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Biological Agents in the Treatment of Rheumatoid Arthritis

Joan M. Von Feldt, M.D., Michael Maldonado, M.D., Peter E. Callegari, M.D., and William V. Williams, M.D.

From The Department of Medicine, Rheumatology Division, University of Pennsylvania School of Medicine.

Address correspondence to: Joan M. Von Feldt, M.D., 570 Maloney, University of Pennsylvania School of Medicine, 3600 Spruce St., Philadelphia, PA 19104.

Abstract: Rheumatoid arthritis (RA) remains a difficult treatment issue for patients with polyarticular disease. Therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids do not prevent disease progression. Several disease modifying anti-rheumatic agents (DMARDs) are in use, but they are ineffective in many patients and have a high incidence of side-effects. These issues have prompted the development of biological agents, which have been evaluated for efficacy in RA. These biologicals include antibodies to lymphocyte subsets, antibodies to cytokines (such as tumor necrosis factor alpha), and recombinant soluble receptors. Some of these agents have shown striking effects in controlling disease activity, whereas others have been less effective. This article will summarize the clinical experience with these biologicals, discuss their likely use when approved, and discuss their effect on our understanding of basic disease mechanisms.

Introduction

Rheumatoid arthritis (RA) is a polyarticular inflammatory synovitis that affects up to 1% of the population [20,24,25]. While treatment of RA is available, such as anti-inflammatory and immunosuppressive drugs, the disease is usually relentlessly progressive, significantly disabling, and/or crippling its victims. Current therapies that are most effective borrow from the chemotherapeutic regimens pioneered in oncology and transplantation. These therapies, such as methotrexate, can be quite effective in a number of patients (although not universally so). However, the anti-cellular properties of these drugs and the need for chronic use often leads to untoward side-effects. As such, novel therapeutics are needed that more specifically target the relevant steps in disease pathogenesis.

The emergence of the use of biological agents for the treatment of RA is based on recent advances in the understanding of the pathogenesis of RA. These advances have come about by delving into the pathology of the synovial pannus, and the genetics and immunology underlying disease pathogenesis.

Pathogenesis of RA

Pathologically, RA is characterized by proliferation and activation of synovial tissue. The synovial tissue in RA, termed the "pannus," becomes infiltrated with lymphocytes that are predominately of the CD4+/T helper phenotype. In addition, the synovial lining cells, of which there are macrophage-like and fibroblast-like subgroups, become activated and invade the adjacent cartilage and bone in a manner that has been compared with cancerous [24,25].

RA has been said to be a disease of T-lymphocyte/macrophage immunoregulation [31], based both of the presence of both cell types in the synovial tissue, and on the high level of monocyte/macrophage activation seen [50]. The pathology of RA is strikingly similar to that seen in animal models such as collagen-induced arthritis (CIA). CIA is induced in susceptible strains of mice by immunization with type II collagen, which is expressed only in articular cartilage. In CIA, T cell lines and clones specific for type II collagen are capable of transferring the disease to naive syngeneic mice [28]. In addition, susceptibility of CIA is governed by the class II MHC locus [23,27]. Mice that lack the genetic background characterized by a sequence motif in the MHC class II molecule I-A beta chain are not susceptible to developing CIA. This situation is exactly analogous to RA, where a conserved motif in the HLA-DR beta chain is genetically linked to disease susceptibility [21,22,45]. In CIA, the genetic linkage is attributable to the function of class II MHC molecules, which bind to type II collagen peptides and present them to arthritogenic T-cell receptors. A similar role has been postulated for the HLA-DR molecules in RA.

In RA, synovial T cells are predominantly of the helper (CD4+) phenotype, more specifically the CD4+CDw29+ subset [69]. Such CD4+ T-cells are typically activated by an antigenic peptide complexed with class II MHC molecules, such as HLA-DR. Many studies indicate high levels of HLA-DR expression in rheumatoid synovium [20,24,25]. The high HLA-DR expression suggests that persistent antigen presentation leads to stimulation of the T-cell infiltrates, which, in turn produce cytokines inducing synovial activation and joint destruction. The result is an autoimmune cycle of persistent antigen presentation, T-cell stimulation, cytokine secretion, synovial cell activation, and joint destruction. The antigen(s) that may trigger this response are as of yet unknown. A current view of the pathogenic scheme in RA is depicted in Figure 1.

