Etanercept Versus Methotrexate in Patients With Early Rheumatoid Arthritis

Two-Year Radiographic and Clinical Outcomes


Objective. To compare the clinical and radiographic outcomes in patients with rheumatoid arthritis (RA) who received monotherapy with either etanercept or methotrexate (MTX) for 2 years and to assess the safety of this therapy.

Methods. In the Enbrel ERA (early rheumatoid arthritis) trial, 632 patients with early, active RA were randomized to receive either twice-weekly subcutaneous etanercept (10 mg or 25 mg) or weekly oral MTX (mean dosage 19 mg per week) for at least 1 year in a double-blind manner. Following the blinded phase of the trial, 512 patients continued to receive the therapy to which they had been randomized for up to 1 additional year, in an open-label manner. Radiograph readers remained blinded to treatment group assignment and the chronologic order of images.

Results. At 24 months, more 25-mg etanercept patients than MTX patients met American College of Rheumatology 20% improvement criteria (72% and 59%, respectively; \( P = 0.005 \)), and more had no increase in total score and erosion scores on the Sharp scale (\( P = 0.017 \) and \( P = 0.012 \), respectively). The mean changes in total Sharp score and erosion score in the 25-mg etanercept group (1.3 and 0.66 units, respectively) were significantly lower than those in the MTX group (3.2 and 1.86 units, respectively; \( P = 0.001 \)). Significantly more patients in the 25-mg etanercept group (55%) than in the MTX group (37%) had at least 0.5 units of improvement in the Health Assessment Questionnaire disability index (\( P = 0.001 \)). Fewer patients in the etanercept group than in the MTX group experienced adverse events or discontinued treatment because of adverse events.

Conclusion. Etanercept as monotherapy was safe and was superior to MTX in reducing disease activity, arresting structural damage, and decreasing disability over 2 years in patients with early, aggressive RA.

Etanercept (10 mg or 25 mg) or weekly oral MTX (mean dosage 19 mg per week) for at least 1 year in a double-blind manner. Following the blinded phase of the trial, 512 patients continued to receive the therapy to which they had been randomized for up to 1 additional year, in an open-label manner. Radiograph readers remained blinded to treatment group assignment and the chronologic order of images.

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shown to be safe and effective in rapidly reducing
disease activity in adults with rheumatoid arthritis (RA)
and in sustaining that improvement (1–5). It is equally
effective in children with polyarticular juvenile RA (6).
Etanercept is approved for use as monotherapy, as well
as combination therapy with methotrexate (MTX), for
the treatment of RA.

Loss of function and radiographic change occur
early in the course of disease. These changes can be
delayed or prevented with the use of certain disease-
modifying antirheumatic drugs (DMARDs). Although
several DMARDs are initially clinically effective and
well tolerated, many of these drugs become less effective
or exhibit increased toxicity over time. Based on its
efficacy and tolerability, MTX has become the standard
therapy by which other treatments are measured (1,7).

In the first year of the Enbrel ERA (early rheu-
matoid arthritis) trial, etanercept was shown to be
significantly more effective than MTX in improving
signs and symptoms of disease and in inhibiting radi-
ographic progression (1). We now report results from
the second year of the study, which was designed to compare
etanercept alone and MTX alone in terms of safety,
sustained efficacy, and prevention of radiographic pro-
gression in patients with early, aggressive RA.

PATIENTS AND METHODS

The study design and results of the double-blind
portion of this trial have been previously reported (1).
Institutional review boards at each study site approved the protocol,
and all patients gave written informed consent.

Patients. At study entry, all participants were at least
18 years of age, had had RA for no more than 3 years, and had
not been treated with MTX. To ensure that only patients at
high risk for radiographic progression of disease were enrolled,
subjects were required to have a positive test for rheumatoid factor or at least 3 bone erosions evident on radiographs of the
hands, wrists, or feet; at least 10 swollen joints and at least 12
tender or painful joints; and an erythrocyte sedimentation rate
>28 mm/hour, a C-reactive protein concentration >2.0 mg/dl,
or morning stiffness that lasted at least 45 minutes (1).

