Etanercept and methotrexate combination therapy

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ABSTRACT

Tumor necrosis factor (TNF) is a major proinflammatory cytokine in the rheumatoid joint. TNF activity can be neutralized by administration of a recombinant version of its soluble p75 TNF receptor linked to the Fc portion of human immunoglobulin IgG1 (etanercept). The present study examined the combination of etanercept with methotrexate (MTX) in a group of patients with rheumatoid arthritis (RA) who had persistent activity despite monotherapy with MTX. The etanercept-MTX group had a significantly better outcome than the placebo-MTX group using American College of Rheumatology (ACR) criteria. At 6 months, 71% of the patients in the etanercept-MTX group had an ACR 20% response (versus 27% in the placebo-MTX group). In the etanercept-MTX group, 39% had an ACR 50% response (versus 3% in the placebo-MTX group), and 15% in the etanercept-MTX group versus 0% in the placebo-MTX group met the robust ACR 70% response. The present study indicates that etanercept is a novel and robust drug in combination with MTX for the treatment of RA.

Rationale for anti-tumor necrosis factor (TNF) α therapy

The intense inflammatory reaction that characterizes the rheumatoid synovium is associated with the production of protein mediators which are called cytokines. *In vitro* studies have shown that rheumatoid synovial tissue produces a mixture of these molecules, which have either proinflammatory or anti-inflammatory properties (1, 2). The proinflammatory cytokines include TNF, two types of interleukin (IL-1α and IL-1β), granulocyte macrophage colony stimulating factor, IL-6, and IL-8. Anti-inflammatory molecules include cytokines such as IL-10 and transforming growth factor as well as cytokine inhibitors that consist primarily of IL-1 receptor antagonist and soluble TNF receptor. The latter anti-inflammatory cytokines and cytokine inhibitors are found in increased concentrations in the joint, but not in sufficient concentrations to neutralize the inflammatory cytokines. Findings of studies utilizing rheumatoid synovial cultures are consistent with the fact that TNFα is the principal regulator of IL-1 and other proinflammatory mediators and with the fact that inhibition of TNFα inhibited other proinflammatory cytokines (3).

Clinical studies with anti-TNF monotherapy

In view of the central role of TNF in the inflammatory cytokine cascade in the rheumatoid joint, research was initiated to inhibit TNF by several approaches. One of the first intervention trials attempted blocking TNFα by means of a monoclonal antibody (4). This trial involved 73 patients with active disease who had failed multiple disease-modifying antirhematic drugs (DMARDs). The patients were given a single infusion of 1 mg/kg or 10 mg/kg of the chimeric monoclonal antibody (infliximab). Seventy-nine percent of the patients had a 20% improvement at week 4 while 50% of patients experienced at least a 50% improvement in the same time interval. In an additional study, 8 of the original 20% from the initial study who experienced a subsequent flare of their disease were given 3 additional infusions of infliximab (5). Each additional infusion produced a response with undiminished magnitude.

A second approach to reduce the functional level of TNFα in the rheumatoid joint was the administration of a recombinant version of the soluble p75 TNF receptor linked to the Fc portion of human immunoglobulin IgG1. This TNF receptor:Fc receptor fusion protein (etanercept; Enbrel, Wyeth-Ayerst Laboratories/Immunex Corp.) competitively inhibits the binding of TNF to cell surface receptors and thereby decreases the functional activity of TNF. This dimeric molecule has higher affinity for TNF than does the soluble monomeric TNF receptor, and has a longer half-life *in vivo* than the monomeric TNF receptor.

In 1997, a multicenter, double-blind, randomized, placebo-controlled study of monotherapy with etanercept was reported for the treatment of recalcitrant rheumatoid arthritis (RA) (6). This phase II study used American College of Rheumatology (ACR) evaluation criteria. It was a 3-month trial with 3 doses of etanercept given parenterally twice a week to 180 patients at eleven sites. All patients had active disease and generally had failed at least one DMARD. All DMARDs were discontinued at least 4 weeks before entry into the trial. Allowable concomitant medications included 10 mg or less of prednisone and nonsteroidal anti-inflammatory drugs (NSAIDs). The highest dose (16 mg/m^2) resulted in a mean level of reduction in the tender/swollen joint counts of 50%, which returned to baseline after discontinuation of the drug. The ACR 20% response rate was 59% at month 1 and 75% at month 3. At month 3, 57% of the patients showed an ACR 50% response and 20% an ACR 70% response.

