Etanercept was more effective and safer than methotrexate in reducing disease progression in early rheumatoid arthritis

Bathon JM, Martin RW, Fleischmann RM, et al. **A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis.** N Engl J Med. 2000 Nov 30;343:1586-93.

QUESTION

In patients with early rheumatoid arthritis (RA), is etanercept more effective and safer than methotrexate (MTX)?

DESIGN

Randomized {allocation concealed*}†, blinded (patients and outcome assessors),* placebo-controlled trial with follow-up at 6 and 12 months.

SETTING

{Centers in North America.}†

PATIENTS

632 patients (mean age 50 y, 75% women, 86% white) who were ≥ 18 years of age, had RA ≤ 3 years, had no other major conditions, and had not been treated with MTX. Other inclusion criteria were a positive result on serum testing for rheumatoid factor; ≥ 3 bone erosions evident on radiography; ≥ 10 swollen joints; ≥ 12 tender or painful joints; and an erythrocyte sedimentation rate of ≥ 28 mm/h, a serum C-reactive protein concentration of ≥ 2 mg/dL, or morning stiffness lasting ≥ 45 minutes. Follow-up at 12 months was 100%.

INTERVENTION

Patients were allocated to self-administered etanercept, two 10-mg (n = 208) or 25-mg (n = 207) injections, or to MTX (n = 217), three 2.5-mg tablets, each week. The MTX dose was increased at the 4th week to 15 mg and at the 8th week to 20 mg total. Patients with aminotransferase levels that increased ≥ 2.5 times the normal upper limit were allowed one 5-mg MTX or placebo reduction.

MAIN OUTCOME MEASURES

Disease activity (based on American College of Rheumatology [ACR] criteria); hand, wrist, and foot joint changes (based on the Sharp scoring method [range 0 to 398]); and adverse events (based on the Common Toxicity Criteria of the U.S. National Cancer Institute).

MAIN RESULTS

Analysis was by intention to treat. On the basis of the area under the curve of disease activity measured by ACR criteria, the 25-mg dose of etanercept was more effective than the 10-mg dose ($P < 0.03$). More patients receiving etanercept (25 mg) than patients receiving MTX had no increase in the joint erosion score (72% vs 60%, $P = 0.007$). The mean increase in the erosion score at 6 months was 0.30 in patients receiving etanercept (25 mg) and 0.68 in patients receiving MTX ($P = 0.001$). At 12 months, it was 0.47 and 1.03, respectively ($P = 0.002$). The difference between the mean total Sharp score increase in patients receiving etanercept (25 mg) and those receiving MTX was significant at 6 months (0.57 vs 1.06, $P = 0.001$). More patients receiving MTX had adverse events than did those receiving a 10-mg ($P = 0.04$) or 25-mg ($P = 0.02$) dose of etanercept.

CONCLUSIONS

In patients with early rheumatoid arthritis, etanercept, 25 mg/wk, was more effective than methotrexate in slowing bone erosion. Both doses of etanercept resulted in fewer adverse events than did methotrexate.

Source of funding: Immunex.

For correspondence: Dr. J.M. Bathon, Johns Hopkins Asthma and Allergy Center, Johns Hopkins University, 5501 Hopkins Bayview Circle, Room 5A24, Baltimore, MD 21224, USA. FAX 410-550-2625. ■

*See Glossary.

†Information supplied by author.

COMMENTARY

The central role of tumor necrosis factor (TNF) in perpetuating synovial inflammation in RA has been convincingly shown in clinical trials of 2 biological agents that inhibit TNF. Etanercept is a fusion protein that competes with the TNF receptor, and infliximab is a monoclonal antibody against TNF itself (1). After the apparent early success of TNF inhibitors, interest has moved to more specific questions about the place of these agents in the treatment of RA: Are they superior to conventional drugs? At what stage should they be introduced? Do they fundamentally alter the course of the disease by suppressing joint damage? Are they safe? Are they affordable? Which of these agents is preferable?

The sophisticated trials reported by Bathon and colleagues and by Lipsky and colleagues explore these issues. Bathon and colleagues compared the efficacy of etanercept and MTX (now the standard disease-modifying drug) in early RA (defined as disease not exceeding 3 years' duration). Although other disease-modifying drugs were stopped, about 40% of patients continued to receive steroids. Etanercept, used in a twice-weekly subcutaneous dose of 25 mg, controlled disease activity more rapidly than did MTX in the first 6 months of treatment.

Although little difference existed in disease activity after 12 months of treatment, radiographic analysis showed that etanercept in this dose slowed the rate of bone erosion more effectively than did MTX over the 12-month trial period. Etanercept, used in a lower dose of 10 mg, induced a lower incidence of significant improvement at 12 months than did MTX and was no more effective in slowing joint erosion. A reaction at the injection site was the most troublesome adverse event from etanercept.

Lipsky and colleagues examined the effects of infliximab in patients with well-established RA (mean duration > 10 y) that was resistant to other drug treatment. All patients continued to receive MTX but not other disease-modifying drugs. The effects of different dose schedules of infliximab were compared with placebo infusions over a 54-week observation period. Infliximab in all doses reduced disease activity and improved function more effectively than did MTX alone. Furthermore, infliximab in all doses prevented further joint destruction even in patients in whom this process was already advanced. The incidence of

(continued on page 3)

Infliximab plus methotrexate was more effective than methotrexate alone in rheumatoid arthritis

Lipsky PE, van der Heijde DM, St. Clair EW, et al., for the Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. **Infliximab and methotrexate in the treatment of rheumatoid arthritis.** N Engl J Med. 2000 Nov 30;343:1594-602.