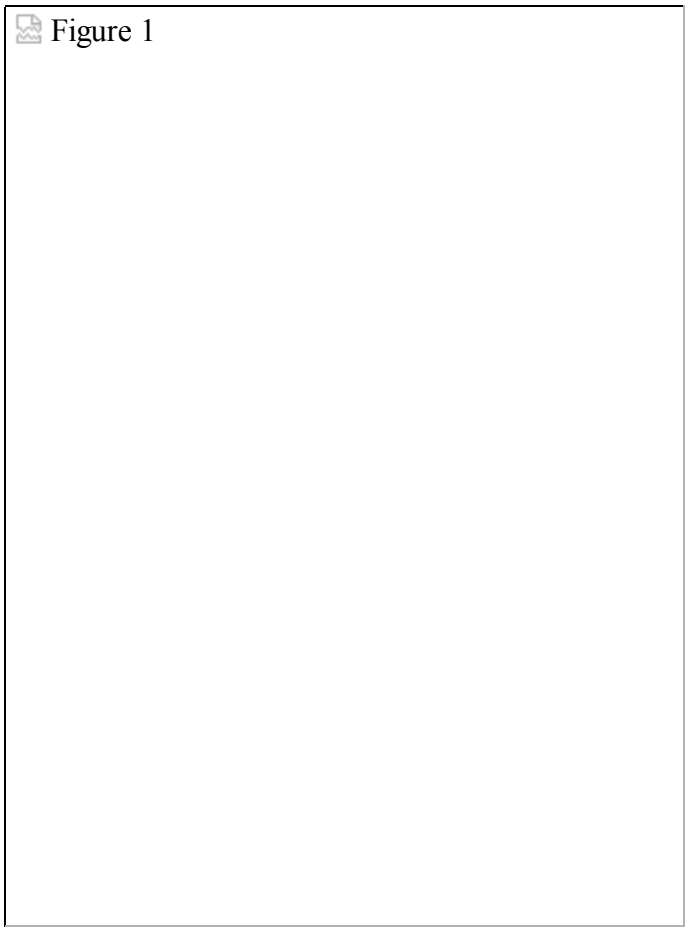

Fig. 1. Postulated cellular events involved in the pathogenesis of RA. HLA-DR, human major histocompatibility complex (MHC) class II molecules; Ag, antigenic peptide; TCR, T-cell receptor; CD4, a surface molecule on a T-cell subset that responds to antigens presented by class II MHC molecules; CD80/86, costimulatory molecules (CD80 or CD86) needed for T-cell stimulation; CD28, co-stimulatory receptor for CD80/86. In step 1, presentation of an unknown antigen by synovial antigen presenting cells triggers a CD4+ T-cell response. In step 2, activated T-cells secrete cytokines that, in turn, elicit fibroblast activation (with resultant synovial proliferation), B cell activation (with rheumatoid factor production), and macrophage activation. In step 3, the activated macrophages secrete monokines that result in autostimulation of macrophages and macrophage-like synoviocytes to secrete degradative enzymes, with resulting joint destruction. Step 3 may or may not depend on the continued presence of T-cells.

As can be seen in Figure 1, the different stages of RA pathogenesis may be differentially responsive to interventions. For example, strategies aimed at the T-cell component may be more effective earlier in the disease process, while those aimed at the macrophage component may also be effective later on in the disease. The recent availability of a variety of biological agents targeting specific cell types, cytokines, and pathologic events has made the investigation of the role of these factors in human RA a reality in recent years. The purpose of this review is to summarize these studies, what we have learned from them, and the role of these agents in the future treatment of RA (Table 1).