Study protocol. Patients were randomly assigned to
receive 10 mg of etanercept by subcutaneous injection twice
weekly and 3 placebo tablets weekly; 25 mg of etanercept by
subcutaneous injection twice weekly and 3 placebo tablets
weekly; or three 2.5-mg tablets of MTX weekly and twice-
weekly subcutaneous injections of placebo. The initial 7.5-mg
dose of MTX and its placebo was rapidly increased, to 8 tablets
(20 mg) at week 8 if any joints were actively involved. All
patients received folate supplementation (1 mg/day).

After the last patient enrolled had completed 12
months in the study, placebo treatments were discontinued,
but no other dosing changes were made. Patients who did not
withdraw from the study at this time continued to receive the
therapy to which they had originally been assigned for up to 1
additional year. Because the time of entry into the blinded
phase of the trial was staggered, a minimum of 13.8 months
and a maximum of 23.6 months elapsed from the time patients
received a first dose until the study was unblinded (average
18.4 months). The mean dose of MTX was 19 mg/week, and
the median dose was 20 mg/week.

Study end points. The American College of Rheuma-
tology (ACR) core set of variables for each patient was
collected, and disease activity was assessed according to ACR
20% improvement criteria; ACR 50% and ACR 70% improve-
ment rates were calculated in an analogous manner (8). For
the clinical end points, data collected during the blinded phase
of the study were pooled with data collected during the
open-label phase. Sensitivity analyses showed no significant
difference in results when blinded data from the second year
were compared with unblinded data from that period.

Radiographs of the hands, wrists, and feet were ob-
tained at baseline and at 6, 12, and 24 months (or at the time
of study termination for patients who discontinued prematurely).
The films were digitized (9) and scored for erosions and
joint space narrowing by 2 of 6 radiologists or rheumatologists
using the Sharp scoring method. One pair of readers scored
each patient’s set of images, and the average score was used in
the analysis. The baseline, 6-month, and 12-month films were
scored at the end of the first year (1). At the end of the second
year, these images, along with the 24-month film, were scored
again by the same pair of readers. The readers remained
blinded to treatment group assignment and chronologic order
of the images, even after unblinding of the study to patients
and investigators. Results from the reading that included the
24-month films were used for the present analyses.

During the second year of the study, patients were
evaluated every 3 months for safety and efficacy, including use
of the disability index of the Health Assessment Questionnaire
(HAQ) (10). Serum samples obtained at baseline and at
months 6, 12, 18, and 24 were tested for anti- etanercept
antibodies by an enzyme-linked immunosorbent assay
(ELISA) as previously described (1,2). Cumulative safety data
for the entire 2-year study are included. Tests for autoantibod-
ies, including antinuclear antibodies, anti-double-stranded
DNA antibodies, and anticardiolipin IgM and IgG antibody
titers, were performed at screening and every 6 months
thereafter.

Statistical analysis. For the ACR20, ACR50, and
ACR70 responses, last observation carried forward (LOCF)
analyses were performed, using the last observation recorded
while patients were receiving the study drug to which they had
been randomized. Although there are sometimes difficulties
with the LOCF method (11), its use was considered appropri-
ate in these analyses because the ACR responses were fairly
stable in all treatment groups. LOCF analyses were also used
for HAQ disability index scoring. The binary end points
(ACR20, ACR50, and ACR70 responses) were compared
among treatment groups using a chi-square test.

For the radiologic end points, changes in Sharp scores
over 24 months were compared. For radiographic scores, linear
extrapolations or interpolations, adjusted over time, were used
for patients whose final-month radiograph deviated from the
planned 24-month time point. Fifteen patients who had only 1
film (at baseline) were excluded from the analyses; inclusion of
these patients did not change the results. Rank tests (van Elteren tests [12]) were used to compare the 3 treatment groups. Predicted yearly progression rates were calculated.