QUESTION

In patients with rheumatoid arthritis (RA), is infliximab combined with methotrexate (MTX) more effective than MTX alone?

DESIGN

Randomized {allocation concealed*}†, blinded (patients and outcome assessors),* placebo-controlled trial with follow-up at 54 weeks.

SETTING

Academic rheumatology centers in the United States, Canada, and Europe.

PATIENTS

428 patients (mean age 53 y, 52% men) who were receiving ≥ 12.5 mg/wk of MTX for treatment of active RA (defined as ≥ 6 swollen joints, ≥ 6 tender joints, and ≥ 2 of the following: morning stiffness ≥ 45 min, erythrocyte sedimentation rate ≥ 28 mm/h, or a serum C-reactive protein level of ≥ 2 mg/dL) participated in the study. Follow-up was 100%.

INTERVENTION

All patients continued MTX as previously prescribed and were initially allocated to 3 groups: infusion of placebo (n = 88), 3 mg/kg of body weight of infliximab (n = 172), or 10 mg/kg of infliximab (n = 168) to be received at 0, 2, and 6 weeks. The placebo group continued with placebo infusions every 4 weeks, and the groups receiving 3 or 10 mg/kg of infliximab were divided into subgroups receiving the same dose at 4- or 8-week intervals until week 54.

MAIN OUTCOME MEASURES

Disease activity (based on American College of Rheumatology [ACR] criteria), hand and foot joint erosion and narrowing (based on the Sharp scoring system modified by van der Heijde [range 0 to 440]), and adverse events.

MAIN RESULTS

Infliximab plus MTX reduced disease activity more than did MTX alone (Table). Mean increase in the joint erosion score was 0.5 in patients receiving any dose of infliximab plus MTX and 4 for patients receiving MTX alone (P< 0.001); mean increase in the joint-narrowing score was 0.4 and 2.9, respectively (P < 0.001). Adverse events, including serious infections, did not differ between the patients receiving MTX alone or in combination with infliximab.

CONCLUSION

In patients with rheumatoid arthritis, infliximab combined with methotrexate was more effective than methotrexate alone in reducing disease activity and slowing radiologic progression.

Source of funding: Centocor.

For correspondence: Dr. P.E. Lipsky, National Institutes of Health, 9000 Rockville Pike, Building 10, Room 9N228, Bethesda, MD 20892-1820, USA. FAX 301-402-0012.

*See Glossary.

†Information provided by author.

Percentage of patients with rheumatoid arthritis receiving methotrexate who show reduced disease activity on placebo vs infliximab*

Percentage of improvement at 54 wk (ACR criteria)	Placebo	Infliximab			
		3 mg/kg every 8 wk	3 mg/kg every 4 wk	10 mg/kg every 8 wk	10 mg/kg every 4 wk
20	17%	42%	48%	59%	59%
50	8%	21%†	34%	39%	38%
70	2%	10%‡	17%	25%	19%

*ACR = American College of Rheumatology. All comparisons vs placebo are P < 0.001 unless otherwise specified.
†P = 0.027.
‡P = 0.04.

COMMENTARY *(continued from page 2)*

the adverse event of immediate concern, namely serious infection, was not increased in infliximab-treated patients. Antibodies to double-stranded DNA were provoked in about 10% of patients.

These studies show that TNF inhibitors suppress disease activity in some patients with RA. Their superior ability to slow or possibly reverse joint erosion in advanced disease over a 12-month period has also been shown. However, the latter point has not been established in patients with early disease because of the possible confounding effect of concomitant steroid treatment (2). Only 50% of patients treated with etanercept at an early stage of disease and 27% of patients treated with infliximab at a late stage of disease had a 50% reduction in disease activity. No guidelines as yet exist to select likely responders. Furthermore, an observation period of 1 year is too short to judge either the long-term clinical and radiologic effects of these biologic agents or their propensity for causing side effects. Although the appearance of antibodies to double-stranded DNA has little clinical significance in the short term (3), longer-term observation is necessary. Frequent subcutaneous injections of etanercept can be self-administered, but the high incidence of local reactions raises practical and medicolegal concerns. However, these reactions were rarely bothersome enough to stop treatment. Intravenous infliximab is unlikely to be self-administered and is given relatively infrequently.

On current evidence, rheumatologists are unlikely to resort to infliximab or etanercept in early RA and will reserve their use for selected patients resistant to other treatment.

A. Michael Denman, MD
Northwick Park NHS Trust Hospital
Middlesex, England, UK

References

1. **Maini RN, Taylor PC.** Annu Rev Med. 2000;51:207-29.
2. **Hickling P, Jacoby RK, Kirwan JR, and the Arthritis and Rheumatism Council Low Dose Glucocorticoid Study Group.** Br J Rheumatol. 1998;37:930-6.
3. **Charles PJ, Smeenk RJ, De Jong J, Feldmann M, Maini RN.** Arthritis Rheum. 2000;43:2383-90.