Biologic Therapies in Clinical Development for the Treatment of Rheumatoid Arthritis

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Abstract: The therapeutic objective in patients with rheumatoid arthritis (RA) is reduction of disease activity with an ultimate goal of disease remission. Limitations of currently available disease-modifying antirheumatic drugs and biologic therapies suggest that there remains an unmet need for agents that advance these goals in a greater proportion of patients. Progress in our understanding of the regulatory molecules and pathways that mediate the immune and inflammatory responses necessary for the initiation and perpetuation of RA has led to the identification of new targets for therapy. It is expected that the therapeutic modulation of these targets, which include proinflammatory cytokines, T and B cells, adhesion molecules, chemokines, and intra- and extracellular signaling pathways, can provide new treatment strategies in patients with RA and other autoimmune disorders. Toward this end, a series of novel agents with diverse mechanisms of action are in development. Although many of these agents are still beyond the clinical horizon, several of them have shown promise in recent trials. This article reviews a few of the many treatment strategies currently being evaluated, which are hoped to lead to greater benefits and better disease management in the clinical setting.

Key Words: rheumatoid arthritis, biologic response modifiers, cytokines, B cells, T cells, adhesion molecules

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A rational approach to therapy requires an understanding of the disease process and the identification of appropriate targets whose modulation will interfere with propagation of the disease state yet limit interference with normal homeostatic mechanisms. Rheumatoid arthritis (RA) is a progressive chronic disease whose treatment is still often symptomatically driven, mainly as a result of incomplete characterization of the underlying disease process. Despite drawbacks of potential toxicity and limited efficacy, the disease-modifying antirheumatic drugs (DMARDs), of which methotrexate is the most widely used, have been an important component of the RA therapeutic paradigm.[1]

Recent advances in our understanding of RA pathogenesis, reviewed in this supplement by Firestein,[2] have resulted in the identification of new therapeutic targets with the goal of enhancing our ability to modify the disease process and delaying or arresting progression.

Concomitant with the progress in our understanding of RA has been the evolution of new immunologic and molecular techniques that can be used to create or alter biologic entities such as antibodies and fusion proteins. The result has been a new group of agents that have been termed "biologic response modifiers" (BRMs).

Four BRMs have been approved and are commercially available for the treatment of RA. Three of these BRMs, infliximab, adalimumab, and etanercept, target tumor necrosis factor-α (TNF-α), and the fourth, anakinra, targets interleukin-1 (IL-1). Both TNF-α and IL-1 are cytokines identified as being present in the synovium of patients with RA and characterized as potential mediators of the inflammatory events contributing to joint damage.[3]

Infliximab and adalimumab are anti-TNF-α monoclonal antibodies, of which the former is chimeric (murine/human) and the latter is human. Etanercept is a recombinant fusion protein consisting of the ligand-binding domains of the TNF-α receptor and the Fc portion of immunoglobulin (Ig)G1. All 3 agents have demonstrated significant clinical response and remission in combination with methotrexate compared with methotrexate alone in early and established RA, and have additionally demonstrated the ability to slow radiographic progression, suggesting long-term disease modification.[4–9] Although no trials have yet evaluated these agents in head-to-head comparisons, an indirect comparison has suggested similar efficacy among the 3 TNF antagonists.[10]

Extension studies supporting the long-term efficacy and safety of etanercept and adalimumab have been reported for periods of up to 7 years.[11,12] However, these extension studies represent a population that self-selects for both safety

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and efficacy, and in clinical practice, many patients have an inadequate response or loss of response after treatment.[13] Clinical trials have suggested that the most common side effects of TNF antagonists are injection site reactions and infusion reactions. However, the immunosuppressive nature of these agents has raised other safety issues. In particular, these agents have been associated with infectious complications,[14] including an observed increase in the incidence of tuberculosis among treated patients,[15] and the potential for increased risk of lymphoma.[16] Several recent epidemiologic studies suggest that patients with RA may be at increased risk for both of these complications,[17–19] but insufficient data are available to determine a causal relationship with anti-TNF therapy.

