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J R Kalden

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How Do the Biologics Fit into the Current DMARD Armamentarium?

JOACHIM R. KALDEN

ABSTRACT. Most disease modifying antirheumatic drugs (DMARD) are discontinued within 5 years because of loss of clinical efficacy or toxicity. As a result, there has been a concerted effort to develop new immunomodulatory agents, particularly biological agents, that block the putative proinflammatory cytokines. Among the agents developed thus far, inhibitors of tumor necrosis factor (TNF) have shown perhaps the greatest promise as therapeutic agents for rheumatoid arthritis (RA). Two TNF-blocking agents, etanercept (Enbrel®) and infliximab (Remicade®), have been approved in the US and more recently in Europe, for the treatment of patients with RA. The results of randomized placebo controlled trials have shown that both agents significantly decrease the intensity of synovitis and prevent or retard the progression of cartilage destruction, especially when combined with methotrexate. Their side effect profiles appear to be acceptable, although rare cases of lupus-like diseases and of severe infections have been reported. Although the early clinical experience with these agents has been encouraging, their longterm safety and continuing efficacy in the general population with RA, as well as in high risk patient subsets (i.e., patients with malignancies or chronic infections), remain to be determined. In addition, the costs of these newer agents must be justified on clinical grounds. Because of the questions still surrounding these new treatment principles, several consensus conferences have been held in Europe and the US to address the role of the new biologicals in the current RA armamentarium. (J Rheumatol 2001;28 Suppl 62;27–35)

Key Indexing Terms:
RHEUMATOID ARTHRITIS DMARD BIOLOGICALS
TUMOR NECROSIS FACTOR ETANERCEPT INFLIXIMAB

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology. The natural history of the disease is characterized by the infiltration of immunocompetent cells into the synovial fluid and tissue, and stimulation and proliferation of synovial fibroblasts. Ultimately, this cascade of events leads to the formation of pannus tissue, which invades and destroys articular cartilage and, possibly, bone. Epidemiologic studies have shown that 30% of patients develop pathological joint erosions within the first year and 70% within 2 years[1]. Based on the epidemiologic data, RA can no longer be considered a benign disease that only affects joint function, since statistical analyses have shown increased mortality as compared with the average population[2]. Only 2% of patients who are treated with currently available therapeutic agents experience a remission for more than 3 years. More than 40% of patients with RA withdraw from the labor force within 4 years after diagnosis[3]. This poor outcome is due in part to the fact that most available disease modifying antirheumatic drugs (DMARD) are discontinued within 5 years due to clinical inefficacy and/or severe side effects[4,5]. The longterm outcomes in RA include not only joint destruction, work and functional disability, and psychosocial dysfunction, but treatment related side effects and comorbidity as well (Figure 1). Any or all of these can potentially compromise quality of life (QOL) and life expectancy. Based on our present knowledge of tissue destructive mechanisms, it has therefore become necessary to develop new therapeutic modalities.

Limitations of DMARD. One of the major limitations of the DMARD is that their duration of use is frequently limited by loss of efficacy and/or toxicity. In one 14 year prospective evaluation of 1017 consecutive newly diagnosed patients with RA seen at an outpatient clinic, the median time to treatment discontinuation was 2 years or less for hydroxychloroquine (HCQ), penicillamine, intramuscular gold, and auranofin[4]. Although the continuation rate was significantly higher with methotrexate (MTX), the median time to discontinuation was still only slightly more than 4 years. The most common reason for stopping treatment in this study was adverse reactions. Interestingly, demographic factors or disease related characteristics were not reliable predictors of treatment discontinuation. These findings are consistent with a large, practice-based observational study, which evaluated longterm DMARD dis-

From the Department of Internal Medicine III and Institute for Clinical Immunology, University of Erlangen-Nuremberg, Erlangen, Germany.

J.R. Kalden, MD, Professor of Internal Medicine, Director and Head of the Department for Internal Medicine III and the Institute for Clinical Immunology.

Address reprint requests to Professor J.R. Kalden, Department for Internal Medicine III and Institute for Clinical Immunology, Krankenhausstrasse 12, D-91054 Erlangen, Germany.

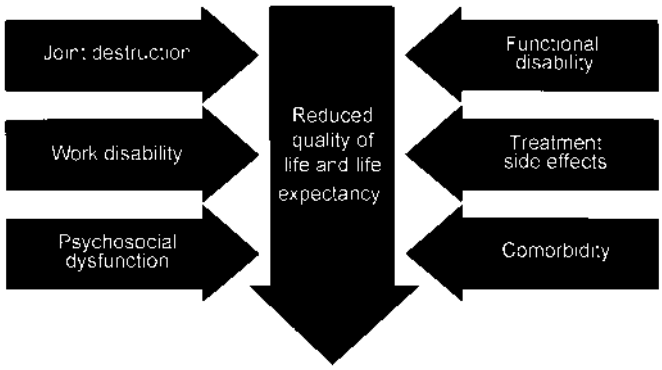

Figure 1. Longterm outcomes in RA.

continuation rates in patients followed from the time of their initial diagnosis to their final consult[5]. Of the 2296 courses of DMARD therapy analyzed over a 10 year period, 50% were discontinued within 16 months of use and 75% within 4.5 years. Once again, MTX showed an advantage over other DMARD during the initial years of treatment, but any appreciable differences between treatments were no longer evident after 5 years. Other studies have similarly reported high discontinuation rates associated with the longterm use of DMARD[6,7,8].