An additional phase II study extended the duration of therapy to 6 months at fixed doses of either 10 mg or 25 mg twice a week (7), in 234 patients with active RA who had an inadequate response to DMARDs, as in the previous study. Etanercept significantly reduced disease activity in a dose-related manner. At 6 months, 59% of the 25 mg group and 11% of the placebo group achieved a 20% ACR response. Using a 50% ACR response (ACR50), the response rates were 40% for the 25 mg group versus 5% for the placebo group. The reductions in the number of tender and swollen joints at 6 months were 56% and 47% in the 25 mg group compared with 6% and -7% in the placebo group.

Rationale for combination therapy with methotrexate

At the present time, methotrexate (MTX) has become the initial DMARD of choice for patients with moderate-to-severe RA. MTX was used by about 50% of patients with RA by 1992 (8), and is currently used in approximately 65-70% of patients with early RA (9). The response to MTX, however, is often suboptimal, although the secondary failure rate is less and sustained efficacy is better than that of other DMARDs (10). Furthermore, MTX induces remissions in 5% or less of patients. The probability of MTX continuation at 10 years from the time of cohort entry was 30%. In addition, a greater than expected number of deaths from infection was observed (11). Thus, the next step in etanercept therapy for RA was to determine whether etanercept combined with MTX could produce an additive effect over MTX monotherapy in RA patients who were still active despite long-term MTX therapy. This study is described below.

Clinical trials of combination etanercept and MTX therapy

A clinical trial was designed to compare results using etanercept and MTX versus etanercept and placebo (12). Eligible patients were at least 18 years of age, fulfilled the 1987 criteria for the diagnosis of RA (13), and were functional class I, II, or III (14). All participants had active disease as defined by the presence of at least 6 joints that were swollen and 6 that were tender at the time of enrollment. All patients had been taking MTX for at least 6 months and had been on a stable dose of 15 - 25 mg/week for the last 4 weeks. The patients discontinued sulfasalazine and hydroxychloroquine at least 2 weeks prior to initiation of the study and had stopped other DMARDs aside from MTX at least 4 weeks before enrollment. Stable doses of NSAIDs and prednisone (10 mg/day) were continued. A 2:1 randomization scheme was utilized in the protocol. The demographic and clinical characteristics of the patients are shown in Table I.

A total of 14 men and 75 women were enrolled. The mean age was 50 years (range 26-71), and the mean duration of disease was 13 years. The mean weekly dose of MTX was 18 mg in the placebo-MTX group and 19 mg in the etanercept-MTX group. Fifty-nine patients were enrolled in the etanercept-MTX group and 57 (97%) completed the 6-month study. Two patients withdrew because of adverse events unrelated to etanercept (abdominal surgery and traumatic fracture). Of the 30 patients randomly assigned to the placebo-MTX group, 24 (80%) completed the study. Four patients from this group withdrew because of lack of efficacy, one had a myocardial infarction, and one was lost to follow-up.

Efficacy

The etanercept-MTX group had significantly better outcomes than the placebo-MTX group according to ACR responder criteria (Table II).

The proportion of patients who achieved the ACR20 endpoint at 24 weeks was 71% in the etanercept-MTX group versus 27% in the placebo-MTX group (P

Table I. Baseline demographic and clinical characteristics of the study patients.

Characteristic*	Placebo + MTX (n = 30)	Etanercept + MTX (n = 59)
Mean age (yrs.)	53	48
Female sex (%)	73	90
White race (%)	83	76
Mean duration of disease (yrs.)	13	13
Positive test for rheumatoid factor (%)	90	84
Mean no. of prior DMARDs	2.8	2.7
Receiving DMARDs other than MTX at screening (%)	20	8
Receiving NSAIDs (%)	80	75
Receiving corticosteroids (%)	70	53
Mean duration of MTX therapy (mos.)	35	58
MTX dose (%)		
12.5 mg/wk	3	3
15 - 19 mg/wk	60	58
20 - 25 mg/wk	36	40

*DMARDs: disease-modifying antirheumatic drugs; MTX: methotrexate; NSAIDs: nonsteroidal antiinflammatory drugs.