Anakinra is a recombinant IL-1 receptor antagonist. In contrast to the anti-TNF agents that directly target the ligand, anakinra competes with the IL-1 ligand for binding to the receptor site but does not itself induce signal transduction once bound. Anakinra combined with methotrexate has demonstrated significant efficacy compared with methotrexate alone in reducing RA disease activity and slowing radiographic progression,[20,21] although the efficacy of anakinra may be perceived to be weaker than that of the anti-TNF agents.[22]

The demonstrated therapeutic benefits of these BRMs in the clinical setting have resulted in their widespread use. Nevertheless, the American College of Rheumatology (ACR) improvement criteria 20, 50, and 70 response rates of 40% to 85%, 20% to 50%, and 10% to 30%, respectively, that have been reported with these agents suggest that a substantial proportion of patients fail to achieve clinically significant levels of improvement. Therefore, there still exists an unmet need for new therapies that can provide greater efficacy in a larger proportion of patients.

There are a myriad of interrelated pathways that contribute to RA pathogenesis, and numerous potential targets have been identified. This article reviews a few of the most interesting and/or promising agents that are now appearing on the horizon or are just over the horizon for the treatment of RA (Table 1).

NEW RHEUMATOID ARTHRITIS THERAPIES ON THE HORIZON

Two new BRMs in development, and one already approved for use in cancer are on the horizon for the treatment of RA. These 3 drugs, rituximab, MRA (atlizumab), and abatacept, are currently in clinical trials.

Because RA is characterized by autoantibody production, B-cell depletion is a rational approach to treatment. Rituximab is a chimeric (murine/human) monoclonal antibody with a long half-life (72 hours for a single dose, 206 hours for multiple dosing) that has been approved for the treatment of non-Hodgkin lymphoma.[23] It consists of 2 heavy chain and 2 light chain variable regions of murine anti-CD20 antibody coupled to the human IgGκ region. Its targeting of the B-cell population bearing the CD20 surface marker results in a selective and transient depletion of the B-cell population through several mechanisms, including antigen-

TABLE 1. New Agents for the Treatment of Rheumatoid Arthritis and Their Targets for Disease Modification

	Agent	Mechanism/Target
On the horizon	Rituximab	Monoclonal antibody against CD20 surface antigen; B-cell depletion
	MRA (atlizumab)	Monoclonal antibody against IL-6 receptor
	Abatacept	Fusion protein; T-cell modulator (blocks costimulation)
Over the horizon		
Cytokine modulation	GW3333; TMI-005	Inhibitors of TACE
	SCIO-469	p38 MAP kinase inhibitor
	CDP-870	Human monoclonal antibody against TNF-α; pegylated for long half-life
	CNTO 148	Human monoclonal antibody against TNF-α
	IL-1 TRAP	High-affinity solubilized IL-1 receptor
	Pralnacasan	ICE inhibitor (phase IIb trials suspended)
	AMG 714	Human monoclonal antibody against IL-15
B-cell targets	PRO70769	Humanized monoclonal antibody to CD20 antigen on B cells
	Belimumab	Human monoclonal antibody to BLyS
	TACI-Ig	Solubilized fusion protein of BLyS receptor
Adhesion molecule targets	Alefacept	Fusion protein of the LFA-3 receptor
Bone remodeling	Zoledronic acid	Bisphosphonate; inhibition of osteoclast activation
	AMG 162	Monoclonal antibody to RANKL; modulates bone remodeling
Chemokine inhibition	ABN912	Human monoclonal antibody against CCL2/MCP-1 chemokine

dependent, cell-mediated cytotoxicity and complement-dependent cytotoxicity.[24] Clinical administration of rituximab may be expected to result in B-cell depletion in the peripheral blood supply, and possibly in the synovium and central lymphoid organs.[25]

In a double-blind, placebo-controlled trial, patients (n = 161) with an inadequate response to methotrexate were randomized to treatment with methotrexate monotherapy, a single course of rituximab on days 1 and 17, rituximab plus cyclophosphamide, or rituximab plus methotrexate.[26] In all groups receiving rituximab, nearly complete B-cell depletion (>90%) was observed (Fig. 1). These levels of B-cell depletion were maintained over the 24 weeks of follow up, with some recovery observed between 24 and 48 weeks, by which time the level of B cells in the rituximab groups was 20% to 40% of baseline values.[27] At the end of 48 weeks, the ACR responder rates were higher among patients in the rituximab groups compared with methotrexate alone (Fig. 2). Importantly, despite substantial B-cell depletion, the incidence and severity of adverse events was observed to be similar to that of methotrexate alone with no significant differences in infectious complications and a lower incidence of RA exacerbation among patients taking rituximab. However, these data are for only a single course of therapy, and additional evaluation is needed to determine the efficacy and safety of rituximab using multiple courses of treatment as well as in combination with corticosteroids and DMARDs other than methotrexate.

