

Monoclonal antibodies and fusion proteins and their complications: Targeting B cells in autoimmune diseases

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The immune system consists of a complex array of immunocompetent cells and inflammatory mediators that exist in complex networks. These components interact through cascades and feedback circuits, maintaining physiologic inflammation and immunosurveillance. In various autoimmune conditions, a foreign or auto-antigen may 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 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. The 2 most common classes of biologic agents are monoclonal antibodies and fusion proteins. These agents can inhibit targets with exquisite specificity to optimize outcomes and minimize toxicity. B cells contribute significantly to the initiation and perpetuation of the immune responses. B cells not only can produce potentially pathologic autoantibodies and proinflammatory cytokines but also can present antigens to T cells and provide costimulatory signals essential for T-cell activation, clonal expansion, and effector function. This review focuses on biologic agents targeting B cells in the treatment of rheumatoid arthritis and systemic lupus erythematosus. (*J Allergy Clin Immunol* 2010;125:814-20.)

Key words: B-cell therapy, rheumatoid arthritis, systemic lupus erythematosus, monoclonal antibody, fusion protein

The immune system is composed of a complex array of diverse immunocompetent cells and proinflammatory and anti-inflammatory mediators that exist in complex networks. These components interact through cascades and positive and negative feedback circuits to maintain normal inflammation and immunity. In recent years, there has been tremendous progress delineating

Abbreviations used

ADCC: Antibody-dependent cellular cytotoxicity
APRIL: A proliferation-inducing ligand
BAFF: B cell-activating factor
BAFF-R: B cell-activating factor receptor
BCMA: B-cell maturation protein
BLyS: B-lymphocyte stimulator
BR3-Fc: BAFF-R fusion protein
CD40L: CD40 ligand
CDC: Complement-dependent toxicity
CDR: Complementarity-determining region
DMARD: Disease-modifying antirheumatic drug
mAb: Monoclonal antibody
NHL: Non-Hodgkin lymphoma
PML: Progressive multifocal leukoencephalopathy
RA: Rheumatoid arthritis
RF: Rheumatoid factor
SLE: Systemic lupus erythematosus
SMIP: Small modular immunopharmaceutical protein
TACI: Transmembrane activator and calcium-modulator and cyclophilin ligand interactor
TGF- β : Transforming growth factor-beta
TNF: Tumor necrosis factor

the specific components of the immune system that contribute to various aspects of normal immunity and to specific disease states. With this greater understanding of pathogenesis coupled with advances in biotechnology, many specific immunomodulatory therapies called biologic agents have been introduced for the treatment of various autoimmune conditions. Biologic agents can work through several mechanisms. The simplest is 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 immunoglobulins; and (3) surface receptors for these mediators. Biologic agents may alter cell populations by engaging effector functions including the complement cascade and antibody-dependent cellular cytotoxicity (ADCC). Cell depletion can also be induced by apoptosis subsequent to ligation of appropriate targets. The 2 most common classes of biologic agents approved are mAbs and fusion proteins. By inhibiting targets with exquisite specificity, these agents have the potential to optimize outcomes through more thorough modulation of specific parts of the dysregulated immune response and to minimize potential adverse events compared with more broad methods of immunosuppression.

Work from multiple laboratories has shown that various components of the immune system including proinflammatory

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TABLE I. Biologic agents targeting B cells for the treatment of RA and SLE

Agent	Approval date*	Indication	Structure	Target antigen	Key references
B-cell modulators					
Rituximab	1997 for NHL 2006 for RA		Chimeric mAb	CD20	1, 2, 14, 19
Ocrelizumab	In development		Humanized mAb	CD20	26
Veltuzumab	In development		Humanized mAb	CD20	25
Ofatumumab	In development		Human mAb	CD20	27, 28
TRU-015	In development		SMIP	CD20	29, 30
Epratuzumab	In development		Humanized mAb	CD22	31
Belimumab	In development		Human mAb	BLyS	35, 39, 40, 42
Atacicept	In development		Receptor fusion protein	BLyS and APRIL	48, 49
Cytokine inhibitors					
Tocilizumab	2010 for RA		Humanized mAb	IL-6 receptor	53, 54

BLyS, B-lymphocyte stimulator.