Figure 1. Schematic diagram showing number of study participants in each group who withdrew and the number who completed the trial. MTX = methotrexate.

Figure 2. Percentage of patients with rheumatoid arthritis who discontinued use of the study drugs during the 2-year trial. Values shown are the percentage of patients who completed the trial.

Table 1. Characteristics of patients at baseline and at year 2

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<thead>
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<tr>
<td></td>
<td>MTX</td>
<td>10 mg</td>
<td>25 mg</td>
<td>MTX</td>
<td>10 mg</td>
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<tr>
<td></td>
<td>(n = 217)</td>
<td>(n = 208)</td>
<td>(n = 207)</td>
<td>(n = 169)</td>
<td>(n = 166)</td>
<td>(n = 177)</td>
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<td>Mean age, years</td>
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<td>50</td>
<td>51</td>
<td>49</td>
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<td>Age range</td>
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<td>21–82</td>
<td>21–79</td>
<td>19–84</td>
<td>21–82</td>
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<tr>
<td>% age ≥ 65 years</td>
<td>15</td>
<td>14</td>
<td>18</td>
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<td>% female</td>
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<td>75</td>
<td>74</td>
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<tr>
<td>% Caucasian</td>
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<td>84</td>
<td>86</td>
<td>88</td>
<td>86</td>
<td>86</td>
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<tr>
<td>Mean duration of RA, months</td>
<td>12</td>
<td>11</td>
<td>12</td>
<td>12</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>% rheumatoid factor–positive</td>
<td>89</td>
<td>88</td>
<td>87</td>
<td>90</td>
<td>89</td>
<td>88</td>
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<td>Mean C-reactive protein level, mg/dl†</td>
<td>3.7</td>
<td>4.4</td>
<td>3.3</td>
<td>4.0</td>
<td>4.5</td>
<td>3.6</td>
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<td>% who previously took DMARDs</td>
<td>46</td>
<td>39</td>
<td>40</td>
<td>47</td>
<td>39</td>
<td>41</td>
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<tr>
<td>Mean no. of DMARDs taken</td>
<td>0.6</td>
<td>0.5</td>
<td>0.5</td>
<td>0.6</td>
<td>0.4</td>
<td>0.5</td>
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<td>% receiving concomitant therapy at baseline NSAIDs</td>
<td>80</td>
<td>76</td>
<td>86</td>
<td>79</td>
<td>77</td>
<td>88</td>
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<td>Corticosteroids</td>
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<td>42</td>
<td>39</td>
<td>46</td>
<td>37</td>
<td>36</td>
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<td>Mean daily dosage, mg</td>
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<td>9</td>
<td>7</td>
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<td>9</td>
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<tr>
<td>Mean ± SD no. of tender joints</td>
<td>30 ± 16</td>
<td>31 ± 16</td>
<td>31 ± 16</td>
<td>30 ± 16</td>
<td>31 ± 16</td>
<td>31 ± 16</td>
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<tr>
<td>Mean ± SD no. of swollen joints</td>
<td>24 ± 12</td>
<td>24 ± 12</td>
<td>24 ± 12</td>
<td>24 ± 12</td>
<td>24 ± 12</td>
<td>24 ± 12</td>
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<tr>
<td>Mean ± SD total Sharp score</td>
<td>12.9 ± 13.8</td>
<td>11.2 ± 14.8</td>
<td>12.4 ± 15.8</td>
<td>11.3 ± 13</td>
<td>9.7 ± 13.8</td>
<td>10.8 ± 14.8</td>
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<tr>
<td>Mean ± SD erosion score</td>
<td>7.5 ± 9.2</td>
<td>6.1 ± 9.0</td>
<td>6.4 ± 9.0</td>
<td>6.9 ± 8.5</td>
<td>5.7 ± 8.6</td>
<td>5.7 ± 8.5</td>
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<tr>
<td>Mean ± SD joint space narrowing score</td>
<td>5.4 ± 6.1</td>
<td>5.0 ± 7.7</td>
<td>6.0 ± 8.2</td>
<td>4.4 ± 5.8</td>
<td>4.0 ± 6.9</td>
<td>5.1 ± 7.6</td>
</tr>
<tr>
<td>% with erosions</td>
<td>87</td>
<td>85</td>
<td>88</td>
<td>86</td>
<td>80</td>
<td>84</td>
</tr>
<tr>
<td>Estimated rate of progression, units/year</td>
<td>9</td>
<td>8</td>
<td>9</td>
<td>11</td>
<td>10</td>
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<tr>
<td>Total Sharp score</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>7</td>
<td>6</td>
<td>6</td>
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<tr>
<td>Joint space narrowing score</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
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</table>