Similar to TNF-α, IL-6 is a pleiotropic cytokine with proinflammatory activity, including activation of T cells, activation of osteoclasts, and induction of autoantibodies.[28] Consequently, blocking ligand access to its receptor may be considered an appropriate approach to disease modification. MRA (atlizumab) is a humanized monoclonal antibody that targets the IL-6 receptor. A recent dose-ranging study, CHARISMA (Chugai Humanized Antihuman Recombinant Interleukin-6 Monoclonal Antibody), evaluated 3 doses of MRA as both monotherapy and in combination with methotrexate in patients with an inadequate methotrexate response.[29,30] Although the highest dose used, 8 mg/kg, demonstrated efficacy as monotherapy, the best efficacy was obtained in combination with methotrexate, resulting in a greater proportion of patients achieving ACR 20, 50, and 70 responses than with methotrexate alone (Fig. 3).[29] Additionally, a higher percentage of patients achieved remission (disease activity score [DAS] 28 $\leq$ 2.6) in this group compared with methotrexate monotherapy (14% versus 0%), and normalization of acute-phase reactants was observed in a majority of patients.[30] However, a number of treatment-related serious adverse events were reported among patients taking MRA, including 5 serious infections (with 2 cases of sepsis), 5 cases of anaphylaxis, and a demyelinating event.

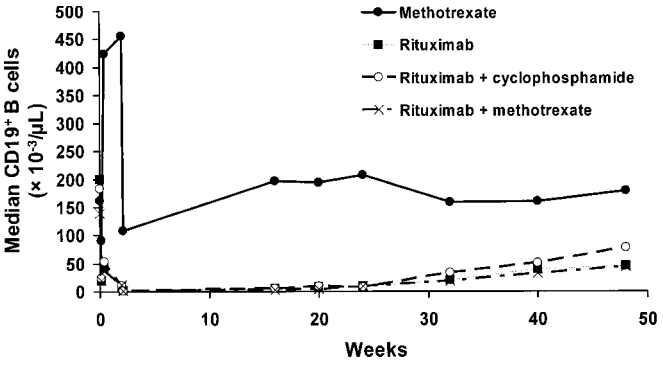

FIGURE 1. Depletion and recovery of CD19 B cells in patients with rheumatoid arthritis treated with rituximab. CD19 is a surface antigen that is coexpressed on CD20-bearing B cells. Used with permission of Nahir et al.[27]

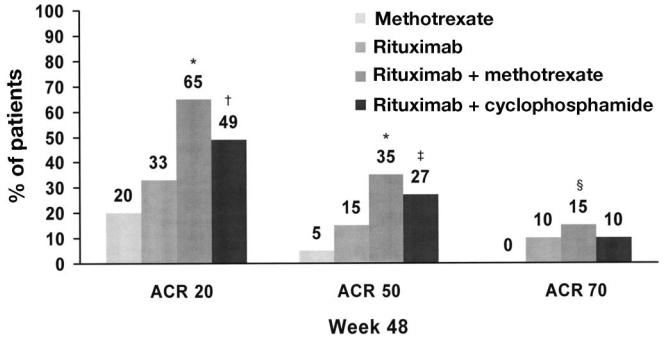

FIGURE 2. American College of Rheumatology responder rates at 48 weeks in a trial of rituximab in patients with rheumatoid arthritis who failed methotrexate therapy. Comparisons are against methotrexate monotherapy: *P = 0.001; †P = 0.01; ‡P = 0.002; §P = 0.03. Adapted with permission from Edwards et al.[26]