*As of February 2010.

cytokines (eg, TNF, IL-1), T cells, and B cells are dysregulated in common autoimmune conditions such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).¹⁻⁶ This review focuses on biologic agents targeting B cells in the treatment of RA and SLE (Table I). B cells can contribute significantly to the initiation and perpetuation of the immune response. B cells not only can produce potentially pathologic autoantibodies (eg, rheumatoid factor, antinuclear antibody) and proinflammatory cytokines but also can present antigens to T cells and provide costimulatory signals essential for T-cell activation, clonal expansion, and effector function.¹⁻⁶

MONOCLONAL ANTIBODIES

mAbs to human targets are generated either in other species—for example, in mice—or through recombinant engineering. With chimeric mAbs, the variable region of a murine-derived mAb is fused to the Fc piece of a human IgG molecule. The resulting construct is approximately one quarter murine and three quarters human. For humanized mAbs, only the complementarity-determining regions (CDRs) from the original murine mAb are retained, resulting in a construct that is approximately 95% human. There are a number of theoretical approaches to creating human mAbs to human targets, including immunizing severe combined immunodeficient mouse chimeras, or using EBV-transformed human B cells. One of the most commonly used methods has been repertoire cloning. In this procedure, target antigen is used to capture human CDRs generated from vast human cDNA libraries. In general, the more human the construct is, the less immunogenic the mAb. However, even small molecules whose amino acid sequences are identical to human and fully human mAbs with slight differences in patterns of glycosylation can be immunogenic. In addition, some of the mAb immunogenicity appears to be idiotypic where patients who develop antibodies after treatment with 1 chimeric mAb might not be expected to demonstrate equal reactivity to another chimeric mAb. Other key factors that are relevant to the immunogenicity of a compound include route of administration (intravenous vs subcutaneous), treatment paradigm (continuous vs intermittent), and concurrent immunosuppressive therapy. In clinical practice, these factors have proven to be relevant considerations for the therapeutic use of mAbs.

The standard nomenclature for mAbs makes note of their source as the last 4 or 5 letters of the mAb name: *-omab*, murine;

-ximab, chimeric; *-zumab*, humanized; and *-umab*, human. The middle part of the name refers to the disease indication for which the mAb is intended: *-lim-* for immune and inflammatory diseases, *-cir-* for cardiovascular disorders, and *-tu-* for tumors or neoplastic conditions. The first 3 or 4 letters are chosen by the sponsor/developer. Although numerous mAbs have been approved by the US Food Drug and Administration, this review focuses on several key mAbs against B cells approved or under investigation for the treatment of RA and SLE.

FUSION PROTEINS

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 Fc portion of human immunoglobulin is used as the linker, which achieves the desired effect by enhancing the pharmacokinetic properties of the construct. The Fc portion of the fusion receptor can be functional and bind to complement and cell surface Fc receptors. Alternatively, the construct can be engineered such that the Fc portion is unable to execute effector functions. As their primary mechanism of action, fusion receptors competitively inhibit the binding of a ligand to its specific counter receptor and thereby prevent downstream effects, such as activation of inflammatory cascade.

TARGETING CD20

As B cells develop from hematopoietic stem cells to mature plasma cells, specific cell surface markers are expressed at different stages of maturation. CD20 is a 33-kd to 37-kd cell surface marker expressed on the surfaces of pre-B cells through memory B cells. It is absent on stem cells and antibody-producing plasma cells. On binding to antibodies, CD20 is not shed or internalized, making it an ideal target for B cell-directed therapy.

