

The following abstracts, from medical journals containing literature on rheumatoid arthritis, were selected for their relevance to this Special Report supplement.

Future Role of Anti-TNF Therapies for Rheumatoid Arthritis Treatment

Tumor necrosis factor α (TNF α) is a potential target for anticytokine therapy in patients with rheumatoid arthritis (RA). TNF is overproduced in the joints of RA patients, as are other proinflammatory mediators (interleukin-1 [IL-1], IL-8, IL-6, granulocyte—macrophage colony-stimulating factor, platelet-activating factor). However, TNF α has been particularly associated with the joint inflammation of this disease. Agents studied in clinical trials include a chimeric human/mouse monoclonal anti-TNF α antibody (infliximab; cA2) and a recombinant human soluble TNF α receptor fusion protein (sTNFR:Fc). Patients with long-standing disease who were treated with these agents experienced rapid improvement in their symptoms, including pain scores and swollen joint count. Some laboratory markers of disease (eg, erythrocyte sedimentation rate, blood cytokine levels, rheumatoid factor titre, synovial histology) also showed improvements. These therapies represent the first attempt to modify the actual pathogenesis of RA. However, RA is a chronic disease, and the long-term effectiveness of these therapies has yet to be determined. In addition, TNF α is a component of host defenses against infection and tumors, and adverse effects may be associated with its long-term suppression. Because cytokines other than TNF α (eg, IL-1) also may contribute to the joint destruction in RA, there is interest in designing protocols that could result in inhibition of multiple mediators of this disease.

Camussi G, Lupia E. The future role of anti-tumor necrosis factor (TNF) products in the treatment of rheumatoid arthritis *Drugs* 1998;55:613-620.

Combining TNF and Methotrexate for Rheumatoid Arthritis Treatment

The chimeric anti-tumor necrosis factor α (TNF α) monoclonal antibody cA2 (infliximab) was evaluated for efficacy, immunogenicity, and safety in a 26-week, double-blind, placebo-controlled trial involving 101 patients with active rheumatoid arthritis (RA) who had either a partial response or a disease flare while receiving methotrexate at doses of 7.5 to 15 mg/week. A total of 87 patients received intravenous doses of cA2 at 1, 3, or 10 mg/kg per dose, with or without low-dose oral methotrexate (MTX; 7.5 mg/week). A control group received intravenous placebo and low-dose MTX. Infusion of cA2 at 3 or 10 mg/kg over 14 weeks, whether alone or with MTX, produced a response in ~60% of the patients, as measured by 20% Paulus criteria; median duration of this response was 10.4 to >18.1 weeks. The benefit of therapy in patients receiving cA2 at 3 or 10 mg/kg with MTX generally was sustained through the entire 26-week study period. The median duration of response in the control group was 0 weeks. Synergy was noted when cA2 at 1 mg/kg was given with MTX. The 2 higher dosages of cA2 were associated with decreased immunogenicity, as was the combination of cA2 and MTX at all doses. Infections requiring antibiotic treatment (mostly minor) were observed in 32.2% of patients receiving cA2. Future trials are needed to assess the long-term safety and effectiveness of anti-TNF α therapy.

Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998;41:1552-1563.

Protocol for Evaluating Rheumatoid Arthritis

Although extensive data are available on inflammatory activity in patients with rheumatoid arthritis (RA), not much information is available on long-term damage and outcomes. The proposed standard protocol to evaluate rheumatoid arthritis (SPERA) was developed to enable collection of baseline information about RA for long-term observational studies. SPERA can be used in most clinical settings and can be completed in 30 to 45 minutes. Page 1 is a patient self-report questionnaire. The form on page 2 is to be completed by the investigator; it collects information on whether the patient meets criteria for RA, as well as the patient's functional class, family history of RA, comorbidities, extraarticular disease, joint surgeries, radiographic score, and laboratory findings. Page 3 includes a 32-joint count with five variables: (1) joint normal/abnormal, (2) tenderness or pain on motion, (3) swelling, (4) limited motion or deformity, and (5) surgeries; this page also contains a review of physical measures of function (eg, grip strength). Page 4 includes a medication review and work history. Rheumatoid arthritis may have severe long-term consequences, including progressive joint damage concomitant with unchanged or even improved measures of inflammatory activity. A standard protocol to assess activity, damage, and outcomes in RA patients will help in analysis of long-term outcomes.

