

Articles

Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial

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Summary

Background Etanercept and methotrexate are effective in the treatment of rheumatoid arthritis but no data exist on concurrent initiation or use of the combination compared with either drug alone. We aimed to assess combination treatment with etanercept and methotrexate versus the monotherapies in patients with rheumatoid arthritis.

Methods In a double-blind, randomised, clinical efficacy, safety, and radiographic study, 686 patients with active rheumatoid arthritis were randomly allocated to treatment with etanercept 25 mg (subcutaneously twice a week), oral methotrexate (up to 20 mg every week), or the combination. Clinical response was assessed by criteria of the American College of Rheumatology (ACR). The primary efficacy endpoint was the numeric index of the ACR response (ACR-N) area under the curve (AUC) over the first 24 weeks. The primary radiographic endpoint was change from baseline to week 52 in total joint damage and was assessed with the modified Sharp score. Analysis was by intention to treat.

Findings Four patients did not receive any drug; thus 682 were studied. ACR-N AUC at 24 weeks was greater for the combination group compared with etanercept alone and methotrexate alone (18.3%-years [95% CI 17.1–19.6] vs 14.7%-years [13.5–16.0], $p < 0.0001$, and 12.2%-years [11.0–13.4], $p < 0.0001$; respectively). The mean difference in ACR-N AUC between combination and methotrexate alone was 6.1 (95% CI 4.5–7.8, $p < 0.0001$) and between etanercept and methotrexate was 2.5 (0.8–4.2, $p = 0.0034$). The combination

was more efficacious than methotrexate or etanercept alone in retardation of joint damage (mean total Sharp score -0.54 [95% CI -1.00 to -0.07] vs 2.80 [1.08 to 4.51], $p < 0.0001$, and 0.52 [-0.10 to 1.15], $p = 0.0006$; respectively). The mean difference in total Sharp score between combination and methotrexate alone was -3.34 (95% CI -4.86 to -1.81 , $p < 0.0001$) and between etanercept and methotrexate was -2.27 (-3.81 to -0.74 , $p = 0.0469$). The number of patients reporting infections or adverse events was similar in all groups.

Interpretation The combination of etanercept and methotrexate was significantly better in reduction of disease activity, improvement of functional disability, and retardation of radiographic progression compared with methotrexate or etanercept alone. These findings bring us closer to achievement of remission and repair of structural damage in rheumatoid arthritis.

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Introduction

Rheumatoid arthritis affects almost 1% of the population¹ and is associated with rapid functional loss^{2,3} and reduced life expectancy.⁴ Guidelines^{5,6} delineate goals for treatment, including preservation of function, prevention or control of joint damage, and remission of disease activity.

Tumour necrosis factor (TNF) is a key cytokine in the pathogenesis of rheumatoid arthritis.^{7–9} Successful treatment of clinical signs and symptoms and radiographic progression has been reported for three TNF-blocking drugs, two monoclonal antibodies^{10,11} and a recombinant TNF receptor.^{12–14}

Etanercept is a human, soluble, dimeric, TNF type II receptor linked to an IgG1-Fc moiety that binds to and inactivates TNF.¹⁵ Etanercept administered to patients with early rheumatoid arthritis more rapidly reduced disease activity and slowed joint destruction compared with methotrexate.¹² In patients with active rheumatoid arthritis despite treatment with methotrexate, addition of etanercept to methotrexate was superior to methotrexate alone in reduction of disease activity.¹⁴

Although TNF-blocking drugs have been studied in patients with rheumatoid arthritis treated with methotrexate,^{10,11,14} none of these studies included the three arms necessary to fully evaluate the clinical and radiographic efficacy of the combination of TNF-blockade and methotrexate compared with the two monotherapies. Our aim was to compare safety and efficacy of the combination of etanercept and methotrexate with the monotherapies in patients with rheumatoid arthritis who had failed previous disease-modifying antirheumatic drug treatment other than methotrexate; we report 52-week results.