Rituximab

Rituximab is a chimeric monoclonal IgG₁ antibody directed against the B-lymphocyte surface antigen, CD20 (Fig 1). Although the precise mechanism of rituximab remains unclear, it is thought to induce CD20-positive B-cell lysis by several mechanisms including complement-dependent toxicity (CDC), ADCC, and induction of apoptosis. Rituximab was initially

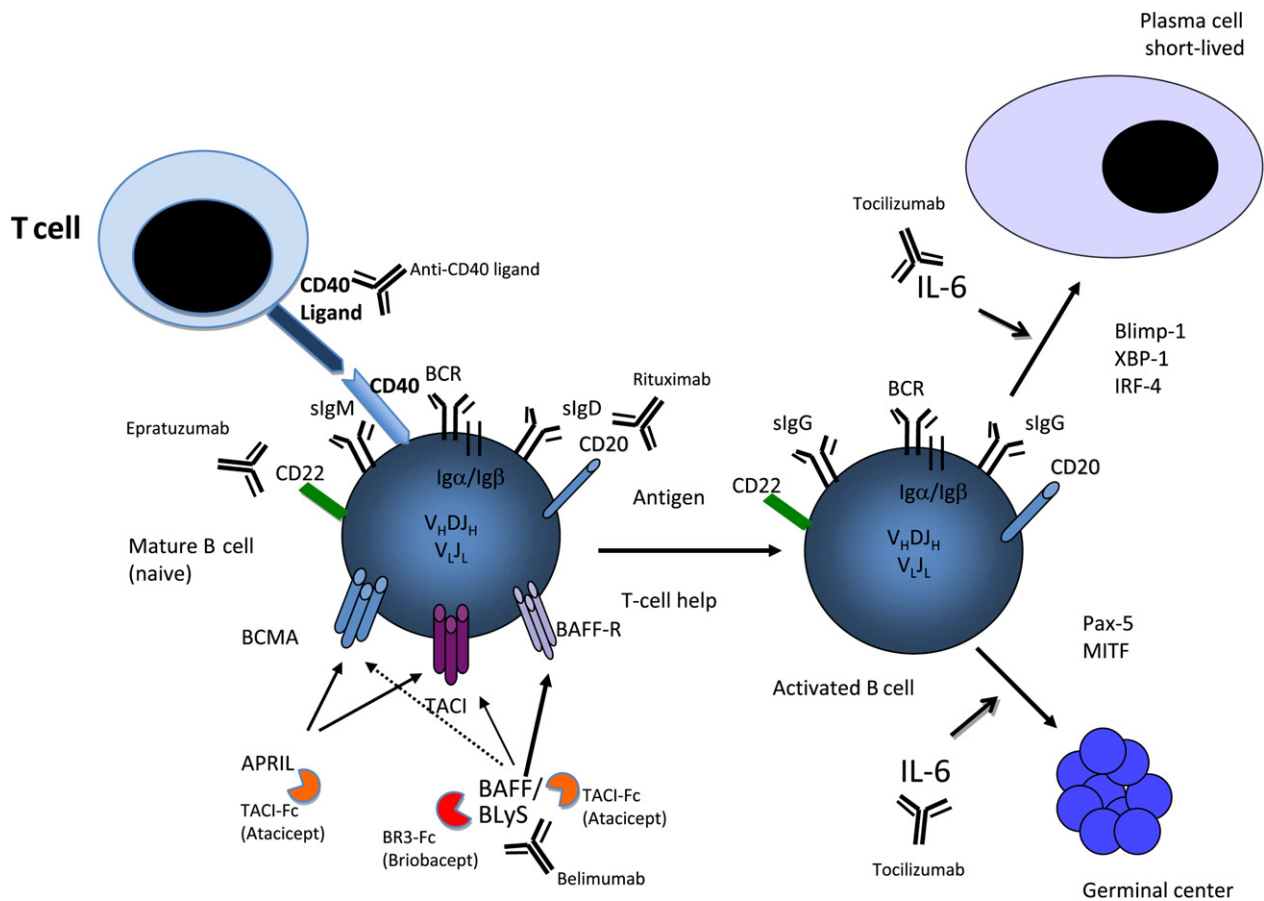


FIG 1. B cell-targeted therapy with mAbs and fusion receptor proteins. The 2 principal targets on B cells are CD20 and CD22. CD20 was the first B-cell surface molecule targeted for B cell-directed therapy with mAbs, eg, rituximab. More recently, second-generation and third-generation anti-CD20 mAbs that are humanized (ocrelizumab and veltuzumab) and fully human (ofatumumab) are in clinical trials. Epratuzumab is a humanized mAb directed at CD22. BAFF (B-lymphocyte stimulator; *BLyS*) and APRIL are important survival and growth factors for B cells that are potential targets in autoimmune diseases. BAFF and APRIL interact with 3 different receptors on B cells: BAFF-R, TACI, and BCMA. Belimumab is a human mAb that binds soluble BAFF, preventing the binding to the BAFF-R. BR3-Fc is a BAFF-R fusion protein linked to the Fc domain of IgG that binds BAFF. Atacicept (TACI-Ig) is a fusion protein that binds both BAFF and APRIL growth factors. Tocilizumab is a humanized anti-IL-6 receptor mAb that blocks the action of IL-6, an important cytokine in the terminal differentiation of B cells and inflammatory processes. *BCR*, B cell receptor; *sIgM/sIgD*, etc, soluble IgM/IgD, etc; *Blimp-1*, B lymphocyte-induced maturation protein-1; *IRF-4*, interferon regulatory factor-4; *MILF*, microphthalmia-associated transcription factor; *Pax-5*, paired box-5; *XBP-1*, X-box binding protein-1.

approved by the US Food and Drug Administration for the treatment of CD20-positive B-cell non-Hodgkin lymphoma (NHL) in 1997 and later for the treatment of RA in 2006. B cells are thought to play a pathogenic role in RA by producing autoantibodies (ie, rheumatoid factor, anticyclic citrullinated protein) and inflammatory cytokines and by activating T cells. Rituximab is given as an intravenous infusion at 375 mg/m² weekly for 4 weeks for NHL and 500 to 1000 mg every 2 weeks for 2 doses for RA. Rituximab has a half-life of approximately 21 days and can deplete peripheral B cells for 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, quality of life, and retard radiographic progression of disease in patients with RA who had previously failed to respond to methotrexate or TNF inhibitors.^{1,2} Repeated treatment in patients who did not respond to initial cycle did not induce a clinical response.⁷ In addition, fixed retreatment at 6 months among clinically responsive patients regardless of their disease activity at