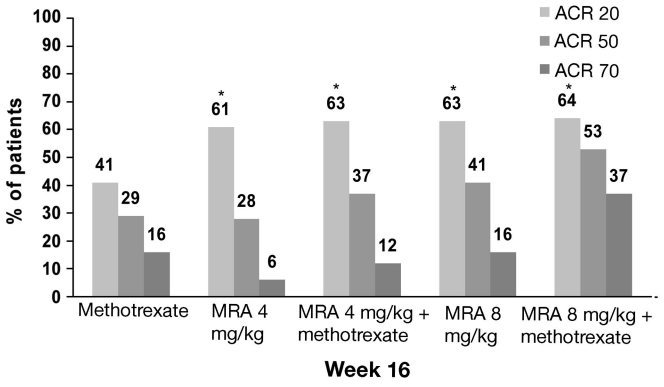

FIGURE 3. American College of Rheumatology responder rates at 16 weeks in a trial of MRA (atlizumab) in patients with rheumatoid arthritis who failed methotrexate therapy. *$P < 0.05$ versus methotrexate monotherapy. Data from Maini et al.[29,30]

Furthermore, several safety issues were noted in patients administered MRA. In addition to abnormalities of liver function (elevated transaminase levels), especially with combination therapy, increases in total cholesterol, high-density cholesterol, and total triglycerides were observed, although no overall change in the atherogenic index was reported.[29] These side effects may be related to the abrupt withdrawal of the homeostatic functions of IL-6.

A central role of T cells in the orchestration of the inflammatory response that accompanies the joint destruction associated with RA, and the identification of a dual signal for T-cell activation, suggested a potential target for therapy. The development and evaluation of abatacept, a soluble fusion protein that attenuates the activation of T cells by modulating the costimulatory pathway, has shown promise for the treatment of RA and is the subject of an accompanying article in this supplement.[31]

OVER THE HORIZON: BIOLOGIC RESPONSE MODIFIERS AND OTHER TARGETED THERAPIES CURRENTLY IN DEVELOPMENT

Although the previously mentioned therapeutic strategies that are on the horizon represent drugs of imminent value to the RA therapeutic armamentarium, many potential and hypothetical targets are actively being evaluated using a variety of BRMs and other drugs that are still in the early phases of clinical development. Consequently, these agents may be considered over the horizon, and their entry into clinical practice is still some time in the future.

Cytokine Modulation

Because the inflammatory process is at least partially under the control of cytokines, modulation of these regulators of inflammation continues to be a goal in the development of new agents. Although technically, some of the anticytokine therapies are not biologic agents, they nevertheless attenuate the inflammatory response by modifying biologic response pathways. Mechanisms of anticytokine therapies that are currently used or are under evaluation for the treatment of RA are shown in Figure 4.

Among the cytokines, TNF-α continues to be a popular target for blockade, although not necessarily in the same manner as with the agents discussed previously. Activation of TNF-α requires conversion of the precursor membrane-bound form into the mature soluble form by a metalloproteinase called TNF-α conversion enzyme (TACE).[32] Theoretically, inhibition of TACE should reduce the concentration of soluble TNF that would be available for regulation of inflammation. Current TACE inhibitors that are in development are dual inhibitors of TACE and matrix metalloproteinases (MMPs), which degrade the extracellular matrix and result in joint destruction. Although it is still unclear which specific MMPs will provide the best therapeutic target in RA, several MMPs are expressed in the synovial fluid of patients with RA[33,34] and a decrease in MMP concentration occurs in patients undergoing remission.[35] One dual inhibitor, GW3333, in an adjuvant arthritis animal model, inhibited both the inflammatory response and joint destruction in contrast to an anti-TNF monoclonal antibody, which had little effect.[36] Another dual inhibitor, TMI-005, is in phase II clinical trials.[37] Although these agents have the advantage of oral bioavailability, further evaluation of their efficacy and safety is required, especially during prolonged use.

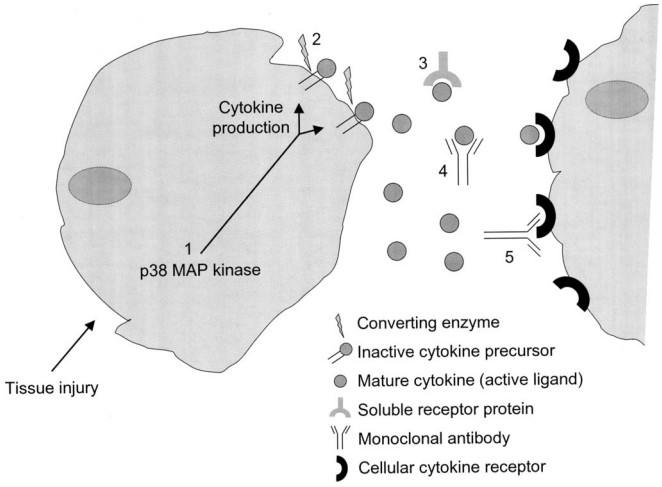

FIGURE 4. Simplified schematic of the targeted mechanisms of cytokine modulation in the treatment of rheumatoid arthritis. 1) Inhibition of p38 MAP kinase; 2) inhibition of converting enzyme; 3) soluble receptor protein; 4) monoclonal antibody to cytokine; 5) monoclonal antibody to cellular cytokine receptor.