Another problem with DMARD is that discontinuing treatment in patients who are in remission can lead to the recurrence of synovitis (i.e., a flare). This observation was supported by a randomized, double blind, placebo controlled, multicenter study, which evaluated the effect of terminating second line therapy in 285 patients with a favorable response to longterm treatment[9]. The median duration of second line treatment at the time of study enrollment was 5 years (range 2 to 33). Half of the patients continued on treatment and the remainder continued on placebo. At the end of 52 weeks, the cumulative incidence of a flare was 38% in the placebo group and 22% among those receiving second line drug therapy, a statistically significant ($p = 0.002$) difference between groups.

Even in the case of MTX, there is also radiologic progression of disease, despite clinical improvement. Overall, the longterm outcome is poor, despite ostensibly effective therapies.

NEW APPROACHES TO IMMUNOINTERVENTION IN AUTOIMMUNE DISEASE.

Because conventional DMARD therapy is only partially effective and may produce an array of adverse effects in a large proportion of patients with RA, the search has continued for new and better tolerated therapies that will arrest inflammation and pain, and halt the progression of erosive joint damage[10]. One new agent approved by the US Food and Drug Administration (FDA) for the treatment of RA is leflunomide, an isoxazole immunosuppressive/immunomodulatory compound that inhibits pyrimidine synthesis. In addition, various biological agents have been developed that block tumor necrosis factor (TNF) or other pro-inflammatory cytokines such as interleukin 1 (IL-1). In clinical trials, these agents have demonstrated a marked beneficial effect on the clinical course of RA. Table 1 lists some of the new forms of immunointervention and other approaches used to treat RA and other autoimmune diseases. The focus of this paper is on the 2 new biological agents approved by the FDA for the treatment of RA etanercept (Enbrel®) and infliximab (Remicade®) — both of which are TNF antagonists.

TNF-blocking agents. To understand the mechanism of action of etanercept and infliximab, it is useful to recapitulate the important role of cytokines in inflammatory autoimmune diseases such as RA[11]. Cytokines are a large family of low molecular weight soluble proteins involved in the regulation of the immune system. They are synthesized by many types of cells, which exert their physiologic (or pathologic) effects after binding to cell surface receptors. Numerous cytokines provide a system for activation and information exchange among the cells that comprise the immune system. Two classes of cytokines are involved in the pathogenesis of RA: proinflammatory cytokines (actively produced in the rheumatoid joint) and antiinflammatory cytokines (which block the effects of pro-inflammatory cytokines)[11]. The former include IL-1, IL-6, IL-8, TNF-α, chemokines, and granulocyte macrophage colony stimulating factor (GM-CSF); the latter include IL-3, IL-4, IL-10, IL-13, and transforming growth factor. *In vitro* and *in vivo* studies of rheumatoid synovial tissue have shown that there is an imbalance in favor of the proinflammatory cytokines TNF-α, IL-1α, IL-1ß, GM-CSF, IL-6, and IL-8[12]. Given that cytokine abnormalities are prominent in RA, it is not surprising that the actions of many widely used antirheumatic drugs are partly related to their effects on these small proteins (Table 2)[12].

One of the key cytokines involved in both normal inflammatory and immune responses is TNF-α, which plays a pivotal role in many biological activities and is a principal modulator of the immune system. TNF-α has been shown to induce apoptosis of immune cells, stimulate the release of several other proinflammatory cytokines, induce the release of matrix metalloproteinases, induce the expression of endothelial adhesion molecules, and block the action of lipoprotein lipase[13,14]. Although TNF-α originates in various cells

Table 1. New approaches for immunointervention in autoimmune disease.

- New immunosuppressive drugs (cyclosporin A, FK506, rapamycin, brequinar, leflunomide, mycophenolic acid, 15 deoxyspergualin)
- Cytokine-targeted therapy (anti-TNF-α, IL-1 receptor angonist)
- Cytokine therapy (antiinflammatory cytokines)
- Cell surface molecule-targeted therapy (anti-adhesion molecule therapy, nondepleting anti-CD4 Mab, anti-CD28 Mab, anti-CD5 Mab, IL-2 fusion protein)
- Application of autoantigens/peptides (i.e., collagen II, HC-gp 34)
- Combination therapy including new anti-TNF-α medication
- Gene therapy
- Bone marrow stem cell transplantation

Table 2. Effects of antirheumatic drugs on cytokines[12].

Glucocorticoids
- Suppress gene transcription
- Decrease mRNA translation
- Interfere with other post-transcriptional events
- Suppress production in monocytes/macrophages of hemopoietic growth factors and MCAF

Cyclosporin A and D-penicillamine
- Suppress IL-2 production

Gold Compounds
- Reduce circulating IL-6 levels
- Reduce expression of IL-1, TNF, and IL-6 in the rheumatoid synovium

MTX
- Reduces circulating IL-6, soluble IL-2, TNF receptors, synovial fluid IL-1 levels

throughout the body, including synovial cells, T-lymphocytes, and mononuclear phagocytes, its main site of origin in RA appears to be activated macrophages. The fact that TNF-α levels in rheumatoid synovial fluid are 4 to 5 times higher than in plasma supports the important pathophysiologic role of this cytokine in RA[14]. The discovery that the use of TNF-α-blocking antibody decreases the IL-1 production in synovial cells in patients with RA and that TNF-α-blocking antibody or a dimeric TNF receptor-Fc IgG fusion protein could greatly reduce disease activity in transgenic mice and rat collagen-induced arthritis, led to studies that have confirmed the important role of this proinflammatory cytokine in RA[12,13]. It is now known that anti-TNF agents bind and inactivate TNF-α in the fluid phase, bind to transmembrane TNF-α, downregulate expression of other proinflammatory cytokines, block cell trafficking, and inhibit joint destruction[11].