the time of retreatment did not confer additional benefit.⁸ Optimal treatment schedules are currently under investigation, but repeated treatment is generally recommended after 6 months for patients whose disease flares in association with normalization of B-cell counts and who had initially responded to rituximab therapy. Although rituximab can be used alone or in combination with disease-modifying antirheumatic drugs (DMARDs), combination therapy yielded better clinical outcome.^{2,9} Also, patients with RA who are seropositive for rheumatoid factor (RF) seemed to have a greater clinical response than seronegative patients.⁹

Rituximab has also shown promising results in the treatment of other autoimmune diseases such as SLE, primary Sjögren syndrome, idiopathic thrombocytopenic purpura, chronic inflammatory demyelinating polyneuropathy, multiple sclerosis, and vasculitis (eg, Wegener granulomatosis, relapsing polychondritis).⁸⁻¹⁴ Additional trials are underway that should answer questions regarding dosing, treatment intervals, safety, and tolerability of rituximab in these conditions.

Although there are ongoing clinical trials assessing the role of rituximab in RA and SLE, the largest safety experience comes from oncology patients, mainly those with NHL.¹⁴ Despite the potential for immunodeficiency related to depletion of mature B cells, only small increases in infections, either serious or opportunistic, were reported in both patients with RA and patients with NHL treated with rituximab. The overall levels of serum immunoglobulins generally remained 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 may become a safety concern, because plasma cells may not be replenished by memory B cells. Thus far, some patients have undergone more than 6 cycles of rituximab without an apparent increased risk of serious infection or adverse events.^{15,16} In 2006, the safety of rituximab was amended to highlight an increased risk of certain viral infections including cytomegalovirus, herpes simplex virus, varicella-zoster virus, hepatitis B virus, and JC virus.^{17,18} JC virus, latent in more than 80% of the general population, can be reactivated in immunosuppressed patients to cause a fatal demyelinating disease of the central nervous system called progressive multifocal leukoencephalopathy (PML). Although more common among patients with hematologic malignancies, few cases of PML have been reported among patients with SLE and patients with RA who were treated with rituximab.¹⁹ 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 biological agents.