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Methods

Patients

Between October, 2000, and July, 2001, we screened individuals for inclusion in TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes). Eligible patients were those aged 18 years or older with disease duration of 6 months to 20 years who had active, adult-onset rheumatoid arthritis (American College of Rheumatology [ACR] functional class I–III), defined as ten or more swollen and 12 or more painful joints and at least one of the following: erythrocyte sedimentation rate 28 mm/h or greater; plasma C-reactive protein 20 mg/L or greater; or morning stiffness for 45 min or more. Eligible patients should also have had a less than satisfactory response at the discretion of the investigator to at least one disease-modifying antirheumatic drug other than methotrexate. Individuals previously treated with methotrexate could be enrolled provided they had not had clinically important toxic effects or lack of response, at the discretion of the investigator, and had not been treated with methotrexate within 6 months of enrolment.

Patients were ineligible if they had previously received etanercept or other TNF antagonists. Other exclusion criteria included previous treatment with immunosuppressive drugs within 6 months of screening; use of any investigational drug or biological agent within 3 months of screening; any other disease-modifying antirheumatic drug or corticosteroid injection within 4 weeks of baseline visit; and presence of relevant comorbidity, including active infections.

Patients gave written informed consent at the time of enrolment. The protocol was approved by appropriate local regulatory agencies and ethics committees for every participating centre. The trial was undertaken in accordance with the Declaration of Helsinki and was consistent with the

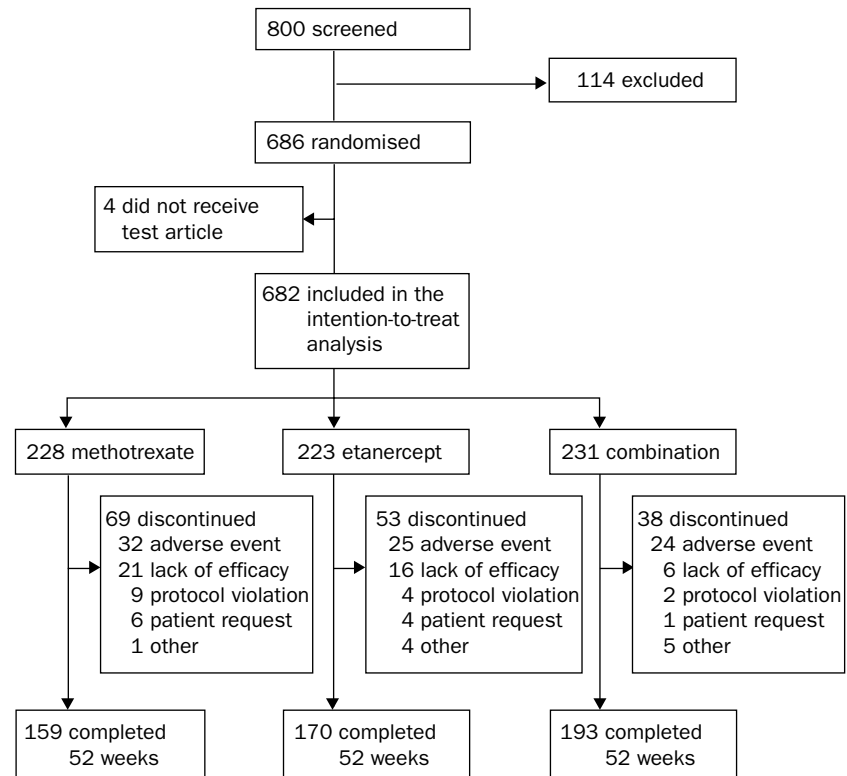


Figure 1: Trial profile

principles of the International Conference on Harmonisation guidelines for Good Clinical Practice (1996 revision) in the European Community.