Figure 2 describes the 4 compounds that have been developed to block TNF. These include the 2 products that have been approved in the US by the FDA for the treatment of RA: etanercept and infliximab. Two others, CDP 870 (an engineered chimeric mouse/human Fab conjugated with PEG) and D2E7 (a humanized IgG1 monoclonal antibody) are still experimental. Infliximab, D2E7, and CDP 571 are anti-TNF monoclonal antibodies, whereas etancercept is a soluble TNF receptor fusion protein. Both etanercept and infliximab have been demonstrated to significantly decrease the intensity of synovitis and to prevent (or retard) the progression of cartilage destruction, especially when used in combination with MTX. Other anti-TNF monoclonal antibodies, such as D2E7 and CDP 571, are still being tested in clinical trials and are not yet available for treating RA in daily practice.

Etanercept. Etanercept is a dimeric fusion protein, which consists of the extracellular ligand-binding portion of the human 75 kDa (p75) TNF receptor linked to the Fc portion of human IgG1. It is produced by recombinant DNA technology in a

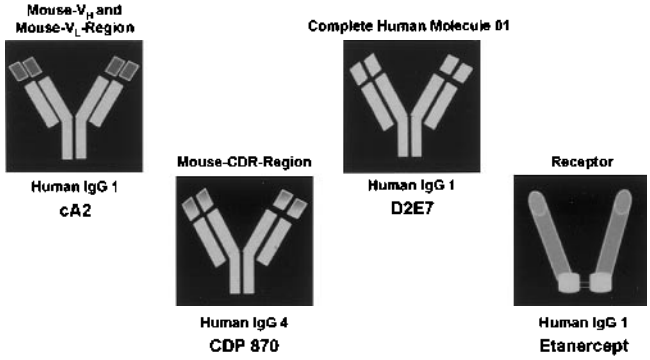

Figure 2. Approved and experimental TNF-blocking agents.

hamster ovary mammalian cell expression system. Etanercept binds specifically to TNF and blocks its interaction with cell surface TNF receptors, thereby rendering TNF biologically inactive. Studies have shown that it inhibits the activity of TNF *in vitro* and in several animal models of inflammation, including murine collagen induced arthritis[15]. It also modulates biological responses induced or regulated by TNF, including expression of adhesion molecules involved in leukocyte migration such as matrix metalloproteinase-3, and cytokines such as IL-6[16].

Etanercept was initially approved by the FDA in November, 1998, for the treatment of moderately to severely active RA in patients who have had an inadequate response to one or more DMARD. However, the indication for etanercept was expanded in June, 2000, and etanercept is now approved for reducing the signs and symptoms, and delaying structural damage, in patients with moderately to severely active RA regardless of prior DMARD treatment. It can also be used in combination with MTX in patients who do not respond adequately to MTX alone. Etanercept is also indicated for reducing the signs and symptoms of moderately to severely active polyarticular juvenile RA in patients who have had an inadequate response to one or more DMARD. The recommended dose of etanercept for adults with RA is 25 mg twice per week as a subcutaneous injection 72 to 96 hours apart. Patients may continue using MTX, glucocorticoids, salicylates, NSAID, or other analgesics during treatment.

Several randomized, double blind, controlled studies have evaluated the efficacy and safety of etanercept, both as single agent and combination therapy. Moreland *et al* conducted a Phase II double blind randomized placebo controlled trial in 180 patients with active RA who had failed an average of 3 DMARD regimens[17]. Patients were required to discontinue DMARD therapy for at least one month before being randomly assigned to treatment with one of 3 dosing regimens of etanercept (0.25, 2, or 16 mg/m^2) or placebo administered subcutaneously twice per week for 3 months. The results of this trial showed that etanercept 16 mg/m^2 produced significant improvement according to all clinical and biologic measures of disease activity when compared with placebo, includ-

ing pain and duration of morning stiffness, as well as the erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP). It also significantly improved scores on QOL measures and physicians' and patients' global assessments. Fifty-seven percent of patients in the high dose etanercept group demonstrated at least 50% improvement by American College of Rheumatology (ACR) criteria, as compared with 7% of patients receiving placebo. Likewise, 75% of patients had at least 20% improvement, as compared with 14% of the placebo group. Patients receiving high dose etanercept experienced a mean reduction of 61% in total swollen joint count, as compared with 25% of patients in the placebo group. All of the above differences between etanercept 16 mg/m^2 and placebo were statistically significant ($p < 0.001$).

The same investigators conducted a Phase III, randomized, double blind, placebo controlled study in 234 patients with severe RA who had not demonstrated an adequate response to one or more DMARD[18]. The patients were randomly assigned to treatment with one of 2 dosing regimens of etanercept (10 or 25 mg) or placebo given subcutaneously twice per week for 6 months. The results showed that etanercept had a rapid onset of action and produced significant improvement of disease activity at 3 and 6 months when compared with placebo (Figure 3). At 6 months, 15% of patients in the etanercept 25 mg group improved by at least 70% according to ACR criteria, 40% improved by at least 50%, and 59% improved by at least 20%. Patients receiving etanercept also reported significantly better functional status and well being than did those receiving placebo based on various rating scales, including the Health Assessment Questionnaire and the Medical Outcomes Study (MOS)[19].