Other notable adverse events include rare neutropenia and thrombocytopenia that can occur up to 5 months after the therapy.²⁰ In general, rituximab has been well tolerated, with infusion reaction the most common adverse event. Infusion reactions are more common during the first infusion and among patients with lymphoma rather than RA.²⁰ Rituximab has also been associated with Stevens-Johnson syndrome and type III hypersensitivity reactions (serum sickness), occurring more commonly among patients with underlying autoimmune conditions than hematologic malignancies.^{21,22} In NHL, rituximab infusions have been associated with a severe, potentially life-threatening condition referred to as cytokine release syndrome. Patients often present with fever, nausea, rash, multiple laboratory abnormalities (eg, elevated liver function tests, uric acid, lactate dehydrogenase, thrombocytopenia, prolonged coagulation time), and high cytokine levels (eg, TNF- α , IL-6). Seventy percent of cases occur during the first infusion and more frequently in those with higher baseline lymphocyte counts ($>50 \times 10^6/L$). Although the exact mechanism is unknown, it is hypothesized to be related to complement activation by leukostasis and apoptosis of CD20-positive cells, similar to tumor lysis syndrome.²³ Last, every effort should be taken to give vaccination before initiating rituximab therapy, because suboptimal response to some vaccines has been seen with rituximab.

Second-generation and third-generation anti-CD20 mAbs: ocrelizumab, ofatumumab, and veltuzumab

Frequent infusion reactions and potentially neutralizing anti-chimeric antibody associated with rituximab have prompted development of several humanized and fully human anti-CD20 mAbs including ocrelizumab, ofatumumab, and veltuzumab.

Ocrelizumab is a recombinant humanized anti-CD20 mAb that binds to the same epitope as rituximab. Veltuzumab is a humanized anti-CD20 mAb with CDRs identical to rituximab except for the replacement of asparagine with aspartic acid at position 101. *In vitro* studies have demonstrated that veltuzumab has an improved binding avidity and CDC activity compared with rituximab.²⁴ Ofatumumab is a fully human monoclonal IgG₁ antibody against CD20 but binds to a different epitope than rituximab, located in the second extracellular loop of the N-terminus from alanine residue in position 170 and a proline in position 172. This unique binding property has resulted in a longer binding time and stronger CDC activity of ofatumumab than rituximab without inducing apoptosis.

Both ocrelizumab and ofatumumab are given intravenously and have shown promising results among patients with RA who have failed to respond to at least 1 DMARD and/or TNF inhibitors.²⁵⁻²⁸ Veltuzumab can be given either intravenously or subcutaneously and has shown favorable results in early studies for B-cell lymphoproliferative malignancies. Studies are ongoing to evaluate the efficacy and safety of ocrelizumab, veltuzumab, and ofatumumab in NHL, chronic lymphocytic leukemia, idiopathic thrombocytopenic purpura, and multiple sclerosis both as monotherapy and as combination therapy with currently available chemotherapy.

These agents have been generally well tolerated in clinical trials, with infusion reactions the most commonly reported adverse events. As expected with fully human and humanized mAbs, ofatumumab, ocrelizumab, and veltuzumab have been associated with less immunogenicity and fewer infusion reactions than rituximab.^{3,25-28} However, given some of their similarities to rituximab, concerns remain for potential unforeseen adverse events such as PML.