Table II. Patients with 20, 50, and 70 percent improvement according to the criteria of the American College of Rheumatology (ACR).*

Amount of improvement and duration of treatment	Placebo + MTX (n = 30)	Etanercept + MTX (n = 59)	P value
20% (ACR 20)			
12 wks.	33	66	0.003†
24 wks.	27	71	< 0.001†
50% (ACR 50)			
12 wks.	0	42	< 0.001†
24 wks.	3	39	< 0.001†
70% (ACR 70)			
12 wks.	0	15	0.03§
24 wks.	0	15	0.03§

* Patients who withdrew from the study were considered not to have had a response at all points after withdrawal, irrespective of the actual clinical response.
† P value calculated by the chi-square test; § P value calculated by Fisher's exact test.

Table III. Median values for measures of disease and quality of life at baseline and at 12 and 24 weeks.

Measure and treatment	At baseline	At 12 wks.	P value†	At 24 wks	P value†
No. of tender joints¥					
Placebo	28	17	< 0.001	17	< 0.001
Etanercept	28	7		7	
No. of swollen joints¥					
Placebo	17	15	< 0.001	11	< 0.001
Etanercept	20	7		6	
Physician's assessment§					
Placebo	6.5	5.0	0.003	4.0	0.003
Etanercept	6.0	2.0		2.0	
Patient's assessment§					
Placebo	6.0	4.5	0.009	4.0	0.008
Etanercept	6.0	2.0		2.0	
Pain (on visual analogue scale)¶					
Placebo	5.6	4.0	0.004	4.4	0.001
Etanercept	5.0	2.0		1.8	
Morning stiffness (min)					
Placebo	120	60	< 0.001	75	< 0.001
Etanercept	90	10		10	
Disability index ‖					
Placebo	1.5	1.1	0.006	1.1	< 0.001
Etanercept	1.5	0.9		0.8	
Erythrocyte sedimentation rate (mm/hr)**					
Placebo	36	38	0.004	30	0.004
Etanercept	25	12		15	
C-reactive protein (mg/dl)††					
Placebo	2.6	1.8	< 0.001	1.6	< 0.001
Etanercept	2.2	0.3		0.5	

* All patients received methotrexate in addition to placebo or etanercept.
† P values were calculated by analysis of variance, except for P values for morning stiffness and C-reactive protein, which were calculated by the Kruskal-Wallis test.
¥ The tender-joint count evaluated 71 joints; the swollen-joint count evaluated 68, omitting the hips and cervical spine.
§ On this scale, 0 indicates no symptoms and 10 indicates severe symptoms.
¶ On this scale, 0 indicates no pain and 10 indicates severe symptoms.
‖ The disability index is a section of the Health Assessment Questionnaire; on this scale, 0 = best and 3 = worst.
**The normal ranges are 1-13 mm/hr for men and 1-30 mm/hr for women. The baseline value was missing for one patient in the placebo-plus-methotrexate group.
†† The normal range is 0-0.79 mg/dl.

< 0.001). The response in the etanercept-MTX group began at week 1. Likewise, a significantly greater proportion of patients in the etanercept-MTX group achieved the ACR50 and ACR70 responses at 12 weeks and 24 weeks. At baseline the patients had a median of 28 tender joints and 18 swollen joints. At 24 weeks the median number of tender joints was 7 in the etanercept-MTX group and 17 in the placebo-MTX group, which represented an improvement of 75% versus 39%, respectively. The median number of swollen joints was 6 in the etanercept-MTX group and 11 in the placebo-MTX group, which represented an improvement from baseline of 78% and 33%, respectively.