Patients with RA who respond poorly to DMARD may be good candidates for receiving a TNF antagonist in combination with their initial therapeutic regimen. The benefits of combination therapy were demonstrated in a Phase III, double blind, placebo controlled study in 89 patients with persistently active RA, despite 6 or more months of therapy with MTX (at a moderate, stable dose for at least one month)[20]. The patients were maintained on a stable dose of MTX after being randomized to treatment with etanercept 25 mg or placebo given subcutaneously twice per week for 6 months. Patients in the etanercept group had significantly better outcomes based on all measures of disease activity when compared with those receiving placebo. Specifically, 71% of etanercept-treated patients achieved an ACR 20 response at 24 weeks, as compared with only 27% of patients in the placebo group ($p < 0.001$). The percentage of patients who achieved an ACR 50 response at 6 months was 39 versus 3%, respectively. Once again, etanercept produced a rapid and sustained response when compared with placebo (Figure 4).

A longterm, Phase III double blind, randomized, multicenter study (the ERA study) was recently completed in 632 patients with active, early stage RA who were MTX- naïve[21]. The patients were randomized to receive etanercept 10 or 25 mg given subcutaneously twice per week, or up to 20 mg of MTX once a week, for 12 months. To ensure blinding of the study treatments, patients received etanercept injections twice per week plus placebo pills weekly, or MTX pills weekly plus placebo injections twice per week. The percentages of patients treated with etanercept achieving ACR 20 and 50 responses at Month 12 were 72 and 49%, respectively. Slightly more than 10% of patients achieved a major clinical response (i.e., maintenance of an ACR 70 response over 6 months). This study differed from other etanercept trials in that structural joint damage was assessed radiographically, and was reported as change in total Sharp Score (TSS) and its components: erosion

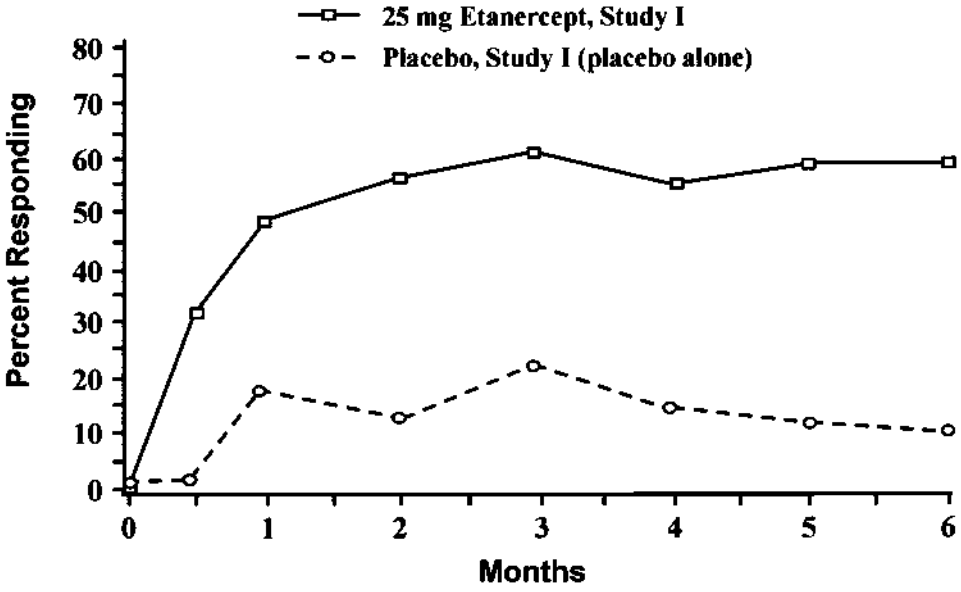

Figure 3. Time course of ACR 20 responses with etanercept *vs* placebo (Phase II trial) (reprinted courtesy of Immunex Corporation)[16].

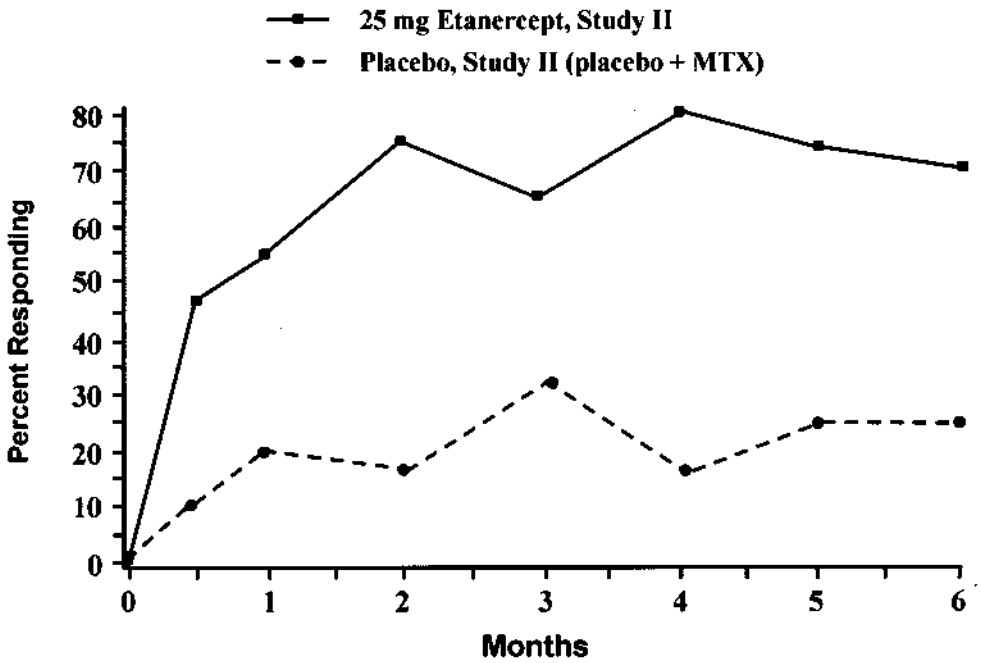

Figure 4. Time course of ACR 20 responses with etanercept vs. placebo (Phase III trial) (reprinted courtesy of Immunex Corporation)[16].