Table 1. Biological agents in rheumatoid arthritis (RA)

Biologic	Trade name(s)	Biologic effect	Adverse effects (AE)	Clinical efficacy

Anti-CD4 (T cell depleting)	cM-T412	Depletion of CD4 subsets of T cells	Long-term depletion of CD4 cells	Limited early success hampered by AE
Anti-CD4 (T cell non-depleting)	IDEC-CE9.1® mAB 4162W94 Orthoclone OKTcdr4a	"disabling" CD4 subsets of T cells	Emergence of leukocytoclastic vasculitis in high dose group Long-term depletion of CD4 cells	Highly effective against placebo
Anti-CD5 ricin-linked Immunoconjugate (CD5-IC)		Delivering a toxic agent (ricin A chain) to specific cells with CD5 on their cell surface (T cells, subset of B cells and thymocytes)		Not better than placebo
Anti-CD7	CHH-380	Depletion of periperal CD 7 cells		Modest response in early studies
Anti-CD52	CAMPATH 1H	Depletion of human lymphocytes monocytes and macrophages	Long-term depletion of CD4 cells	Significant clinical benefit
Gamma interferon (gammaIFN)		Replacement of gammaIFN (relatively deficient in rheumatoid synovium) and favorably alter immunoregulation		Five studies with conflicting reports
Anti-TNFalpha	CDP571 HTA cA2 (Avakine®)	Depletion of TNFalpha, a monokine in a dominant position within the cytokine cascade	Development of antinuclear antibodies (ANA) (without clinical symptoms) Potential risk of malignancy	Highly effective against placebo
Soluble forms of TNFalpha	TNFR-Fc (Embrel)		Development of ANA (without	Good clinical

receptors (TNFR)	Anti-TNFR 55-IgG1		clinical symptoms) Potential risk of malignancy	response
Anti-ICAM-1 (CD54)		Inhibition of lymphocyte and leukocyte migration into the joint		Clinical responses seen in 50--75% of patients

Specific Agents

Use of T-cell depleting agents

Monoclonal antibodies (m Ab) directed at cell surface markers that identified lymphocytes were among the first biologicals to enter clinical trials in patients with RA. These agents were mostly targeted at T-cells (either broadly or at subsets), although at least one agent had a broader pan-lymphocyte specificity. Their expected mechanism of action was, many times, not clearly outlined. The binding of the mAb to the cell surface marker was at least expected to interfere with proper function by blocking normal function. They could also be expected to lead to the elimination of the coated cells through complement-mediated depletion or other mechanism. Early reports of the use of theses agents found them to be well tolerated, and some agents demonstrated enough efficacy to enter phase II and III trials and encourage the identification of other candidate agents. Most subsequent work, however, has showed these agents to be of marginal benefit under controlled conditions, and some have even demonstrated significant and sobering side effects.

Anti T-cell agents were logical early choices for this type of therapeutic intervention attributable to the prevailing understanding that T-cells were central to the pathogenesis of RA. Experimental work in mouse models of RA and diabetes, among others, demonstrated that these autoimmune syndromes could be prevented and even treated with the use mAbs directed at lymphocytes, especially the CD4 T-cell co-receptor. Whereas the results of these experiments in established disease models were less encouraging with the use of single agents, some combinations suggested that there was room for improved therapy.

Trials in RA patients, as in other diseases, are hampered by the inherited antigenicity of the mAbs that are primarily animal in origin. The use and repeated exposure to mAbs of mouse origin, for example, leads to the development of HAMAs (human anti-mouse antibodies) with neutralizing or sensitizing capability. The humanizing of these agents, by engineering chimeric antibodies in which all but the antigen binding portion of the mAb are replaced by human derived components, has mostly succeeded in preventing this undesired events.

The first and most popular target used was directed at the CD4 co-receptor that principally identifies the T-helper subset. The first reagents used were unmodified mouse derived mAb (MAX16H5, MT151, BL4 and B-F5) that elicited significant HAMA production and did not receive as much subsequent attention as chimeric agents. cM-T412 is an anti-CD4 humanized chimeric mAb that underwent extensive clinical testing [9,41,61]. In spite of early successes, two double-blind, placebo-controlled studies investigating monthly single-dose administrations

demonstrated no benefits but did note significant and long-lived depletion of circulating CD4+ cells in the patients treated with the agent [43,60]. No opportunistic infections were noted during these trials, or in 30-month follow-up evaluations, in spite of persisting peripheral blood CD4+ T cell depletion [42]. A second group using the same agent attempted to demonstrate that the lack of efficacy may be attributable to the dosing schedule [10]. Daily infusions, followed by weekly infusions, were more effective at "coating" CD4+ T cells in synovial fluid, and this appeared to correlated with the degree of clinical improvement. Follow-up studies; however, suggested that the activated/memory CD4+ subset was selectively resistant to the effects of the anti-CD4 monoclonal antibodies [59].