Similarly, inhibition of p38 mitogen-activated protein (MAP) kinase may be expected to reduce the inflammatory response. MAP kinase is part of the intracellular signaling system that regulates several pathways involved in RA progression and joint destruction. It not only regulates the production of proinflammatory cytokines, including TNF-α and IL-1, but it is also implicated in osteoclast differentiation and the regulation of other proinflammatory pathways such as the cyclooxygenase/arachidonic acid cascade.[38] Although p38 MAP kinase inhibition would have the advantage of oral administration, the function of MAP kinase in physiological homeostasis suggests that inhibition of MAP kinase may represent a delicate balance between efficacy and toxicity.[39] This balance was highlighted by VX-745, a compound that demonstrated proof of concept for MAP kinase inhibition in a small (n = 59) clinical trial of 12 weeks' duration in patients with established RA.[40] In the trial, the proportions of patients with ACR 20 and ACR 50 responses were higher in the active-treatment group compared with the placebo group (43% versus 17% and 17% versus 0% for ACR 20 and 50, respectively), and the active-treatment group also showed

greater improvement in tender and swollen joint counts. However, further evaluation of this drug was terminated as a result of neurotoxicity in long-term animal studies.[41] Because p38 MAP kinases represent a family of similar isoforms, selective targeting to specific members may be useful in minimizing inhibition of the homeostatic functions of these regulatory proteins. Another MAP kinase, SCIO-469, is currently undergoing phase II clinical trials in patients with RA.[42]

Several BRMs that directly target TNF-α are also under evaluation. CDP-870 is a PEGylated (linked to polyethylene glycol) humanized antibody fragment that binds to TNF-α.[43] The PEGylation increases the circulating half-life to approximately 14 days to prolong availability and enhance exposure. In an 8-week, randomized, double-blind, dose-ranging study in patients with RA who failed DMARD therapy (n = 36), a single dose of 20 mg/kg, the highest dose evaluated, demonstrated clinical efficacy with ACR 20 and 50 response rates (75% and 50%, respectively) that were similar to other anti-TNF-α monoclonal antibodies.[43] During the trial, only low rates of generation of anti-CDP-870 antibodies were observed. Although the treatment was reported to have an adequate safety and tolerability profile, further evaluation is required over a greater duration of time and with multiple administrations.

Yet another humanized monoclonal antibody to TNF-α, CNTO 148, has been reported to be undergoing clinical trials, and appears promising.

In addition to TNF-α, agents modulating other cytokines are also in development. Cytokine "traps" are designer molecules that are based on the ability to construct a soluble cytokine receptor with high affinity for the ligand.[44] In the case of IL-1 TRAP, this has been accomplished by forming a recombinant molecule consisting of 2 receptor components (IL-1 receptor type 1 and IL-1 receptor accessory protein) to provide the high affinity that is then solubilized by linkage to human IgG1 Fc. IL-1 TRAP is given weekly subcutaneously, but in a recent dose-ranging study, even the highest dose (100 mg) failed to achieve a statistically significant difference from placebo for the primary end point (ACR 20 response rate; 41% versus 31% for placebo).[45] However, the dose-dependent reductions from baseline that were observed for acute-phase reactants, and the significant improvements in DAS 28 scores in the active-treatment group compared with placebo, suggest that further evaluation may be warranted.