score and joint space narrowing (JSN) score. Etanercept 25 mg produced significantly greater improvement than MTX at 6 months in both the TTS and the erosion scores. There continued to be a significant advantage for etanercept over MTX at Month 12 based on the erosion score. These findings provided the basis for the expanded indication for etanercept as first line treatment of patients with moderately to severely active RA.

Placebo controlled studies in which patients have been allowed to continue on open label treatment with etanercept 25 mg for up to 2 years indicate that its efficacy over this prolonged period is similar to that observed in shorter placebo controlled trials[22]. Favorable results have also been reported at the 15th Annual Meeting of the EULAR in June, 2000, in patients treated with etanercept for up to 43 months. In addition, the results of a 2-part study in 69 patients with polyarticular juvenile RA who were refractory to, or could not tolerate MTX have demonstrated that etanercept is effective in a pediatric population[23].

Infliximab. Infliximab is a chimeric (mouse/human) IgG1 monoclonal antibody, which neutralizes the biological activity of TNF-α [but not TNF-ß (lymphotoxin α)] by binding with high affinity and specificity to the soluble and transmembrane forms of TNF-α, thereby inhibiting binding of TNF-α with its receptors. Infliximab is thought to exert a beneficial effect in RA by a down regulation of other proinflammatory cytokines, IL-1, IL-6 and by inhibiting the production of vascular endothelial growth factor, thereby preventing angiogenesis and proliferation of pannus. It also downregulates TNF-α-induced expression of adhesion molecules on vascular endothelium and in the synovium, leading to decreased migration of inflammatory cells into involved joints.

Infliximab was approved by the FDA for the treatment of RA in November, 1999. Infliximab, in combination with MTX, is indicated for reducing the signs and symptoms of RA in patients who have had an inadequate response to MTX. It was previously approved for treating Crohn's disease. Infliximab was the first monoclonal antibody to be investigated for use in the treatment of RA and provided the first evidence for the utility of TNF inhibitors in this disease. The presently recommended dose of infliximab is 3 or up to 10 mg/kg given as an intravenous (IV) infusion, followed by additional 3 mg/kg doses 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Infliximab should be given in combination with MTX.

One of the first studies to demonstrate the efficacy of infliximab in RA was a double blind randomized placebo controlled multicenter trial, which showed that more than half of patients receiving a single 10 mg/kg dose of infliximab by 2 hour IV infusion experienced at least 50% improvement in their disease[24]. Notably, 79% of patients demonstrated 20% improvement at Week 4. A continuation of this study, published in the same issue of Lancet, indicated that repeated treatment in patients with disease flares resulted in a favorable clinical response following each cycle of treatment[25]. However, the time between flares decreased with each subsequent dose. In a subsequent double blind, placebo controlled, multicenter study in patients randomized to treatment with various dosing regimens of infliximab, with or without MTX, or placebo, the coadministration of MTX had a synergistic

effect and prolonged the duration of the response[26]. In addition, the antibody formation was reduced and the duration of clinical response was significantly prolonged.

The results of the ATTRACT (the Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy) study, one of the largest clinical trials ever conducted in patients with advanced RA, also suggest that the combination of infliximab and MTX is more effective than MTX alone[27]. In this international, Phase III double blind placebo controlled trial, 428 patients who had received MTX for at least 3 months (the majority had taken it for ≥ 3 years) and who remained on a stable dose (≥ 12.5 mg for ≥ 4 weeks) prior to the study, but still had active RA, were randomized to treatment with placebo or one of 4 dosing regimens of infliximab: 3 mg/kg every 4 or 8 weeks, or 10 mg/kg every 4 or 8 weeks. All treatments were given by IV infusion at weeks 0, 2 and 6, with additional infusions given every 4 or 8 weeks thereafter. All patients continued to receive a stable dose of MTX.

As shown in Figure 5, the results of this study demonstrated a statistically significant advantage for combination therapy with infliximab plus MTX as compared with placebo plus MTX based the ACR 20 response. Fifty percent of patients receiving infliximab 3 mg/kg plus MTX attained an ACR 20 at Week 30, as compared with 20% of patients receiving placebo plus MTX ($p < 0.001$). The respective figures for the ACR 50 response at Week 30 were 27 versus 5%, respectively; the respective figures for the ACR 70 response were 8 versus 0%. Patients receiving infliximab 3 mg/kg also demonstrated significant improvement on virtually all other ACR response components, including number of tender/swollen joints, pain (VAS), physicians' and patients' global assessments, ESR, and CRP. A subsequent study has confirmed that a single infusion of infliximab provides significant clinical improvement when compared with placebo in patients with active RA receiving MTX, and that multiple doses produce sustained therapeutic effects for up to 40 weeks[28]. The use of infliximab in combination with high dose MTX has also proven effective for longterm therapy for up to 54 weeks[29].