More recent work directed at the CD4 co-receptor used mAb with different properties. Unlike their predecessors, these agents seem not to cause depletion of peripheral CD4+ T-cells. Instead, they seem to simply interfere with the proper function of these cells by coating the co-receptor without depletion of the targeted cells. This may allow for both the use of higher doses, which could reach all CD4+ T cells, especially in synovium, and avoid the deleterious long-term depletion of CD4+ T cells seen with other agents. The first of these "non-deleting" agents was the Primatized® IDEC-CE9.1 mAb [36]. Open labeled studies show no adverse events with only transient lowering of peripheral CD4+ T-cell counts. A double-blind, placebo controlled trial of 136 RA patients was then performed. Three dose groups were randomized to receive a twice weekly intravenous infusion. The agent seemed highly effective compared with placebo, in a dose-dependent fashion. The higher, most efficacious, dose group, however, had to be discontinued because of the emergence of leukocytoclastic vasculitis. Eight of the patients, similar to earlier agents, showed significant lowering of CD4+ T-cell levels (lasting over 3 months in five patients). Additional studies demonstrated that clinical improvement correlated with a decrease in the number of activated lymphocytes found in blood [58]. Two additional "non-depleting" agents are also under investigation. 4162W94 is a humanized mAb that was reported to decrease TNF and IL-6 levels in synovial fluid along with a clinical response in a dosing trial of 24 active RA patients [11]. Orthoclone OKTcdr4a was also reported to provide immediate, although temporary, benefits without altering the number of circulating CD4+ T-cells in an initial trial [54].

A notable, novel approach used a murine anti-CD5 mAb conjugated to a ricin A chain, termed anti-CD5 ricin-linked immunoconjugate (CD5-IC) [56]. The ricin A chain inhibits protein synthesis and is, therefore, highly toxic. By complexing with a mAb directed at CD5, which is expressed T-cells, thymocytes and a subset of B cells, a broad, mainly T-cell specific immunosuppressive effect, was hoped. A multi-center, double-blind, multiple-dose, placebo-controlled study of CD5-IC did not, however, prove to be better than placebo and had dose-dependent adverse events [46].

The CD7 molecule, found on T-cells, thymocytes, and natural killer cells, is involved in T-cell activation and is capable of potent immunosuppressive effects in animal models. These cells were targeted with the use of CHH-380, a humanized form of the mouse anti-CD7, RFT-2 [34]. Depletion of peripheral CD7+ cells was documented along with modest responses in preliminary studies but no subsequent experience was reported.

An extensive experience has been accumulated with CAMPATH 1H, a genetically engineered rat hypervariable complementarity-determining regions grafted into a human immunoglobulin framework specific for the CD52 antigen. CD52 is predominantly expressed on human lymphocytes, macrophages and monocytes, and antibodies directed at it are lympholytic in vivo. Whereas interest in this agent for oncological therapy persists, its use in RA has met with moderate responses in

the setting of short- and long-term adverse outcomes. An initial report of a lymphocyte depleting regimen of CAMPATH-1H in eight patients with refractory RA reported significant clinical benefit with "negligible" adverse effects [30]. Subsequent trials show lesser therapeutic benefits with noticeable toxicity [39,65]. A major adverse effect of CAMPATH-1H seems to be a sustained depletion of CD4 + T-cells [5]. This long-lived depletion of peripheral circulating CD4+ T-cells is even more remarkable in light of persistence of CD4+ T -cells in the arthritic joint of treated RA patients [19].

Use of gamma interferon

Gamma interferon (gammaIFN) was one of the earliest cytokines available for evaluation in RA. Its use was based in part on the finding that gammaIFN is relatively deficient in the inflammatory mileau of the rheumatoid joint, and that replacement may alter immunoregulation and thereby synovitis. There have been many attempts to evaluate the possible role of gammaIFN in the treatment of rheumatoid arthritis [1,7,8,35,37,55,62,63]. The results are somewhat contradictory. We can discuss the studies individually.