* MTX = methotrexate; RA = rheumatoid arthritis; DMARDs = disease-modifying antirheumatic drugs; NSAIDs = nonsteroidal antiinflammatory drugs.
† Normal range 0–0.8 mg/dl.
using the baseline film and duration of disease. The proportion of patients who had no progression in total Sharp score, erosion score, and joint space narrowing score were calculated. No progression was defined as <0.5 units of change from baseline. This definition was chosen because readers scored using whole numbers only, and scores from 2 readers were averaged for each patient. To maintain the Type I error at 5%, pairwise comparisons at the 0.05 level were considered significant only if the overall comparison (3 groups) was significant at $P < 0.05$.

**RESULTS**

**Patients and study completion.** Of the 632 patients enrolled at baseline, 512 patients entered the second year of the study (Figure 1). In the 25-mg etanercept group, 74% of patients received the study drug for 2 years, compared with 59% of patients in the MTX group (Figure 2). The demographic characteristics of the patients who entered year 2 of the study were similar among groups (Table 1), and the cohort continuing in the second year was similar to the entire population of the original study at baseline (1).

Significantly more patients in the MTX group than in the combined etanercept groups discontinued use of the study drug because of adverse events ($P = 0.01$, MTX versus all etanercept). Over the entire 2-year period, 12% of patients in the MTX group discontinued due to adverse events, compared with 5% in the 10-mg etanercept group and 7% in the 25-mg etanercept group. During the 2-year study, 11% of patients in the MTX group withdrew due to lack of efficacy, compared with 16% of patients in the 10-mg etanercept group and 8% in the 25-mg etanercept group.

**ACR responses.** The improvement in arthritis (as measured by ACR criteria) seen during the first year of the study was sustained through the second year. Although etanercept was numerically superior to MTX, both agents continued to be effective in reducing disease activity (Figure 3). At month 24, significantly more patients in the 25-mg etanercept group than in the MTX group had an ACR20 response (72% versus 59%, $P = 0.005$). ACR50 response rates were 49% and 42%, respectively, in the 25-mg etanercept and MTX groups, and ACR70 rates were 29% and 24%, respectively ($P < 0.05$ versus methotrexate).

Consistent with results reported during the first year of the study, the 25-mg etanercept dose was more effective than the 10-mg etanercept dose at month 24, with respect to the ACR20 (61%), ACR50 (35%), and ACR70 (19%) ($P < 0.02$ for all comparisons) (1).

**Radiographic results.** There was significantly less radiographic progression in the 25-mg etanercept group compared with the MTX group (Figure 4). At 2 years, the mean change from baseline in total Sharp score was...
1.3 units in the 25-mg group versus 3.2 units in the MTX group \((P = 0.001)\). Mean changes in erosion score were 0.7 and 1.9 units in the 25-mg etanercept and MTX groups, respectively \((P = 0.001)\). In the 25-mg etanercept group, the median change from baseline at 2 years was 0 for total Sharp score, erosion score, and joint space narrowing score (Figure 5).