Pincus T, Brooks RH, Callahan LF. A proposed 30-45 minute 4 page standard protocol to evaluate rheumatoid arthritis (SPERA) that includes measures of inflammatory activity, joint damage, and longterm outcomes. *J Rheumatol* 1999;26:473-480.

Combining Etanercept and Methotrexate for Rheumatoid Arthritis Treatment

This study was done to determine whether the combination of methotrexate (MTX) and etanercept, a soluble tumor necrosis factor (p75):Fc fusion protein, would provide additional benefit in patients with rheumatoid arthritis (RA) who did not have a satisfactory response to at least 6 months of MTX therapy at a stable dose of 15 to 25 mg/week. A total of 89 patients were randomly assigned to receive etanercept 25 mg or placebo subcutaneously plus oral or subcutaneous MTX. The mean doses of MTX in the etanercept and placebo groups were 19 mg/week and 18 mg/week, respectively. The primary efficacy endpoint was the American College of Rheumatology (ACR) criteria for a 20% improvement in measures of disease activity (ACR 20) at 24 weeks. A rapid, sustained response was seen in the group receiving etanercept and MTX, with 71% of patients meeting the ACR 20 criteria at 24 weeks, compared with 27% of those receiving placebo and MTX. Among patients receiving etanercept and MTX, 39% and 15% met the ACR 50 and ACR 70 criteria, respectively, at 24 weeks. The corresponding percentages for patients receiving placebo and MTX were 3% and 0%. Mild injection-site reactions were the only adverse effects that occurred significantly more often in the group receiving etanercept and MTX than in the group receiving placebo and MTX. The combination of etanercept and MTX was significantly more effective than MTX alone in RA patients with persistent active disease.

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;340:253-259.

Methotrexate Slows Rheumatoid Arthritis Progression

Methotrexate (MTX) has become the leader among disease-modifying antirheumatic drugs (DMARDs) for the treatment of patients with rheumatoid arthritis (RA). To ascertain the progression of disease in patients with RA, those who were treated with MTX for at least 10 months and in whom hand/wrist radiographs had been obtained before MTX was given were studied radiographically. The coded images were read for erosions by 2 experienced readers using the modified method of Sharp. The erosion score and rate of progression of RA per month were calculated. Baseline radiographs revealed one or more erosions in 11 of 24 patients and none in 13. Demographic and clinical features were comparable in patients with and without erosions at baseline, although those with erosions had a longer duration of disease and higher rheumatoid factor positivity than those without erosions. Half the patients showed no progression, whereas 73% of patients with erosions at baseline but only 31% of those without erosions at baseline had progression; rates of progression were 0.017 (\pm 0.033) and 0.049 (\pm 0.078) for the 2 groups. Patients with RA who began MTX before erosions occurred are less likely to develop them; such patients also experienced a lesser degree of disease progression than patients who started MTX when erosions were already present.

Rich E, Moreland LW, Alarcon GS. Paucity of radiographic progression in rheumatoid arthritis treated with methotrexate as the first disease modifying antirheumatic drug. *J Rheumatol* 1999;26:259-261.