Veys et al [63] reported the results of a small (26 patient) double-blind trial comparing recombinant gammaIFN with placebo in rheumatoid arthritis. Twenty-six patients entered the study, and dosing of the recombinant gammaIFN was decreased during the 6-month study period. They reported four drop-outs, but "a significant decrease of the joint tenderness score."

Cannon and colleagues [8] also reported their experience with a 12-week, randomized, prospective, double-blind, placebo-controlled trial of recombinant human gammaIFN. They enrolled 105 patients; 54 patients received gamma-interferon and 51 received placebo. They had 21 patients drop out of the study over the 12-week trial. They reported some clinical improvement in both groups with differences that were not statistically significant.

Sprekeler et al. [55] published the results of a 110-patient placebo-controlled trial for 12 months. They reported an improvement of both clinical parameters and laboratory parameters.

Lemmel and colleagues [35] reported the results of a multi-center placebo-controlled double-blind randomized clinical study of 91 patients with rheumatoid arthritis treated with gammaIFN. Forty out of a total of seventy-nine patients were treated with the active compound. The interferon arm was significantly more efficacious than the placebo arm in "practically all parameters investigated."

Another study was anonymously reported by the German Lymphokine Study Group in Rheumatol Int [1]. Two hundred forty-nine patients with rheumatoid arthritis were enrolled by 16 participating hospitals. One hundred seven patients were treated with gammaIFN with a control group of 116 patients. After 3 months, the treatment group had significantly improved joint indices and was able to reduce the quantity of corticosteroids administered.

Machold [37] reported their results of a double-blind placebo-controlled study in the treatment of RA. Patients treated with gammaIFN improved significantly with respect to morning stiffness, grip strength, swelling of an index joint, and erythrocyte sedimentation rate.

Veys et al. [62] evaluated the efficacy of recombinant gammaIFN in a 24-week, multi-center, randomized, double-blind trial of 197 patients with rheumatoid arthritis. Both recombinant gamma interferon and placebo produced a significant

improvement from baseline. They concluded that recombinant gamma interferon proved no more effective than placebo in this group of patients with RA.

The efficacy of gamma interferon in the treatment of rheumatoid arthritis cannot be simply summarized given these seemingly contradictory findings. There have been a number of double-blind placebo-controlled studies that have used varying dose regimens of recombinant gammaIFN, further clouding the results.

Use of tumor necrosis factor alpha (TNFalpha) antagonists

TNFalpha is another monokine implicated in the pathogenesis of RA synovitis. TNFalpha is widely expressed in RA synovium, including by lining layer cells, in lymphoid aggregates, by endothelial cells, and interestingly at the cartilage-pannus junction. Double staining reveals that most of the TNFalpha is produced by CD11b+/CD14+ macrophages, with some production by T- cells [12]. TNFalpha induces the secretion of many other cytokines, including GM-CSF [26], IL-1, [4], IL-8 [49], and proteases [29] by RA synovial cells. TNFalpha seems to be the key cytokine in these studies, as stimulation with TNFalpha induces release of other cytokines, but stimulation with other cytokines does not induce TNFalpha release [4,18]. Although only one of several inflammatory mediators produced in abundance in RA synovium, the above noted experimental data suggest that it is in a dominant position within the cytokine cascade and is therefore a prime target for directed immunotherapy in this disease.

The two TNFalpha receptors (p55 and p75) are also widely distributed in RA synovial tissue, including at the cartilage-pannus junction [12,13]. Thus, TNFalpha is highly expressed in RA synovium, as are the receptors for TNFalpha. In addition, TNFalpha induces the secretion of multiple pro-inflammatory cytokines in RA. Some of these cytokines are directly linked to cartilage degradation, such as IL-1 [20]. Thus, there is experimental evidence for a central role for TNFalpha in the pathogenesis of RA.

In murine models of RA, such as collagen-induced arthritis (CIA), TNFalpha exacerbates the disease, whereas anti-TNFalpha protects against CIA induction [57]. Anti-TNFalpha administered before the onset of CIA reduces the severity (but not the incidence) of arthritis. When administered after the onset of disease, anti-TNFalpha diminishes the severity of disease by both clinical and histologic criteria [68]. These studies emphasize the central role played by TNFalpha in arthritis pathogenesis, in both human and experimental models.