Defining the role of TNF blockers in RA therapy. Although the introduction of infliximab and etanercept has been met with considerable enthusiasm, the place of these new TNF-blocking agents in the rheumatologic armamentarium has yet to be clarified. One of the concerns of these drugs is their expense. It is estimated that the annual cost of etanercept in the U.S. is approximately $12,000, while that of infliximab is only marginally less[30,31]. Since pharmacoeconomic analyses suggest that the costs of a medication are only one component of the total expense of treating RA, it remains to be determined whether the new biological agents will prove cost effective when such factors as efficacy, tolerability, and onset of action are factored into longterm costs[32]. In addition, the longterm consequences and effectiveness of these agents are not yet fully understood. For these reasons, various forums have been created to provide rheumatologists and other specialists with an opportunity to discuss the exact role of TNF-blocking agents in the treatment of RA.

An international roundtable meeting was held in Lausanne, Switzerland, in February 1999, to discuss the emerging role of anti-TNF therapy. Fifty-eight rheumatologists and other specialists from 13 countries convened for this meeting, entitled

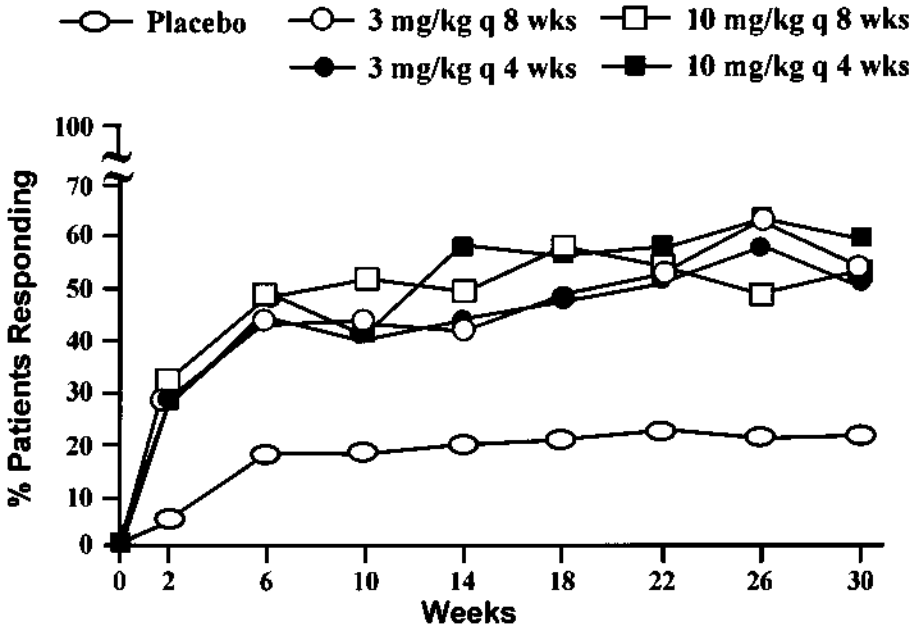

Figure 5. Percentage of patients who achieved an ACR 20 with combination infliximab/MTX treatment[36]. The dosage and frequency of administration of infliximab varied among groups. All groups received MTX (reprinted courtesy of Centocor, Inc.).

Clinical Opportunities of Anti-TNF Therapies in Rheumatoid Arthritis[33]. Another conference, held in March 1999, brought together 80 rheumatologists and bioscientists from 22 countries worldwide[34]. This meeting, entitled, Advances in Targeted Therapies. TNF-α Blockade in Clinical Practice, consisted of small and large group discussions that resulted in the formulation of a consensus statement on the clinical use of TNF-blocking agents. A group of 12 European rheumatologists also met in Vienna in 1999 to develop a consensus statement on the initiation and continuation of TNF-blocking therapies in RA[35]. Various other groups of rheumatologists have convened both formally and informally to discuss and define the role of biological agents in RA. The following discussion reflects the consensus for the use of TNF-blocking agents that has emerged from these gatherings.

What can the new biologics offer? The overall feeling of most authorities in the field is that TNF-targeted therapies should offer an advantage over conventional DMARD with respect to their onset of action, and extent and duration of disease control[33]. In other words, they should ideally provide rapid, sustained, and appreciable control of disease. In addition, they should prevent the pathological and clinical consequences of TNF-α, and improve patients' sense of well being and QOL. It is generally felt that these agents achieve these latter objectives, although definitive, longterm data are not yet available. To justify the costs of these expensive agents, their longterm use should confer an advantage over conventional DMARD with regard to the direct costs associated with RA (i.e., hospitalization, joint replacement), as well as the indirect costs (i.e., disability, mortality).

Which patients qualify for anti-TNF therapy? Based on the consensus findings, it is generally agreed that the use of TNF-blocking agents should be reserved for patients who have failed to demonstrate a sufficient response after a full and adequate trial of one or more DMARD including MTX[34,35]. A patient should, for example, have received 15 to 25 mg/week of MTX for at least 3 months, with or without other DMARD, before anti-TNF therapy is added to the regimen. Although it is not deemed necessary for a patient to have failed additional MTX-based combinations before starting anti-TNF therapy, a patient who has failed to demonstrate an adequate response to a single DMARD other than MTX should undergo a trial of MTX therapy before trying a TNF blocker, unless contraindicated. If a patient has previously achieved remission on a given DMARD, he or she should be restarted on this same therapy.