The 25-mg dose of etanercept was significantly better than MTX in preventing radiographic progression. Sixty-three percent of 25-mg etanercept patients had no increase in total Sharp score, compared with 51% of MTX patients \((P = 0.017)\), and 70% versus 58% had no increase in erosions \((P = 0.012)\) (Figure 6). More patients in the 25-mg etanercept group than in the MTX group had no increase in the joint space narrowing score \((78\% \text{ versus } 69\%)\), but the difference was not significant (overall 3-group comparison \(P = 0.1165\)).

For the radiographic end points, the 25-mg dose was significantly more effective than the 10-mg dose with respect to the change in total Sharp \((P = 0.032)\) and erosion scores \((P = 0.027, \text{ Figure 4})\). The change in the joint space narrowing score was low in all 3 groups \((P = \text{NS})\). Of interest, of the subgroup of patients whose total Sharp scores were 0 at baseline (17 patients in the MTX group, 21 in the 10-mg etanercept group, and 19 in the 25-mg group), a substantial number had no radiographic progression over 24 months. At month 24, 65% of the MTX patients still had a total Sharp score of 0, compared with 86% of patients in the 10-mg etanercept group and 79% of patients in the 25-mg group.

**Function and disability.** The HAQ disability index is the arthritis-specific quality of life instrument used most commonly to assess functional status. It is scored on a scale of 0–3 units, with higher numbers indicating increasing disability \((10)\). A 0.25-unit change in HAQ score is generally considered to be a clinically significant change in the level of disability \((13)\).

At baseline, patients in this study had a moderate degree of disability, with mean HAQ disability index scores of 1.4–1.5 units. By month 12, \(\sim 55\%\) of patients in both the MTX and 25-mg etanercept treatment groups had at least a 0.5-unit improvement in HAQ score (Figure 7). At 24 months, the same proportion \((55\%)\) of patients in the 25-mg etanercept group had at least a 0.5-unit improvement in HAQ score, but the percent of MTX patients maintaining this level of improvement declined to 37% \((P < 0.001)\). Thus, the 25-mg dose of etanercept was significantly more effective than MTX in improving quality of life over 2 years.

**Safety.** As in previous studies with etanercept, the most common adverse event in both etanercept groups over the 2-year study period was injection-site reaction \((1,2,4)\). Of the other noninfectious adverse events that occurred in \(\geq 10\%\) of patients in any treatment group, nausea, alopecia, and mouth ulcers were significantly more common in the MTX group.
Four patients (2%) had pneumonitis as a result of MTX use during this study (14).

Serious infections were rare and did not increase in frequency during the second year of the study. Over the 2-year period of study, 21 patients had infections that required hospitalization or use of intravenous antibiotics, including 9 patients in the MTX group, 5 patients in the 10-mg etanercept group, and 7 patients in the 25-mg group. The types of serious infection observed in the second year were similar to those reported in the first year (1) and included cellulitis (1 patient each in all 3 treatment groups), bronchitis (1 patient in the 10-mg group), pneumonia (1 patient in the 10-mg group), and cystitis (2 patients in the 25-mg group). No cases of tuberculosis and no opportunistic infections were seen.

There were 2 deaths during the first year of the study (1), no deaths during the second year, and no deaths due to infection. Ten patients developed cancer during the entire study period (3 in the MTX group, 3 in the 10-mg group, and 4 in the 25-mg group); these rates are similar to those in the age- and sex-matched general population, using the Surveillance, Epidemiology and End Results data base (15). No predominant cancer type was observed.

Etanercept was not demonstrated to be immunogenic in this trial. Over the 2-year study period, 14
etanercept patients (3.5%), including 8 in the 25-mg group and 6 in the 10-mg group, had at least 1 positive anti-etanercept antibody test, using the ELISA described previously (1,2). None of the antibodies had neutralizing activity, and there was no relationship between safety or efficacy and the presence or absence of these antibodies. There was no consistent difference in the number of patients testing positive for autoantibodies between any of the 3 treatment groups. No new autoimmune features and no adverse events suggestive of systemic lupus erythematosus, demyelinating diseases, or other autoimmune diseases were reported.