Most importantly, treatment of RA with agents that block TNFalpha (such as anti-TNFalpha mAbs) markedly diminishes disease activity [15,16]. Phase I and phase II trials have demonstrated that treatment with TNFalpha antibodies have led to significant reductions in disease activity, and that this beneficial effect is dose related. In the initial study, 20 patients with active RA were treated with 20 mg/kg anti-TNFalpha in an open trial lasting 8 weeks. In this group of patients, marked clinical improvement was seen within 6 weeks, including a drop in the Ritchie articular index from 28 to 6 and fall in the swollen joint count from 18 to 5. In addition, serologic indices of disease activity also improved, including a drop in the C-reactive protein levels (39.5 mg/L dropping to 8 mg/L at week 6). This led to a double-blind, placebo-controlled trial in 73 patients with active RA, treated with single infusions of 1 or 10 mg/kg doses of anti-TNFalpha [15]. The primary endpoint of the study was a Paulus 20% response (ACR 20 response) at week 4 of the trial. This level of improvement was seen in 2/24 placebo patients, 11 of 25 treated with low-dose anti-TNFalpha, and 19 of 24 treated with high-dose anti-TNFalpha. In addition, over half of the high dose anti-TNFalpha treated patients achieved a >50% Paulus response. Disease activity parameters including

tender and swollen-joint counts and in C-reactive protein exceeded 60% for patients receiving high-dose treatment. These studies indicate an impressive clinical response to anti-TNFalpha in RA.

An engineered human antibody, CDP571, that neutralizes human TNFalpha, has also been used in patients with active RA. The effects of the antibody were compared in a double-blind fashion with those of placebo and in an open continuation phase. CDP571 was well tolerated and caused reductions in markers of disease activity [48]. More recently, another humanized TNFalpha Ab (HTA) was studied in an open label, dose ranging safety and pharmacokinetic trial. Most of the patients in the 20 mg/kg dose group achieved an ACR 20 response and adverse effects reported are similar to other trials [17]. Whether chimeric or human engineered anti-TNFalpha monoclonal antibodies will be more effective, or less likely to develop of HAMAs (human anti-mouse antibodies), remains to be determined. There are now at least three companies with recombinant or chimeric TNFalpha antibodies in clinical trials for the treatment of rheumatoid arthritis, and it is likely that these antibodies will be commercially available by the year 2000.

Newer trials have used the antibodies in combination with methotrexate and have shown additive results. In a 100-patient trial, patients with active RA despite methotrexate treatment received infusions of 1, 3, or 10 mg/kg anti-TNFalpha antibody, cA2 at weeks 0, 2, 6, 10, and 14 weeks after randomization [2]. These treatments were administered with or without methotrexate, (7.5 mg/week) as background therapy, and were compared with a "placebo" group receiving methotrexate, (7.5 mg/week) alone. Using the ACR 20 response rate, the majority of patients had a clinical response through 16 weeks. Many of the responses were dramatic, with disease activity parameters reduced by 70--90%. A gradual relapse of disease activity occurred between 16 and 26 weeks in the 1mg/kg treatment group, whereas patients receiving 3mg/kg or 10 mg/kg continued to demonstrate a response at 26 weeks. Patients receiving anti-TNFalpha antibody -cA2 without methotrexate had a more variable, and weaker response. The better maintenance of clinical benefit is postulated to be the absence of neutralizing antibodies in patients receiving methotrexate, with a more stable anti-TNFalpha antibody -cA2 concentration. No difference in adverse effects were seen in the methotrexate plus anti-TNFalpha antibody -cA2 arm.