Both IL-1 and IL-18, which has also been implicated in the RA inflammatory response,[46] require conversion from a precursor into an active form in a manner similar to TNF-α. Inhibition of this interleukin-converting enzyme (ICE) is a rational approach to reducing proinflammatory activity.[47] Pralnacasan was developed as an orally available, small-molecular-weight nonpeptide with inhibitory properties for ICE. Its efficacy in reducing joint damage in osteoarthritis was demonstrated in an animal model.[48] In human RA, pralnacasan provided a statistically significant reduction in the inflammatory response (acute-phase reactants) compared with placebo, although there were no significant differences between treatment groups for ACR 20 response rates.[49] However, observed hepatic toxicity during long-term animal studies resulted in a suspension of the phase IIb clinical trial program, although the phase I program is likely to continue.[50]

IL-15 is another pleiotropic cytokine, which, in its proinflammatory mode within the RA synovium, acts both as a chemoattractant for T cells and as a stimulator of T-cell activation. This activation results in production of other inflammatory cytokines, including TNF-α and IL-17, which induces osteoclastogenesis.[51–53] Results from a placebo-controlled, double-blind, dose-ranging study (n = 110) of AMG 714, a human monoclonal antibody directed toward IL-15, suggested the clinical benefits of this targeted therapy.[54] Patients with an inadequate response to previous DMARDs and naive to other biologic therapies but on stable methotrexate therapy were randomized to placebo or increasing doses of AMG 714 therapy. At the highest dose evaluated, 280 mg, a significantly greater proportion of patients (62%) achieved an ACR 20 response than with placebo (26%; $P = 0.017$). Importantly, the incidence of adverse events and infectious events at this dose, 57% and 33%, respectively, were similar to placebo, 57% and 35%, respectively.

B-Cell Targets

In a manner similar to rituximab, PRO70769 is a monoclonal antibody that targets the CD20 antigen on mature B cells and may be expected to result in B-cell depletion. However, in contrast to rituximab, PRO70769 is humanized and it is therefore likely to have more favorable attributes such as less immunogenicity with long-term treatment. It is currently in phase I/II clinical trials.[55]

B-lymphocyte stimulator (BLyS) protein, also known as B-cell-activating factor (BAFF), is a member of the TNF family of cytokines. Together with its receptor transmembrane activator and calcium modulator and cyclophilin ligand (CAML) interactor (TACI),[56] it forms a ligand–receptor complex with multiple functions. BLyS is integral to B-cell differentiation and activation, resulting in a mature B cell that can subsequently produce antibody and express autoreactivity.[57,58] Additionally, BLyS functions as a costimulatory signal in T cell-mediated responses.[59] Several clinical observations have supported a role of BLyS in autoimmune diseases such as systemic lupus erythematosus and RA. These observations include elevated serum and synovial fluid concentrations of BLyS in a subpopulation of patients with these diseases[60] and production of BLyS within the synovial compartment in patients with inflammatory arthritis.[61]

Based on the role of B cells in inflammatory arthritis and the function of the BlyS–TACI pathway, interruption of

BlyS–TACI signaling is a rational therapeutic target that can be expected to reduce immunoinflammatory components through several possible mechanisms. These mechanisms include a reduction in the level of B cells by preventing mature B-cell formation, removal of survival factors for transitional B cells and existing plasma cells, reducing the antigen presentation function of B cells that potentiates an autoimmune reaction, suppression of the elevated levels of BLyS that perpetuate B-cell recruitment, and limiting T-cell costimulation.[62–65]

Like with other cytokine–receptor complexes, therapeutic approaches to modulation of biologic responses resulting from BlyS–TACI interactions have focused on developing a monoclonal antibody to the ligand, BLyS, and a solubilized fusion receptor protein.

Belimumab (LymphoStat-B) is a human monoclonal antibody to BLyS[66] that has been reported to have a favorable safety profile and results in significant B-cell depletion in patients with systemic lupus erythematosus.[67] It is undergoing phase II trials in RA.[68]

TACI-Ig is a fusion protein consisting of the BlyS-binding domain of the TACI receptor linked to human IgG1 Fc. In murine models of arthritis, TACI-Ig reduces inflammation with a concomitant reduction in joint destruction and disease activity.[62,63] It is currently in clinical trials for systemic lupus erythematosus.