Procedures

TEMPO was a randomised, double-blind, parallel-group study with identical-appearing injectable and oral test articles and consisted of three treatment arms: etanercept only (25 mg twice a week subcutaneously and oral placebo once a week), methotrexate only (7.5 mg escalated to 20 mg oral capsules once a week within 8 weeks if patients had any painful or swollen joints,¹² and placebo subcutaneous

	Methotrexate (n=228)	Etanercept (n=223)	Etanercept and methotrexate (n=231)
Characteristic			
Age (mean [SD], years)	53.0 (12.8)	53.2 (13.8)	52.5 (12.4)
Women	180 (79%)	171 (77%)	171 (74%)
Disease duration (mean [SD], years)	6.8 (5.5)	6.3 (5.1)	6.8 (5.4)
Rheumatoid factor positive (>20 IU/mL)	163 (71%)	167 (75%)	176 (76%)
Number of previous DMARDs (mean [SD])	2.3 (1.6)	2.3 (1.4)	2.3 (1.4)
Previous methotrexate use	96 (42%)	93 (42%)	101 (44%)
Methotrexate dose (median [IQR], mg/week)	10 (7.5–15.0)	10 (7.5–13.8)	10 (7.5–15.0)
Time from last dose (median [IQR], days)	347 (234–888)	414 (254–1135)	343 (240–879)
Corticosteroid use	146 (64%)	128 (57%)	144 (62%)
NSAID use	197 (86%)	197 (88%)	204 (88%)
Number of tender joints (mean [SD])	33.1 (13.4)	35.0 (14.5)	34.2 (14.8)
Number of swollen joints (mean [SD])	22.6 (10.7)	23.0 (10.7)	22.1 (11.3)
C-reactive protein (mean [SD], mg/L)	255 (282)	324 (377)	299 (326)
Disease activity score (mean [SD])	5.5 (1.2)	5.7 (1.1)	5.5 (1.2)
Sharp score (median [IQR])*			
Total Sharp score	26.8 (5.5–70.5)	21.8 (7.5–58.6)	21.8 (5.5–61.6)
Erosion	11.5 (2.5–35.5)	8.0 (2.8–26.0)	9.5 (2.5–30)
Joint-space narrowing	13.3 (2.0–37.0)	11.5 (2.0–30.2)	10.3 (2.0–35.5)
Estimated yearly rate of progression in total Sharp score (mean [SD])*†	10.3 (16.6)	11.0 (25.2)	8.4 (11.9)

Data are mean (SD), number of patients (%), or median (IQR). DMARDs=disease-modifying antirheumatic drugs; NSAID=non-steroidal anti-inflammatory drug.

*Methotrexate (n=212), etanercept (212), and combination (218). †Estimates were based on duration of disease and baseline total Sharp score for every patient.