Results of Clinical Trials of Celecoxib, a New Specific COX-2 Inhibitor

Pain and inflammation can be effectively relieved by nonsteroidal anti-inflammatory drugs (NSAIDs), but their use is tempered by the development of side effects, primarily gastrointestinal (GI). The enzyme cyclooxygenase (COX) is the principal mechanism for both the efficacy and toxicity of NSAIDs. Recent research has revealed that COX exists as at least 2 coenzymes, COX-1 and COX-2. There is strong evidence that COX-1 synthesizes prostaglandins that are involved in the regulation of normal cell activity (including GI cytoprotection), whereas COX-2 seems to produce prostaglandins mostly at sites of inflammation. Such findings have led to the search for compounds that would inhibit COX-2 without affecting COX-1. Several agents are being evaluated in this new therapeutic category, including celecoxib (SC-58635), which was developed as an anti-inflammatory and analgesic agent and has been studied in preclinical and clinical trials. The results of 5 key clinical trials are reported, including an efficacy trial in dental pain, a 2-week osteoarthritis (OA) efficacy trial; a 4-week rheumatoid arthritis (RA) efficacy trial, a 1-week endoscopic trial of GI mucosal effects, and a 10-day study of the effects of celecoxib on platelet function. The arthritis trials identified celecoxib doses that were effective in treating OA and RA and that were distinguished from placebo on standard arthritis scales. In the upper GI endoscopy study, no ulcers developed in subjects who received celecoxib or placebo, whereas 10% of subjects who were given naproxen developed gastric ulcers. In the platelet effects trial, there was no significant difference from placebo observed in the effect of celecoxib on platelet aggregation or bleeding time; by contrast, naproxen use resulted in marked reductions in platelet aggregation as well as a significant increase in bleeding time. The results of these preliminary trials show that celecoxib acts effectively against arthritis through specific COX-2 inhibition without evidence of 2 of the toxic effects of COX-1 inhibition associated with NSAID use.

Geis GS. Update on clinical developments with celecoxib, a new specific COX-2 inhibitor: What can we expect? *J Rheumatol* 1999;26(suppl 56):31-36.

Performance of Etanercept in a Randomized, Controlled Trial

In a phase II trial, etanercept (recombinant human tumor necrosis factor receptor [p75]:Fc fusion protein) was found to produce rapid, safe, dose-dependent improvement in rheumatoid arthritis over a 3-month period. A randomized, double-blind, placebo-controlled trial with blinded joint assessors was conducted in 13 North American centers to confirm the benefit of etanercept therapy of longer duration and simplified dosing in patients with rheumatoid arthritis. Two hundred thirty-four patients with active rheumatoid arthritis who had an inadequate response to disease-modifying antirheumatic drugs were given twice-weekly subcutaneous injections of etanercept, 10 or 25 mg, or placebo for 6 months. The primary endpoints were a 20% and 50% improvement in disease activity, according to American College of Rheumatology (ACR) responses at 3 and 6 months. Other endpoints included 70% ACR responses at 3 and 6 months and other measures of disease activity at 3 and 6 months. Etanercept markedly reduced disease activity in a dose-related manner. At 3 months, 62% of patients who received 25 mg of etanercept and 23% of those who received placebo achieved a 20% ACR response; At 6 months, 59% of the 25-mg group and 11% of the placebo group achieved a 20% ACR response; 40% and 5%, respectively, achieved a 50% ACR response. The respective mean percentage reductions in the number of tender and swollen joints at 6 months was 56% and 47% for the 25-mg group and 6% and -7% in the placebo group. Significantly more etanercept recipients achieved a 70% ACR response, minimal disease status (0 to 5 affected joints), and improved quality of life. Etanercept was well tolerated, with no dose-limiting side effects, demonstrating that it can safely provide rapid, significant, and sustained benefit in patients who have active rheumatoid arthritis.

Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis: A randomized, controlled trial. *Ann Intern Med* 1999;130:478-486

Cyclooxygenase-1 and -2 Use in Health and Disease

Data from animal and human subjects reveal that the upregulation of cyclooxygenase (COX-2) is associated with the pain and inflammation of the disease state. However, the COX-1 isoform is a constitutive enzyme that has homeostatic functions. In contrast to conventional nonsteroidal anti-inflammatory drugs that inhibit both forms of the COX enzyme, the drug celecoxib selectively inhibits COX-2 in vitro. Celecoxib reversed the signs of arthritis and pain in an animal model as effectively as indomethacin. Data from murine studies, as well as in vitro and epidemiologic data, indicate that COX-2 plays a role in the development of colon cancer. In addition, epidemiologic studies suggest that COX inhibition can deter the progression of Alzheimer's disease.

Lipsky PE. Role of cyclooxygenase-1 and -2 in health and disease. *Am J Orthopedics* 1999;28(suppl 3):8-12