Adhesion Molecules

Adhesion molecules are not only primary mediators of the attachment and transmigration of inflammatory cells into the synovial compartment, but they are also capable of signal transduction and amplification of the inflammatory cytokine cascade that occurs in RA.[69] The observation of increased serum levels of adhesion molecules such as the intracellular adhesion molecules (ICAMs) and selectins in patients with RA[70,71] and their identification as markers for disease severity[72] suggested that these molecules may be exploited as a therapeutic target. Although an early study using a mouse monoclonal antibody to ICAM-1 reported a modest clinical response,[73,74] further evaluation was precluded by the immunogenic response that developed to the murine-derived antibody after multiple dosing.[75]

This immunogenic response may be reduced by use of humanized monoclonal antibodies, which inhibit lymphocyte infiltration into areas of inflammation.[76] However, a clinical trial for efalizumab, a monoclonal antibody to lymphocyte function-associated antigen-1 (LFA-1), which interacts with ICAMs, was suspended for lack of efficacy.[77]

The leukocyte function-associated antigen-3 (LFA-3) is the object of another BRM developed to target adhesion molecules. Alefacept, which is already approved for the treatment of plaque psoriasis, is a fusion protein consisting of the CD2-binding domain of LFA-3 linked to the Fc portion of IgG1. The binding of alefacept to CD2 on a subset of T cells blocks the CD2/LFA-3 interaction that results in T-cell stimulation.[78] Although a 12-week course of weekly intravenous injections of alefacept in combination with methotrexate followed by a 12-week follow up suggested clinical benefits superior to placebo, the ACR response rates were only modest,[79] and additional data are unavailable on its potential use as a treatment in RA.

Bone Remodeling

The differentiation and activation of osteoclasts, cells actively involved in bone resorption, is in large part responsible for the bone loss associated with progressive RA.[80] Although targeting osteoclasts may be expected to slow or reverse bone degradation, this approach does not necessarily impact the underlying etiopathogenesis of the disease. Nevertheless, 2 approaches to the treatment of RA are being evaluated that have specific effects on osteoclasts and are likely to result in bone protection, if not disease modification.

Bisphosphonates are compounds that have been recognized as useful agents in the treatment of bone diseases such as osteoporosis, but have had limited exposure for the treatment of RA. Their mechanisms of action include inhibition of osteoclast metabolic pathways as well as induction of apoptosis.[81] Although 1 bisphosphonate, etidronate, was shown to have no effect on radiologic progression of RA,[82] another compound of this class, zoledronic acid, was protective and prevented bone loss in animal models of arthritis.[83,84] Recent data from a small (n = 39), randomized, placebo-controlled trial in patients with early RA evaluated by magnetic resonance imaging (MRI) and radiography showed structural benefits after 26 weeks in patients taking zoledronic acid at weeks 0 and 13.[85,86] Compared with placebo, zoledronic acid resulted in reductions in erosions for all outcomes and reached significance for the number of wrist bones with erosions and the number of hand and wrist bones with erosions (Fig. 5). Additionally, there was a 61% decrease in the mean change in hand and wrist erosions and significant increases in bone mineral density in hands and wrists compared with placebo. Although these results are promising, further evaluation is necessary to determine the safety of this drug and if these structural benefits translate into long-term clinical benefits.

The other approach to bone remodeling focuses on the receptor activator of nuclear factor-κB (RANK) and its ligand, RANKL. This cytokine–receptor complex is a member of the TNF family, and together with osteoprotegerin, it regulates the formation and activation of osteoclasts (Fig. 6).[87] Binding of RANKL to RANK on osteoclast precursor cells results in the differentiation of these cells to mature osteoclasts. RANK is also expressed on mature osteoclasts and these cells become activated on binding RANKL. The soluble RANKL decoy protein osteoprotegerin binds to

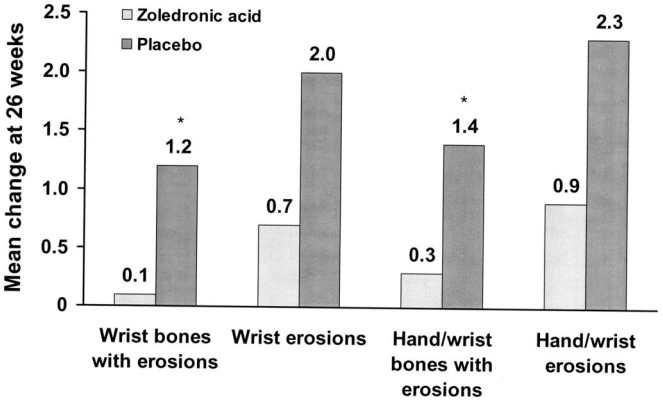

FIGURE 5. Changes in hand/wrist erosions at 26 weeks in a placebo-controlled trial of zoledronic acid in patients with rheumatoid arthritis. Erosions evaluated using magnetic resonance imaging and radiography; $*P < 0.05$ versus placebo. Data from Jarrett et al.[85,86]