TRU-015: CD20-directed small modular immunopharmaceutical protein

To address potential concerns related to tissue penetration of high-molecular-weight mAbs and complement-mediated adverse events, a new small modular immunopharmaceutical protein (SMIP) targeting CD20 has been engineered. SMIPs are dimeric, single-chain polypeptides approximately one third to one half the size of mAbs. Although SMIPs can induce ADCC and apoptosis, by design, they have attenuated complement activation and subsequent lower levels of CDC. TRU-015 is a SMIP that binds to CD20 on pre-B to mature B cells and causes dose-dependent B-cell depletion. Despite its smaller size, TRU-015 has a half-life of approximately 14 days, comparable to mAbs. Earlier studies have been promising with favorable clinical response and safety profile among patients with RA.^{29,30} Studies are ongoing to assess the long-term efficacy and safety in the treatment of RA and lymphoma.

TARGETING CD22

CD22 is a 135-kd cell surface marker specific to B cells and functions as a coreceptor for B-cell receptor. CD22 modulates B-cell interaction with T cells and plays a key role in B-cell development and survival. It is present on pre-B cells to mature activated B cells but absent on memory B cells. Epratuzumab is a humanized anti-CD22 monoclonal IgG₁ antibody that causes internalization of CD22:antibody complex on binding (Fig 1). Unlike anti-CD20 mAbs, epratuzumab does not induce CDC or

apoptosis and only partially (30% to 45%) depletes circulating B cells. Epratuzumab appears to have more of an immunomodulatory than a cytotoxic effect. In a small, open-labeled study of 14 patients with SLE, epratuzumab successfully decreased the level of SLE disease activity as measured by British Isles Lupus Assessment Group score. It was well tolerated with only mild to moderate infusion reactions. Studies are ongoing to evaluate the safety and efficacy of epratuzumab for the treatment of NHL.^{3,25,31}

TARGETING B-CELL ACTIVATING FACTOR AND A PROLIFERATION-INDUCING LIGAND

B cell-activating factor (BAFF) or B-lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL) are members of the TNF cytokine family and are important survival and growth factors for B cells. BAFF binds to 3 different receptors on B cells: transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI), BAFF receptor (BAFF-R), and B-cell maturation protein (BCMA). APRIL binds only to TACI and BCMA.³² BAFF interaction with BAFF-R is important in the generation and maintenance of mature B cells, whereas interaction with TACI receptor induces a T cell-independent B-cell activation, immunoglobulin class-switching, and B-cell homeostasis.³³ BAFF interaction with BCMA is important for the differentiation and survival of plasma cells.³⁴

BAFF and APRIL can form biologically active heterodimers and are overexpressed in SLE, RA, and Sjögren syndrome.³³⁻³⁶ For example, high levels of both BAFF and APRIL have been found in the synovial fluids of patients with RA. In patients with SLE, high serum levels of BAFF and APRIL correlated with the levels of autoantibody titers and disease activity.³⁵⁻³⁸ Therefore, blocking the actions of BAFF, or BAFF together with APRIL, offers therapeutic potential for the treatment of these autoimmune conditions. However, the therapeutic effects of B-cell depletion or B-cell growth/differentiation factor inhibition may depend on the balance and presence of the pathogenic B cells—that is, those producing autoantibodies—and the regulatory roles of B cells.

Belimumab

Belimumab is a recombinant fully human mAb that binds to soluble BAFF and prevents its binding to BAFF-R (Fig 1). In phase I studies, belimumab administered intravenously significantly reduced anti-double stranded DNA (dsDNA) antibodies among patients with SLE.³⁹ Although primary end points were not met in subsequent phase II trials, belimumab stabilized SLE disease activity over the 52-week trial period.^{40,41} In a subgroup analysis, antinuclear antibody–seropositive patients responded better and had less disease flares than seronegative patients with SLE.⁴² Similar findings were noted in phase III trials, in which belimumab-treated patients had less SLE disease activity and flares than placebo-treated patients at 52 weeks. No significant increases in adverse events were noted.⁴³⁻⁴⁵ In a phase II trial of patients with RA, although belimumab decreased the levels of B cells and RF, it failed to improve the overall RA disease activity.⁴⁶

Currently several other molecules to inhibit BAFF are in development, including briacept. This is a recombinant BAFF-R fusion protein (BR3-Fc) in which 2 BAFF-Rs are linked to the Fc domain of human IgG₁ (Fig 1).⁴⁷ Although no clinical data are available, earlier animal studies have suggested that a CD20-specific agent together with BAFF neutralization/

inhibition may have synergistic effects in the treatment of various autoimmune conditions.