The use of TNF blockers is not recommended for the management of acute flare ups. To be eligible for anti-TNF therapy, patients should have active disease based on a Disease Activity Score (DAS28) > 3.2, or a combination of 5 or more swollen and/or painful joints and an abnormal acute phase response. Before initiating treatment, a physician experienced in diagnosing and treating RA should establish specific goals for the patient directed at achieving a reduction in disease activity or, possibly, remission. This should take into account individual differences in disease activity, clinical presentation, and the impact of disease on QOL. In addition, problems associated with previous DMARD, such as toxicity, should be noted. The patient should undergo a complete physical examination and chest radiography to rule out the presence of any condition or disorder that might act as a contraindication to the use of TNF-blocking therapy. Radiographs of the hands and feet should also be obtained at baseline and yearly thereafter to monitor disease progression.

Once anti-TNF therapy is initiated, significant improvement in symptoms and/or laboratory variables should be documented during 8 to 12 (or 16) weeks of treatment at adequate doses. Validated response criteria, such as those established by the ACR or EULAR (European Union Against Rheumatism), should be used to assess patients' response to TNF-blocking therapy. These include an evaluation of the number of tender/swollen joints, as well as an acute phase response. The decision to continue TNF-blocking therapy should be based on improvement in the DAS28 score ≥ 1.2, a DAS28 ≥ 3.2, or ≥ 20% improvement according to ACR criteria.

Patients should discontinue anti-TNF therapy if they do not demonstrate an adequate response (based on predetermined response criteria) within 12 (or 16) weeks after starting treatment at the recommended dosing schedule (or earlier, in the event of serious adverse reactions). Since TNF mediates inflammation and modulates cellular immune responses, anti-TNF therapies could theoretically affect host defenses against infections and malignancies. In fact, serious infections and sepsis (including fatalities) have been reported in post-marketing reports of patients using etanercept and infliximab, some within a few weeks after starting treatment. However, the overall incidence was not greater than expected. Many of these serious events have occurred in patients with underlying diseases (i.e., diabetes, congestive heart failure, a history of active or chronic infections), which could predispose them to develop infections. This is especially true in light of the fact that infections, including serious infections, are more common in the population with RA than in the general public.

Therefore, patients who develop a new infection while undergoing treatment with one of these new biologics should be monitored closely and treatment should be discontinued if the patient develops a serious infection or sepsis. Treatment with anti-TNF therapy also should not be initiated in patients with active chronic or localized infections, and should be used with caution in patients with a history of recurring infections or any underlying condition that might predispose them to infections (i.e., advanced or poorly controlled diabetes). Furthermore, serious active or recent infection (i.e., tuberculosis, bone/joint infection) or recent previous malignancy (particularly lymphoma) should be considered potential contraindications to TNF-blocking therapy. Since the effects of TNF blockade are unknown in patients with lymphoma, lymphoproliferative diseases (and other malignancies), chronic

infections (i.e., HIV, hepatitis B or C), mycobacterial diseases, or during pregnancy and lactation, significant caution should be exercised in such cases. Rare instances of lupus-like disease have been reported in patients receiving anti-TNF agents and the use of such therapy should be discontinued if there is clinical evidence of such a syndrome. However, the presence of anti-nuclear or anti-cardiolipin antibodies, in the absence of clinical symptoms, does not rule out the use of TNF-blocking agents.

It remains to be determined whether a TNF blocker can be replaced with a DMARD once significant improvement (or disease remission) has been achieved, or what should be the optimal dosing regimen for longterm therapy.

CONCLUSIONS

Although DMARD remain the cornerstone of the therapeutic armamentarium in RA, their side effect profile can limit their longterm utility and there is still no evidence that they reverse the disease outcome. Hence, the search has continued for novel therapies for this disease.

Our greater understanding of immune function has yielded a number of biologic agents that show promise for the treatment of RA. While the initial results of clinical trials with the only new biologicals currently approved by the FDA for the treatment of RA, the TNF blockers, etanercept and infliximab are very encouraging, longterm efficacy and safety have to be adequately confirmed in postmarketing studies. Furthermore, questions regarding such issues as which patient subsets are the best candidates for these new drugs, optimal dosage regimens, and possibilities for combination therapy will need to be addressed. Although these drugs can be expected to play an immediate role in patients for whom there is no reasonable alternative therapy, it remains to be seen how extensive this role will be. With these caveats in mind, one can anticipate that the new biologicals will become valuable therapeutic options for patients with RA.