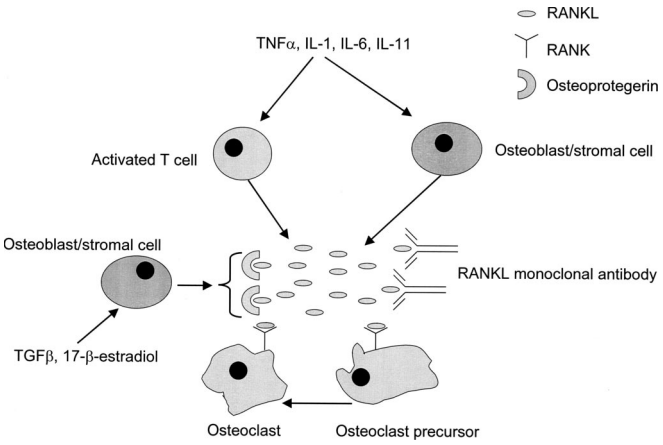

FIGURE 6. The RANKL/RANK/osteoprotegerin pathway of bone resorption as a therapeutic target in rheumatoid arthritis.

RANKL, limiting the amount of ligand available for RANK binding. The RANKL/osteoprotegerin ratio determines the extent of bone resorption, and consequently, appropriate exogenous modulation of the RANKL/RANK interaction by tipping the balance in favor of osteoprotegerin may reduce osteoclastogenesis and provide some degree of bone protection. A human monoclonal antibody to RANKL, AMG 162, has demonstrated proof of concept and efficacy in reducing bone loss with twice-yearly dosing in a clinical trial in postmenopausal women.[88,89] AMG 162 is currently in phase II clinical trials for the treatment of RA.

Chemokine Inhibition

Chemokines are cytokine-like agents with chemotactic properties for leukocytes, recruiting and activating these cells during physiological homeostasis as well as during inflammation. In RA, synovial tissue is characterized by increased levels of chemokines that further promote the inflammation and facilitate the extravasation of leukocytes from the circulation into the inflammatory compartment, resulting in a heavy infiltration of leukocytes.[90] These molecules have recently been considered potential therapeutic targets, and 1 chemokine, CCL2/MCP-1, which promotes transmigration of monocytes, is significantly elevated in the synovium and the peripheral blood in patients with RA.[90]

ABN912, a fully human monoclonal antibody to CCL2/MCP-1, was developed and evaluated in a small (n = 43), randomized, placebo-controlled, double-blind, dose-ranging study in patients with RA who had an inadequate response to methotrexate.[91] Contrary to what was expected, there was not only an absence of clinical response to treatment, but patients administered the antibody had a dose-dependent increase in free MCP-1 concentrations, which also correlated with a significant increase from baseline in a primary marker of inflammation, C-reactive protein, and a trend toward increased levels of synovial macrophages. Although the disappointing results were not explained, it is clear that further assessment is required to characterize the pathways involved.

CONCLUSIONS

The commercial availability of 4 BRMs with demonstrated clinical and radiographic efficacy for the treatment of RA has expanded the range of available therapies, and it provides a greater chance of controlling this disease in many patients. However, insufficient efficacy, development of tachyphylaxis, and safety concerns remain major issues in patients using these agents.

Evidence from the use of these BRMs and a greater knowledge of the immune and inflammatory pathways contributing to joint destruction suggest that modulation of these pathways holds promise in the treatment of RA and other autoimmune diseases. Although many drugs are beyond the clinical horizon, and it is still too early to tell which pathways and what drugs may be the most effective, new mechanistically distinct biologic agents such as abatacept and rituximab have appeared on the horizon. These BRMs have demonstrated therapeutic potential in clinical trials, although still more evaluation is necessary to confirm their efficacy and safety in wider clinical practice. Nevertheless, the development of these drugs combined with the further elucidation of pathogenic pathways and the advent of new technologies has increased the hope that disease modification and remission in RA is a realistic goal.

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