**DISCUSSION**

Recent studies have examined radiographic progression in patients with late-stage RA who have taken leflunomide, MTX, or placebo (16) as well as patients who have taken infliximab plus MTX or placebo plus MTX following a partial response to MTX (17,18). This is the first study to compare the safety and efficacy of MTX monotherapy with those of a biologic response...
ETANERCEPT AND METHOTREXATE IN RA PATIENTS

The current study demonstrates that both etanercept and aggressively dosed MTX are effective as monotherapy for the treatment of early RA. The clinical response and inhibition of structural damage observed with etanercept or MTX as monotherapy are sustained for at least 2 years in patients with early, active RA. Over the 2-year period of the study, some relative advantages of etanercept became apparent. Within the first few months of the study, a difference in clinical response between patients receiving MTX and those receiving etanercept was observed. This difference was thought to be associated with the more rapid onset of action of etanercept compared with MTX. Aggressively dosed MTX did result in a considerable clinical response by month 3 of this study, and although the clinical response at 2 years remained substantial, it was less than that seen with etanercept. Compared with MTX, patients receiving 25 mg of etanercept had a significantly greater clinical response at 2 years as measured by ACR20. Because the analysis of the data was performed using the LOCF, the ACR20 response rate or efficacy of MTX was not lessened based on withdrawal due to side effects or an inability to tolerate the aggressive dose of MTX.

Again, although both agents were effective for inhibiting radiographic progression, the 25-mg dose of etanercept was significantly more effective than MTX as measured by change in total Sharp score and erosion score, as well as the proportion of patients with no progression in total Sharp score, erosion score, and joint space narrowing score.

The radiographic findings of this study and others are impressive and suggest the unequivocal need for the use of DMARDs early in the course of RA. However, differences in study populations, and in design, duration, and end points measured make comparisons among studies difficult if not impossible. Limitations in the sensitivity of the radiographs as well as in the scoring systems themselves make it difficult to comment on healing or reversal of radiographic damage.

A substantial portion of the second year of this study was conducted in an open-label manner, and all patients were required to remain in the originally assigned treatment groups. Because of the staggered nature of the enrollment period, the mean time that patients remained blinded to treatment was 18.4 months. It is possible that for some patients, the period of unblinded therapy influenced clinical assessment. However, the rate of clinical response did not differ before and after unblinding in the second year of the study, suggesting no marked change in perception of outcome or benefit.

Additionally, the open-label nature of a substantial portion of the second year of the study could also have affected the radiographic results. It is possible that the low progression rates in year 1 created an expectation among the readers that the year 2 progression rates would also be low. This might have biased the scoring to minimize change. However, the readers remained blinded to the treatment group and the chronologic order of the images. Therefore, no obvious mechanism exists that would bias in favor of less progression in the 25-mg etanercept group.

Over the 2 years, monotherapy with etanercept or MTX had acceptable side effect profiles, although patients treated with etanercept had fewer noninfectious adverse events and lower rates of discontinuation due to adverse events compared with patients treated with MTX. There was no evidence of an increase in adverse events or cumulative toxicity in the etanercept groups during the second year of the study. These results corroborate those of a recent long-term followup study of 628 adult patients with long-standing RA who were treated with etanercept for up to 43 months, which demonstrated no cumulative safety issues with sustained etanercept therapy (5).

Results of the current trial support the utility of early aggressive therapy, because the significant impact on disease progression may reduce the functional decline that occurs over many years. This impact can be
demonstrated already at 2 years by the significant improvement in function and reduction in disability as measured by the HAQ disability index.

In summary, etanercept and MTX had excellent profiles for initial treatment of patients with active, erosive RA. The benefits of 25-mg etanercept as monotherapy were shown to be superior to those of MTX at 2 years, and improvements in clinical, radiographic, and disability end points were maintained with sustained therapy.

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REFERENCES