REFERENCES

1. Van der Hiejde DM. Joint erosions and the patient with early rheumatoid arthritis. Br J Rheumatol 1995;34 Suppl 2:74-8.
2. Mitchell DM, Spitz PW, Young DY, Block DA, McShane DJ, Fries JF. Survival, prognosis, and causes of death in rheumatoid arthritis. Arthritis Rheum 1986;29:706-14.
3. Dougados D, Suurmeijer T, Krol B, Sanderman B, van Leeuwen M, van Rijswijk M. Work disability in early rheumatoid arthritis. Ann Rheum Dis 1995;54:445-60.
4. Wolfe F, Hawley DJ, Cathey MA. Termination of slow acting antirheumatic therapy in rheumatoid arthritis: a 14-year prospective evaluation of 1017 consecutive starts. J Rheumatol 1990; 17:994-1002.
5. Galindo-Rodriguez G, Avina-Zubieta JA, Russell AS, Suarez-Almazor ME. Disappointing longterm results with disease modifying antirheumatic drugs. A practice based study. J Rheumatol 1999;26:2337-43.
6. Keysser M, Keysser G, Keysser C. Long-term application of disease modifying antirheumatic drugs (DMARD). A single-center, observational study of 1681 patients with rheumatoid arthritis (RA). Z Rheumatol 1999;58:267-76.
7. Sander O, Herborn G, Bock E, Rau R. Prospective six year follow up of patients withdrawn from a randomised study comparing parenteral gold salt and methotrexate. Ann Rheum Dis 1999;58:281-7.
8. Alarcon GS, Tracy IC, Strand GM, Singh K. Macaluso M. Survival and drug discontinuation analyses in a large cohort of methotrexate treated rheumatoid arthritis patients. Ann Rheum Dis 1995; 54:708-12.
9. ten Wolde S, Breedveld FC, Hermans J, Markusse HM, et al. Randomised placebo-controlled study of stopping second-line drugs in rheumatoid arthritis. Lancet 1996;347:347-52.
10. Goldenberg MM. Etanercept, a novel drug for the treatment of patients with severe, active rheumatoid arthritis. Clin Ther 1999;21:75-87.
11. Breeveld FC. Future trends in the treatment of rheumatoid arthritis: cytokine targets. Rheumatology 1999;38 Suppl 2:11-3.
12. Beutler BA. The role of tumor necrosis factor in health and disease. J Rheumatol 1999;26 Suppl 57:16-21.
13. Brennan FM, Chantry D, Jackson A, Maini R, Feldmann M. Inhibitory effect of TNF alpha antibodies on synovial cell interleukin-1 production in rheumatoid arthritis. Lancet 1989; 2:244-7.
14. Moreland LW. Inhibitors of tumor necrosis factor for rheumatoid arthritis. J Rheumatol 1999;26 Suppl 57:7-15.
15. Wooley PH, Dutcher J, Widmer MB, Gillis S. Influence of a recombinant human soluable tumor necrosis factor receptor FC fusion protein on type II collagen-induced arthritis in mice. J Immunol 1993;151:6602-7.
16. ENBREL® (etanercept) [prescribing information 10/2000] Immunex Corporation, Seattle, Washington 98101.
17. Moreland LW, Baumgartner SW, Schiff MH, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. N Engl J Med 1997;337:141-7.
18. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med 1999;130:478-86.
19. Mathias SD, Colwell HH, Miller DP, Moreland LW, Buatti M, Wanke L. Health-related quality of life and functional status of patients with rheumatoid arthritis randomly assigned to receive etanercept or placebo. Clin Ther 2000;22:128-39.
20. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med 1999;340:253-9.
21. Finck B, Martin R, Fleischmann R, Moreland L, Schiff M, Bathon J. A Phase III trial of etanercept vs. methotrexate (MTX) in early rheumatoid arthritis (ENBREL ERA Trial) [abstract]. Arthritis Rheum 1999;42 Suppl 9:S117.
22. Moreland LW, Baumgartner SW, Tindall E, et al. Long term safety and efficacy of TNF receptor (p75) Fc fusion protein (TNFR:Fc; Embrel) in DMARD refractory rheumatoid arthritis (RA) [abstract]. Arthritis Rheum 1998;41 Suppl 9:S364.
23. Lovell DJ, Giannini GH, Reiff A, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. N Engl J Med 2000;342:763-9.
24. Elliott MJ, Maini RN, Feldmann M, et al. Randomised double-blind comparison of chimeric monocloncal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. Lancet 1994;344:1105-10.
25. Elliott MJ, Maini RN, Feldmann M, et al. Repeated therapy with monoclonal antibody to tumour necrosis factor alpha (cA2) in patients with rheumatoid arthritis. Lancet 1994;433:1125-7.
26. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of

multiple iv infusions of anti-tumor necrosis factor alpha monocloncal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998;41:1552-63,
27. Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999;354:1932-9.
28. Kavanaugh A, St. Clair EW, McCune WJ, Braakman T, Lipsky P. Chimeric anti-tumor necrosis factor-alpha monocloncal antibody treatment of patients with rheumatoid arthritis receiving methotrexate therapy. J Rheumatol 2000;27:841-50.
29. Antoni C, Kalden JR. Combination therapy of the chimeric monoclonal anti-tumor necrosis factor alpha antibody (infliximab) with methotrexate in patients with rheumatoid arthritis. Clin Exp Rheumatol 1999;17 Suppl 18:S73-7.
30. Emery P, Panay G, Sturrock R, Williams B. Targeted therapies in rheumatoid arthritis: the need for action. Rheumatology 1999;38:911-6.
31. Matteson EL. Current treatment strategies for rheumatoid arthritis. May Clin Proc 2000;75:69-74.
32. Lipsky PE, Kavanaugh A. The impact of pharmaco-economic considerations on the utilization of novel anti-rheumatic therapies. Rheumatology 1999;38 Suppl 2:41-4.
33. Furst DE, Keystone E, Maini RN, Smolen JS. Recapitulation of the round-table discussion-assessing the role of anti-tumour necrosis factor therapy in the treatment of rheumatoid arthritis. Rheum 1999;38 Suppl 2:50-3.
34. Furst D, Breedveld FC, Kalden JR, Smolen JS. Building towards a consensus for the use of tumour necrosis factor blocking agents. Ann Rheum Dis 1999;58:725-6.
35. Smolen JS, Breedveld FC, Burmester, Combe B, Emery P, Kalden JR. Consensus statement on the initiation and continuation of tumor necrosis factor flocking therapies in rheumatoid arthritis. Ann Rheum Dis 2000;59:504-5.
36. REMICADE® (infliximab) [prescribing information 11/1999] Centocor, Inc., Malvern, PA 19355.