Likewise, the etanercept-MTX group had significantly greater improvement in other measures of disease activity (Table III). For example, the median disability-index score from the Health Assessment Questionnaire improved from 1.5 to 0.8 in the etanercept-MTX group (47% improvement). The score in the placebo-MTX group did not change significantly. Likewise, acute phase reactants improved significantly more in the etanercept-MTX group (C-reactive protein [CRP] levels of 2.2 mg/dl decreasing to 0.3 mg/dl) versus the placebo-MTX group (CRP levels of 2.6 mg/dl decreasing to 1.8 mg/dl). At their last visit (week 24) 44% of the etanercept-MTX group versus 13% of the placebo-MTX group had normal CRP levels.

Overall, the etanercept-MTX group was superior in response parameters regardless of the dose of MTX, the duration of MTX therapy, or each group's use of corticosteroids or NSAIDs.

Adverse effects

The only significant difference in adverse events between the etanercept-MTX group and the placebo-MTX group (42% versus 7%) was in the frequency of reactions at the injection site. These injection-site reactions were mild, and were characterized by erythema with or without itching, pain, and swelling. None of these reactions required the suspension of etanercept, and the mean duration was 3 days. The occurrence of injection site reactions was not predictive of the clinical response to etanercept, since there was no significant difference

in the ACR20 response in patients with site reactions (72%) versus etanercept-MTX patients without site reactions (71%).

Potential antibodies to etanercept were detected in only one patient during the study. The antibody was non-neutralizing and was detected in a patient with a rapid and sustained response to etanercept without any injection site reaction or other adverse effect. Three percent of patients in the placebo-MTX group and 7% of patients in the etanercept-MTX group had positive results in assays for antibodies to double-stranded DNA. At the time of the last visit at 24 weeks, one additional patient in the placebo-MTX group and 4 additional patients in the etanercept-MTX group developed positive tests for antibodies to double-stranded DNA. No patients in either group developed new connective tissue disease, thrombotic events, or thrombocytopenia.

Discussion

In the present study, RA who had persistent disease activity despite aggressive methotrexate therapy underwent an additive, favorable response when the combination of etanercept-MTX was given. At 6 months, 71% of patients in the etanercept-MTX group had an ACR 20 response (versus 27% in the placebo-MTX group). In the etanercept-MTX group 39% had an ACR50 response (versus 3% in the placebo-MTX group), and in the etanercept group 15% (versus 0% in the placebo-MTX group) met the rigorous ACR70 response. The ACR70 response has been proposed by the Food and Drug Administration as the criterion for a major clinical response.

The only significant adverse event seen in the etanercept-MTX group was injection-site reactions. There was no significant difference between the etanercept-MTX and placebo-MTX groups. The adverse events seen in the present study were similar to those seen with MTX alone in RA patients

During the last several years MTX has gained universal acceptance as one of the primary DMARDs for the treatment of RA. MTX has achieved this position of therapeutic dominance because of long-term efficacy and tolerability. It is clear that patients are able to continue on MTX longer than on other DMARDs (8, 15, 16). Nonetheless, in many patients MTX does not adequately control the disease, so that combinations of drugs with MTX have been tried (17). A review by Felson and colleagues in 1994 painted a rather bleak picture of combination therapy in RA, with the conclusion that there was no convincing evidence of the superiority of combination drug therapy to monotherapy (18). A subsequent study utilizing triple therapy with MTX, sulfasalazine, and hydroxychloroquine reported that this combination was superior to MTX alone or to the combination of sulfasalazine and hydroxychloroquine (19). Patients on these combinations still had active RA. Another study examined the combination of MTX and cyclosporine. After 6 months of therapy, 48% of patients in the cyclosporine-MTX group and 16% in the placebo-MTX group met the ACR20 criteria, although only 1% of the cyclosporine-MTX group met the ACR70 response (20).

The present study is a significant addition to our knowledge of combination therapy in RA and appears to be superior in most respects to previous reports. A long-term study has shown that etanercept therapy has sustained efficacy and tolerability for at least 18 months (21). There remain unanswered questions about long-term side effects, but etanercept appears to be a novel and robust drug either alone or in combination with MTX in the treatment of RA.

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