Table 1: Demographic and baseline disease characteristics of patients

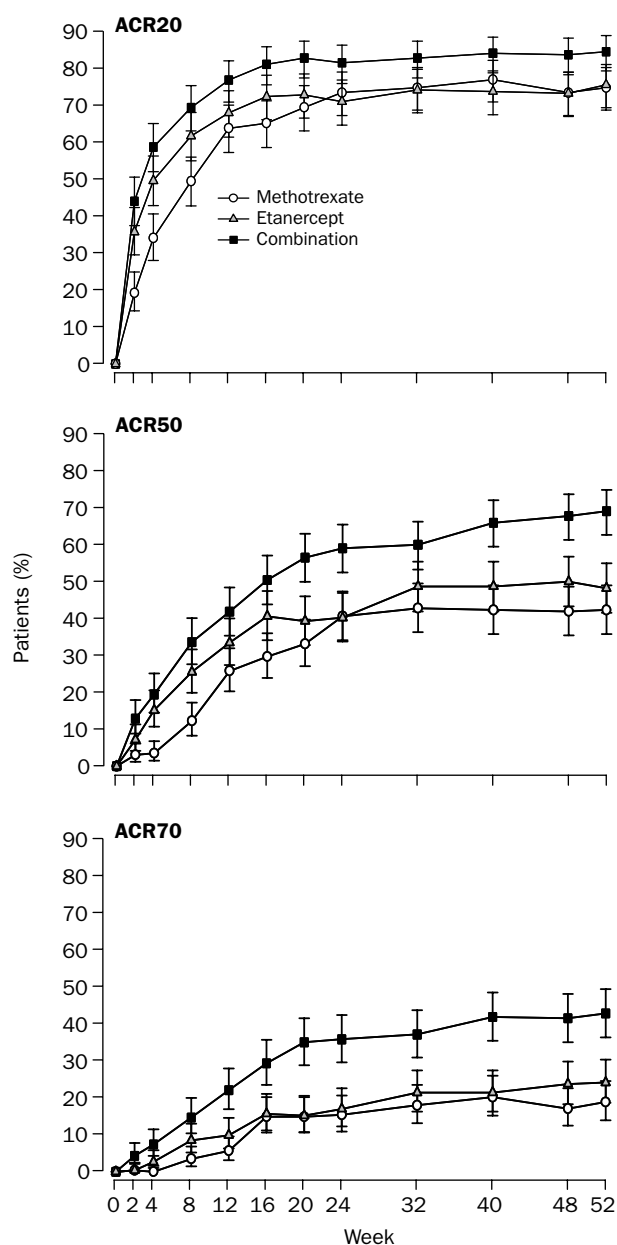


Figure 2: Proportion of patients with rheumatoid arthritis who had improvement relative to baseline according to ACR criteria. Error bars are 95% CIs.

injections twice a week), or etanercept plus methotrexate (combination of 25 mg subcutaneous etanercept injections twice a week and oral methotrexate capsules once a week). All patients received a 5-mg folic acid supplement twice a

week. Centralised telephone randomisation was used. As described in the protocol, we chose 24-week and 52-week timepoints for primary analyses.

The primary efficacy endpoint was the numeric index of the ACR response (ACR-N) area under the curve (AUC) over the first 24 weeks, as defined previously.¹² Other endpoints included ACR20, ACR50, and ACR70 responses¹⁶ and disease activity score.¹⁷ We defined remission as disease activity score less than 1.6.¹⁸ We assessed disability with the health-assessment questionnaire.

The primary radiographic endpoint was change from baseline in total joint damage score (modified total Sharp score=joint erosion score+joint-space narrowing score) over 52 weeks.¹⁹ We obtained radiographs of hands, wrists, and feet at baseline and at weeks 24 and 52 (or final study visit). Digitised random radiographs were read independently by two trained readers from a pool of three independent clinicians masked to treatment assignment and sequence of films in sets for each patient. Inter-reader and intrareader variability, assessed by intraclass correlation coefficient and based on status score, ranged from 0.85 to 0.98 and 0.90 to 0.99, respectively. The smallest detectable difference²⁰ for total Sharp score change was calculated by the average of the three reader pairs, and was 6.2 at 52 weeks.

At patient visits throughout the study we undertook routine physical examinations, assessed vital signs, and did laboratory measurements, and we gathered reports of adverse events. We defined a treatment-emergent adverse event as either an adverse event that was not present at baseline or an event present at baseline that worsened during the study. A serious infection was defined as need for treatment with parenteral antibiotics or admission. National Cancer Institute grade 3 or 4 abnormalities of hepatic enzymes were recorded as concentrations of aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase higher than five times the laboratory's upper normal limits.

Statistical analysis

The planned enrolment of 205 patients per group gave 90% power to detect a pairwise difference between groups of 4.5 units in ACR-N AUC, with a two-sided test at $\alpha=0.05$ and assuming an SD of 14.

The primary clinical endpoint was the 24-week AUC of the ACR-N. The radiographic endpoint of 52-week change from baseline in total Sharp score was a conditional primary endpoint. For both the clinical and radiographic endpoints, we did two primary comparisons—combination versus methotrexate and etanercept versus methotrexate—with Hochberg's approach²¹ for multiple comparisons. Statistical tests were two-sided with significance defined as $p<0.05$. We presented unadjusted p values for all other comparisons.

