosis
Rituximab	Rituxan®	Anti-CD20 antibody	Rheumatoid arthritis, Lupus nephritis, Idiopathic thrombocytopenic purpura, Graft-versus-host disease

Table 2. Monoclonal Antibodies and Biologic Response Modifiers in the Pipeline

Generic Name	Stage in Development	Trial Names	Class	Clinical Uses
Brodalumab	Phase III clinical trials	AMAGINE and AMVISION	IL-17A receptor monoclonal antibody	Plaque psoriasis, Psoriatis arthritis, Ankylosing spondylitis
Guselkumab	Phase II clinical trials	X-PLORE	IL-23 monoclonal antibody	Plaque psoriasis
Tildrakizumab	Phase III clinical trials	-	IL-23 p19 subunit monoclonal antibody	Plaque psoriasis
Anifrolumab	Phase III clinical trials	-	IFN Type I receptor monoclonal antibody	Systemic lupus erythematosus
Ozoralizumab	Phase II clinical trials	-	Anti-TNFα Nanobody	Rheumatoid arthritis
Etrolizumab	Phase III clinical trials	-	Integrin inhibitor	Crohn's disease

CONCLUSION

Monoclonal antibodies and other BRMs have allowed for targeted drug therapy in managing various autoimmune diseases. A number of immune pathways have been exploited in the development of mABs by targeting cytokines, cell-adhesion molecules, co-stimulation signals, and B-cells (**Table 1**). Promising new agents are in the pipeline (**Table 2**), providing additional options for managing autoimmune conditions.

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