The Early Rheumatoid Arthritis (ERA) Trial comparing the efficacy and safety of etanercept and methotrexate

J.M. Bathon, M.C. Genovese

The Johns Hopkins University School of Medicine, Baltimore, Maryland; Stanford University School of Medicine, Palo Alto, California, USA.

Joan M. Bathon, MD; Mark C. Genovese, MD.

Please address correspondence to:
Joan M. Bathon, MD, 5501 Hopkins Bayview Circle, Room 1B.13, Baltimore, Maryland 21224, USA.
E-mail: jbathon@jhmi.edu

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ABSTRACT

The Early Rheumatoid Arthritis (ERA) trial compared monotherapy with etanercept or methotrexate in patients with early erosive rheumatoid arthritis. Over the initial period of 12, and subsequently 24, months both treatments were associated with a profound reduction in radiographic progression of joint damage, as well as a reduction in signs and symptoms of disease. Etanercept showed slight superiority to methotrexate in reducing subsequent radiographic erosions and in the rapidity of the clinical response. Both therapies proved to be safe and well tolerated and, importantly, the relative safety and tolerance of a rapidly escalated dosing regimen for methotrexate was demonstrated. In summary, early aggressive treatment of RA is associated with clinical and radiographic benefit that can be demonstrated after a relatively short period of treatment.

Introduction

The Early Rheumatoid Arthritis (ERA) clinical trial is a landmark study in the treatment of rheumatoid arthritis (RA) (1, 2). It provided proof that biologic monotherapy specifically targeted to inhibit a single cytokine and introduced early in disease could profoundly interrupt the natural history of this disease. Importantly, it also demonstrated the nearly equivalent ability of methotrexate to do the same, and the relative safety of rapid escalation of methotrexate to high dose (0 to 20 mg in 8 weeks). To date, it is the only head-to-head comparison of a biologic to a non-biologic disease-modifying anti-rheumatic drug (DMARD) for the treatment of RA.

Etanercept is a soluble fusion protein consisting of two extracellular ligand-binding portions of the human tumor necrosis factor receptor type II (TNF-RII) coupled to the Fc portion of human immunoglobulin (IgG1) (3). Etanercept binds and inhibits both natural ligands of the TNF receptors, TNF-α and lymphotoxin-α. Dimerization of TNF-RII results in a higher affinity for TNF-α than the monomeric receptor, and linkage to the Fc portion of IgG1 prolongs its half-life (3). In RA patients, the serum half-life of etanercept is approximately 4.8 days (4), and etanercept is administered subcutaneously twice weekly.

A critical role for TNF in the pathogenesis of RA has been established in studies demonstrating profound proinflammatory properties of TNF *in vitro*, the presence of high levels of the cytokine in rheumatoid sera and joints, and the ability of TNF antagonists to reduce significantly joint inflammation in animal models of arthritis (reviewed in detail in reference 5). Initial clinical trials in RA comparing etanercept or the anti-TNF monoclonal antibody, infliximab, to placebo confirmed the efficacy of TNF antagonism in profoundly and rapidly reducing the clinical and laboratory manifestations of RA (6-9). These studies were conducted in patients with long-standing RA who had been poorly controlled by multiple prior non-biological DMARDs and in whom considerable joint damage had already been sustained. The ultimate goal of the treatment of RA, however, is to prevent joint damage and disability, and treatment of RA early in the disease process is therefore warranted (10). Radiographic joint erosions begin to develop early in disease and have been identified as a predictor for subsequent structural damage in RA (11-13). It was therefore important to demonstrate that TNF antagonism could interrupt the progression of radiographically evident joint damage in RA, and to compare its effects to rapidly dose-escalated methotrexate.

The hypothesis tested in the ERA trial

Table I. Sharp radiographic progression scores.

	Methotrexate (N = 217)	Etanercept 25 mg (N = 207)
Baseline Sharp scores		
Total	12.9 ± 13.8	12.4 ± 15.8
Erosion	7.5 ± 9.2	6.4 ± 9.0
Joint space narrowing	5.4 ± 6.1	6.0 ± 8.2
Baseline estimated rate of progression*		
Increase in total Sharp score/year	9	9
Increase in erosion score/year	5	5
Increase in narrowing score/year	4	4
Rate of progression after 12 months of treatment		
Increase in total Sharp score/year	1.59	1.00
Increase in erosion score/year	1.03	0.47**
Increase in narrowing score/year	0.56	0.53
Rate of progression after 24 months of treatment (MTX, n = 169; etanercept, 25 mg, n = 177)		
Increase in total Sharp score/year	3.2	1.3***
Increase in erosion score/year	1.9	0.7***
Increase in narrowing score/year	1.3	0.7

*Estimated annual rates of progression at baseline were calculated by dividing radiographic scores for each patient by years of disease and calculating the mean for each treatment group; **p value = 0.002, comparing the two treatment groups; ***p value = 0.001, comparing the two treatment groups.

was that treatment of RA with etanercept initiated early in the course of disease would be effective in slowing the rate of radiographic progression, and in reducing clinical and laboratory signs of disease activity. The efficacy of etanercept was compared in this trial to methotrexate. Inclusion criteria included: 1) disease duration of less than three years; 2) no prior treatment with methotrexate; 3) at least 10 swollen joints and 12 tender joints; and 4) serum C-reactive protein (CRP) concentration of at least 2.0 mg/dl or morning stiffness of at least 45 minutes. In order to recruit patients who were at high risk for radiographic progression, patients also were required to have either a positive serum test for rheumatoid factor (RF) or at least three bone erosions on radiographs of the hands, wrists or feet at baseline. Patients were randomized to treatment with either etanercept 25 mg twice weekly, etanercept 10 mg twice weekly, or methotrexate rapidly escalated over eight weeks to 20 mg per week (or the maximum tolerated dose). The primary clinical endpoint was overall response during the first six months, as indicated by the area under the curve for ACR-N (see Fig. 1). The percentages of patients with ACR 20, 50 and 70 (14) responses were also assessed. The primary radiographic endpoint was the change in Sharp score with Van der Heijde modification (11, 15) over twelve months.