Atacicept

Because BAFF and APRIL both bind to TACI and BCMA, inhibition of both BAFF and APRIL can be accomplished with a receptor fusion protein against TACI. Atacicept is a fusion protein composed of the extracellular domain of TACI fused with the Fc fragment of human IgG₁ and is designed to have a broader effect on different stages of B-cell differentiation (Fig 1). Several early studies in patients with RA and SLE have shown that atacicept can reduce peripheral blood B cells and serum immunoglobulin without associated toxicity.^{48,49} In a small phase I, dose-escalation study of patients with RA, atacicept depleted B cells, RF, and anticyclic citrullinated autoantibodies by 40% to 50%, 40%, and 25%, respectively.⁴⁹ Phase II and III clinical trials are currently underway assessing the efficacy and safety of atacicept in the treatment of SLE, RA, and relapsing multiple sclerosis.

TARGETING IL-6 RECEPTORS

IL-6 is a multifunctional cytokine that is involved in the acute inflammatory response, regulation of immune responses, and hematopoiesis. IL-6 induces the terminal proliferation and differentiation of B cells, osteoclastogenesis, and acute phase proteins production in the liver. For example, high levels of IL-6 have been found in the synovial fluids from inflamed joints of patients with RA. IL-6, together with transforming growth factor-beta (TGF-β), is also involved in differentiation of IL-17 cells and regulatory T cells.

Tocilizumab is a humanized antihuman IL-6 receptor mAb that blocks the binding of IL-6 with its receptor.⁵⁰ In the United States, tocilizumab was approved in 2010 for the treatment of patients with moderate to severe RA who failed to respond to 1 or more anti-TNF inhibitors. In Japan, it is also approved for the treatment of juvenile idiopathic arthritis and Castleman disease. Phase II studies have shown that tocilizumab administered intravenously (8 mg/kg) every 4 weeks significantly reduced disease activity in patients with RA.⁵¹ Multiple phase 3 studies have shown that tocilizumab improved RA disease activity, functional status, and quality of life. The clinical improvement was rapid and evident within the first 2 weeks of treatment.⁵²⁻⁵⁴ Tocilizumab has also been shown to slow radiographic progression with improvements in bone and cartilage turnover markers.^{55,56} Similarly, among patients with systemic juvenile idiopathic arthritis, 90% of the patients treated with tocilizumab achieved an American College of Rheumatology pediatric score of 70% improvement with no major safety issues.⁵⁶ Although it can be given as monotherapy, tocilizumab appeared to be more effective when used in combination with DMARDs. Tocilizumab was well tolerated either alone or in combination with DMARDs. The most common adverse events were upper respiratory tract infections, headache, hypertension, hyperlipidemia (total cholesterol, high-density lipoprotein, low-density lipoprotein), and increased liver enzymes. Side effects were generally mild and reversible.⁵²⁻⁵⁶

TARGETING COSTIMULATORY MOLECULES

Blockade of the CD40–CD40 ligand (CD40L) costimulatory cell surface molecules can prevent B-cell activation and class switching. CD40 is expressed on T cells and activated endothelial cells. Studies of anti-CD40L in patients with idiopathic

thrombocytopenia and SLE showed some promise.⁵⁷ However, treatment was complicated by thrombosis in clinical trials related to CD40-CD40L interaction between endothelial and platelets. Subsequently, clinical trials assessing the role of anti-CD40L have been placed on hold until further safety data becomes available.

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 as well as 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 about the optimum treatment paradigms and most appropriate patient populations for their use; this will be germane for newer agents as well. As always, high levels of efficacy, with disease remission 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 may 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 may 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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