	Methotrexate (n=212)	Etanercept (n=212)	Etanercept and methotrexate (n=218)
Total Sharp score			
Mean (95% CI)*	2.80 (1.08 to 4.51)	0.52 (-0.10 to 1.15)	-0.54 (-1.00 to -0.07)
Median (IQR)	0.00 (-0.50 to 2.48)	0.00 (-1.00 to 1.01)	-0.50 (-1.50 to 0.00)
Erosion score change			
Mean (95% CI)†	1.68 (0.61 to 2.74)	0.21 (-0.20 to 0.61)	-0.30 (-0.65 to 0.04)
Median (IQR)	0.00 (-0.50 to 1.50)	0.00 (-0.99 to 0.52)	0.00 (-1.00 to 0.38)
Joint-space narrowing			
Mean (95% CI)‡	1.12 (0.34 to 1.90)	0.32 (0.00 to 0.63)	-0.23 (-0.45 to -0.02)
Median (IQR)	0.00 (0.00 to 0.50)	0.00 (0.00 to 0.00)	0.00 (-0.50 to 0.00)

* $p=0.0469$ etanercept vs methotrexate. $p<0.0001$ combination vs methotrexate. $p=0.0006$ combination vs etanercept. † $p=0.0077$ etanercept vs methotrexate. $p<0.0001$ combination vs methotrexate. ‡ $p<0.0001$ combination vs methotrexate. $p=0.0007$ combination vs etanercept.

Table 2: Radiographic analysis at 52 weeks

Analysis was by intention to treat. In the ACR-N AUC analysis, we used the last-observation-carried-forward approach for missing data at 24 weeks. We also used this approach in the analyses of ACR response rates and disease activity score and health-assessment questionnaire mean changes. Disease activity score remission status required patients to be present at a given timepoint; no values were carried forward. For patients who dropped out before 1 year, we did a radiographic examination at the time of discontinuation and estimated the 52-week total Sharp score by linear extrapolation.

We analysed the ACR-N AUC endpoint, disease activity score, and health-assessment questionnaire with an analysis of variance (ANOVA) model, including factors for study centre, treatment, and previous methotrexate use. Radiographic endpoints (total Sharp score, total erosions, and joint-space narrowing) were analysed with an analysis of covariance (ANCOVA) model on the ranks of the change scores that included factors for baseline score rank, study centre, treatment, reader pair, and previous methotrexate use. Estimated yearly total Sharp score progression was defined as score at baseline divided by duration of disease for every patient. We analysed ACR response rates (20%, 50%, and 70%), disease activity score remission, and radiographic non-progression rates by a Mantel-Haenszel approach, stratified by previous methotrexate use.

We undertook supplemental AN(C)OVA analyses to evaluate possible interaction of treatment and previous methotrexate use for the ACR-N AUC, radiographic, disease activity score, and health-assessment questionnaire endpoints. We used logistic regression to assess interaction of treatment response and previous methotrexate use for ACR responses. Mean and 95% CIs are presented. We compared the incidence of treatment-emergent adverse events between treatment groups with Fisher's exact test procedures.

Role of the funding source

Wyeth Research sponsored this trial as a postapproval commitment to the European Agency for the Evaluation of Medicinal Products. The sponsor was responsible for the collection and analysis of data. The authors and the sponsor were involved with study design, interpretation of data, writing this article, and the decision to publish.

Results

686 patients were randomly assigned; four did not receive any drug, 228 received methotrexate (33%), 223 etanercept (33%), and 231 the combination (34%; figure 1). Demographics or baseline disease characteristics including previous methotrexate use did not differ between the treatment groups (table 1).

522 patients completed the first year of the study. Adverse events were the most common reason for discontinuation (24 combination, 32 methotrexate, and 25 etanercept). Fewer patients withdrew for lack of efficacy from the combination group (n=6) than from the methotrexate (21; $p=0.0027$) and etanercept (16; $p=0.0282$) groups.

The mean weekly dose of methotrexate (17.2 mg for the methotrexate group and 16.9 mg for the combination group after week 8) and the mean time necessary to achieve the final dose (data available from authors) were similar in both treatment groups.