The cause of disability in RA is the erosive effect of the arthritis on the adjacent bone of the many joints involved in RA patients. Postulated mechanisms of anti-TNFalpha principle effects continue to evolve [38]. Metalloproteinases have been implicated in this destructive process. A recent study looked at the effect of anti-TNFalpha on serum metalloproteinase levels in RA patients [3]. Matrix metalloproteinase (MMP)-1 and MMP-3 levels were measured in serum samples from rheumatoid arthritis (RA) patients undergoing a double-blinded placebo-controlled trial with the chimeric anti-TNFalpha antibody -cA2. Both MMP-1 and MMP-3 levels were elevated in all RA patients before the commencement of the trial compared with normal controls. After anti-TNFalpha therapy, a significant decrease in serum MMP-3 and MMP-1 levels were observed. Serum MMP-3 levels correlated with C-reactive protein (CRP) both before and after anti-TNFalpha therapy, but it remains to be demonstrated that serum MMP-3 and/or MMP-1 levels reflect the cartilage and bone resorptive processes that are evident in this disease.

The increased `stickiness' of the endothelial cells in the high endothelial cell venules at the synovium has been postulated to be one of the necessities in perpetuating the inflammatory cascade at the synovium. Paleolog and colleagues looked at some of the adhesion molecules before and after treatment with the anti-TNFalpha antibody -cA2 in RA patients [47]. After treatment with anti-TNFalpha antibody, serum E-selectin, and intercellular adhesion molecule 1

(ICAM-1) levels were decreased, but no effect on vascular cell adhesion molecule 1 (VCAM-1) levels was detected. In parallel, there was a rapid and sustained increase in circulating lymphocytes. From this study, the authors concluded that decreased serum levels of adhesion molecules may reflect diminished activation of endothelial cells in the synovial microvasculature, leading to reduced migration of leukocytes into synovial joints, and thus prolonging the therapeutic effect of anti-TNFalpha in RA.

Soluble forms of TNFalpha receptors (TNFR) are now being used in early clinical trials for the treatment of rheumatoid arthritis. These trials have demonstrated efficacy of TNFalpha receptor fusion proteins in ameliorating the symptoms of the RA. In a multi-center, double-blind trial, 180 patients were randomized to receive placebo or subcutaneous injections of TNFR-Fc in three different doses twice weekly for 3 months (0.25, 2 or 16 mg/square meter) [40]. Treatment with the TNF receptor fusion protein led to significant reductions in disease activity, and the therapeutic effects were dose related. In the highest dose group, the majority of patients had an ACR 20 response. There were no dose limiting toxic effects. One hundred and six patients of this group were followed in an open label re-treatment trial. The majority of patients had an ACR 50 response at 6 months. No antibodies to the TNFR-Fc fusion protein were detected [64]. Similar to the anti-TNFalpha trials, continued treatment over months has been possible, but the patients flare once therapy is discontinued. Another TNFalpha receptor fusion protein has been studied in a randomized double blind trial, TNFR 55-IgG1 (RO 45-2081) in severe, refractory rheumatoid arthritis. The eighty patients studied had a good clinical response, that in some patients was sustained over 2 years. A few patients had a sustained effect 6--9 months after the last infusion. Anti TNFR 55-IgG antibodies were detected in some patients, and titers dropped after treatment was discontinued. Anti-nuclear antibodies were detected frequently but clinical symptoms were rare [51--53]. No malignancies have been reported with either TNFR fusion proteins.

There are potential difficulties with these antibodies, including the need for parenteral administration, but the expectation is that these antibodies will be the first generation of biologicals that can be administered to rheumatoid arthritis patients. Patients with rheumatoid arthritis have been reported to have an increased incidence of lymphoproliferative disorders, and this risk increases with the use of agents such as methotrexate and cyclosporin. As with all immunosuppressive therapy, host tumor surveillance may be diminished, and there have been three lymphoproliferative malignancies reported in patients on the TNFalpha antibody treatment, but the significance of this is not yet known, because all patients had been on immunosuppressive therapy before their use of the TNFalpha antibody treatment. Patients receiving TNFalpha antibody and TNFalpha receptor fusion protein treatment have been reported to develop anti-nuclear antibodies, and anti-double stranded DNA antibodies, although the clinical syndrome of systemic lupus erythematosus are rare.

Most of the current clinical trials are using these TNFalpha blocking agents in severe refractory RA, but the hope is that these agents can be used in induction therapy for newly diagnosed RA and perhaps alter the course of the disease. Additionally, because the biologic and clinical effect of these TNFalpha receptors and anti-TNFalpha antibodies is rapid, within 1 or 2 weeks, it is likely that these agents will be used acutely, while allowing slow-acting, disease-modifying drugs (DMARDs) to reach their maximal effect 3 months after institution. Whether these new biologic agents can be used acutely, before major stressors such as surgery, remains to be determined. It is likely that their immunosuppressive effect is similar to other DMARDs, but this has not yet been studied.