Six hundred thirty-two healthy adult patients with RA were enrolled in the trial and were followed for at least twelve months in a double blind fashion (mean 18.4 months prior to unblinding). Following the blinded phase of the trial, 512 patients continued to receive the therapy to which they had been randomized in an open-label protocol for up to one additional year. Enrolled patients consisted predominantly of Caucasian women with a mean age of 50, mean duration of disease of one year, and mean tender and swollen joint counts of 30 and 24, respectively. At baseline, 87% of patients had radiographic erosions, 79% had joint space narrowing, and 88% were RF positive. There were no statistically significant differences in the baseline characteristics among the three treatment groups. The mean methotrexate dose achieved by week eight was 19 mg/week.

Patients treated with etanercept 25 mg exhibited a more rapid clinical response than patients treated with MTX, as evidenced by a higher area under the curve (AUC) for ACR-N over 12 months, and higher levels of ACR 20, 50, and 70 responses in the first several months of treatment. In the second six months of treatment, however, ACR 20/50/70 responses were equivalently robust in all treatment groups and not statistically significantly different. At 24 months the ACR 20/50/70 responses remained impressive in both treatment arms. However, the ACR20 response in the etanercept group was significantly higher than that for the methotrexate group (72% vs 59%, respectively, p = 0.005).

Etanercept treatment was associated with a nearly ten-fold reduction in the rate of anticipated radiographic progression over twelve months by comparing the actual to the calculated baseline rate of progression (Table I). The baseline rate of radiographic progression (prior to initiation of study drug) is estimated by dividing the total Sharp score by the duration of disease. In the etanercept 25 mg group, the calculated baseline annual progression in Sharp scores (total, erosion and joint space narrowing) were 9, 5 and 4 Sharp units/yr, respectively; the progression scores after twelve months of etanercept 25 mg were 1.00, 0.47 and 0.53 Sharp units/yr, respectively.

Fig. 1. Definition of American College of Rheumatology (ACR) clinical response criteria (based on ref. 11).

ACR 20% Response

Must include:

- 20% improvement in tender joint count
- 20% improvement in swollen joint count

and 20% improvement in 3 of 5 of the following criteria:

- Patient pain assessment
- Patient global assessment
- Physician global assessment
- Patient self-assessed disability
- Acute phase reactant value (ESR or CRP)

ACR-N (ACR Numeric Response)

ACR-N is defined as the smallest degree of improvement from baseline in the following three criteria:

- Number of tender joints
- Number of swollen joints
- Median of the five remaining measures of disease activity

Methotrexate (Table I) and etanercept 10 mg (data not shown) also profoundly reduced radiographic progression rates. However, the effect of etanercept 25 mg on slowing radiographic progression was more rapid, as evidenced by statistically significantly lower erosion and total Sharp scores at 6 months compared to methotrexate (p 0.001 for both). At twelve months, etanercept was statistically superior to methotrexate only for the erosion score (p 0.002), while at 24 months the etanercept 25 mg group had significantly lower erosion and total Sharp scores (Table I). The majority of patients had no new or worsening erosions at one year (72% and 60% in the etanercept 25 mg and methotrexate groups, respectively, at one year, $p = 0.007$), and a significant proportion continued to be without new erosions at two years (63% and 51%, respectively, $p = 0.017$).

Monotherapy with either etanercept or methotrexate was well tolerated in patients with early RA. Injection site reactions were the most commonly reported adverse event with etanercept 25 mg and occurred at higher frequency than in the methotrexate treated group at one year (37% vs 7%, respectively, $p < 0.05$), as did sporadic neutropenia (16% versus 8%, $p = 0.01$). In contrast, methotrexate treated patients reported nausea, rash, alopecia and mouth ulcers more commonly than the etanercept 25 mg group (p values < 0.05 for all comparisons), and had higher frequencies of elevated transaminases and lower peripheral blood lymphocyte counts. Rates of serious infections were low in all treatment groups at one year (less than 3%), and no opportunistic infections or infection-related deaths were reported in any treatment group. There was no evidence for an increased rate of cancer in any treatment group.

In summary, initiation of treatment in patients with early, severe erosive RA with a potent inhibitor of TNF-α (etanercept) or with aggressively dosed methotrexate is highly effective both in reducing signs and symptoms of disease, as well as in limiting subsequent radiographic evidence of joint damage. This study provides proof of concept that inhibition of TNF-mediated inflammatory pathways can alter the natural course of RA and thus this strategy merits the designation of "disease modifying" therapy. Importantly, the ERA trial also re-affirmed the potent disease modifying properties of methotrexate, and has provided a now well accepted standard-of-care dosing schedule for rapid escalation of methotrexate for RA.

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