Other cytokine antagonists

In addition to TNFalpha, other monokines are implicated in the joint destruction that is seen in RA. Among these are interleukin-1 (IL-1), which is known to stimulate chondrocytes to release degradative enzymes. IL-1 also plays a role in the activation of synovial macrophages and the proliferation of synovial fibroblast-like cells. In light of these and other observations, a recombinant soluble human interleukin-1 receptor type I (rHuIL-1RI) was developed and evaluated in the treatment of RA. In a phase I/II trial with daily subcutaneous administration of rHuIL-1RI for 28 consecutive days, 4/8 patients who received the highest dose given (1,000 micrograms/m2/day) showed improvement in one of eight measures of disease activity. However, only one of the four subjects had what was considered clinically significant improvement [14]. Two patients developed dose-limiting rashes in this study.

A similar study was conducted using the IL-1 receptor antagonist protein (IRAP) [6]. This study evaluated subcutaneous administration of IRAP at 20, 70, or 200 mg given either daily, three times a week or once a week for 3 weeks. There were frequent injection site reactions (62% of subjects), and 5% had to withdraw because of these reactions. Another 3% had other serious adverse reactions unrelated to dose or frequency. As there were no placebo controls, it was difficult to assess efficacy, but daily dosing did seem more effective than weekly dosing by a number of clinical and laboratory parameters.

Interleukin-6 (IL-6) is another monokine with activities that overlap with those of IL-1. Antibodies against IL-6 have been evaluated in preliminary trials in a few patients with RA [66,67]. Clinical meaningful improvement was seen with a dose of 10 mg/day for 10 consecutive days, and these effects lasted on the average of 2 months [66].

Another approach has been to use engineered cytokines that are conjugated to toxins. One such engineered cytokine is the interleukin-2 diphtheria toxin fusion protein (DAB486IL-2). The theory is that the DAB486IL-2 will bind to IL-2 receptors on activated T-cells in the joint and delete them. A trial of DAB486IL-2 in refractory RA showed an 18% response rate [44]. This low response rate could be attributable to poor penetrance of the DAB486IL-2 into the joint, a parameter that was not investigated. However, studies such as these have led to the hypothesis that T-cells are not essential to the perpetuation of RA synovitis in the chronic phase of the disease.

Inhibition of lymphocyte migration

Lymphocytes arise in the bone marrow and have to migrate into the synovium to effect a synovial inflammatory response. One potential way to to reduce synovial inflammation would be to inhibit lymphocyte migration into the joint. This approach is being investigated with a monoclonal antibody to intercellular adhesion molecule 1 (ICAM-1; CD54), which is a lymphocyte cell surface molecule that is involved in adhesion of lymphocytes to endothelial cells and their migration into tissues, including synovial tissue. Two studies have been performed with anti-ICAM-1 therapy; one in refractory RA [33], and one in early RA [32]. Both studies showed a clinical response to short (5 day) infusion of anti-ICAM-1 in 50--75% of the patients treated. This response lasted for weeks to months, with a few exhibiting sustained clinical benefit. This suggests that lymphocyte migration in and out of the joints of RA patients is important in sustaining ongoing synovitis.

Future Prospects

These studies all point to an evolving understanding of the cellular and molecular interactions in rheumatoid synovium, which have clear therapeutic implications. The most impressive results to date have been seen with inhibitors of monokines, particularly TNFalpha. T-cell depletion strategies, which now seem to be less effective than originally hoped, may end up playing an adjunct role if these therapies become available. One potential role of these therapies of particular relevance to orthopedists is the use of these agents to cool off flares of joint disease in preparation for joint surgery. If this can be shown to be safe, it is quite likely that certain select biological agents that have clear efficacy in disease flares will become the agents of choice in this setting. This may ameliorate the need to use steroids or cytotoxic agents, given their effect on susceptibility to infection and wound healing. These issues will be of great interest to address as these agents become available.

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