Patients who received study drug and had an acceptable baseline and at least one postbaseline film were included in the radiographic analysis (218 combination, 212 methotrexate, and 212 etanercept). These patients did not differ by baseline total Sharp score, erosion scores, joint-space

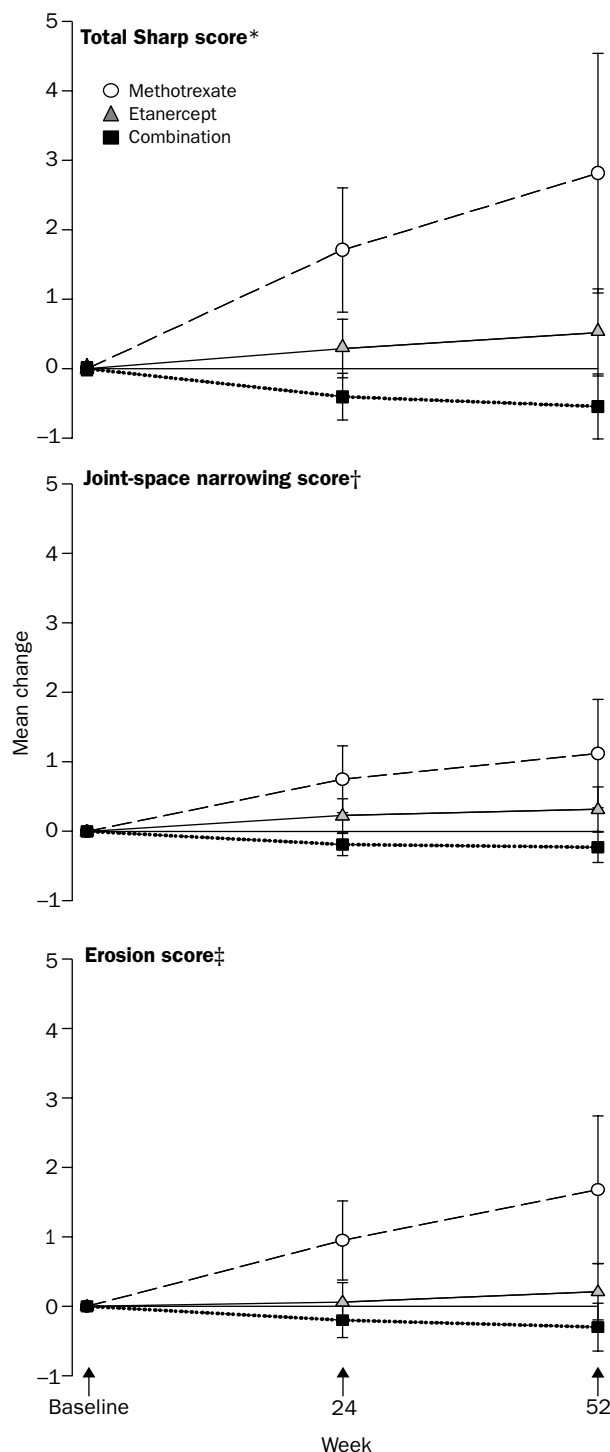


Figure 3: Mean change from baseline in total Sharp scores, joint-space narrowing, scores, and erosion scores at 24 and 52 weeks for patients with rheumatoid arthritis after treatment

Error bars are 95% CIs. *For 24 weeks: $p=0.0112$ etanercept vs methotrexate, $p<0.0001$ combination vs methotrexate, $p=0.0722$ combination vs etanercept; for 52 weeks: $p=0.0469$ etanercept vs methotrexate, $p<0.0001$ combination vs methotrexate, $p=0.0006$ combination vs etanercept. †For 24 weeks: $p=0.0001$ combination vs methotrexate, $p=0.0032$ combination vs etanercept; for 52 weeks: $p<0.0001$ combination vs methotrexate, $p=0.0007$ combination vs etanercept. ‡For 24 weeks: $p=0.0056$ etanercept vs methotrexate, $p=0.0016$ combination vs methotrexate; for 52 weeks: $p<0.0001$ combination vs methotrexate, $p=0.0077$ etanercept vs methotrexate.

narrowing scores, and estimated total Sharp score progression per year (table 1).

The primary efficacy endpoint—ACR-N AUC at 24 weeks—was greater for both the combination group (18.3%-years [95% CI 17.1–19.6]) and etanercept group (14.7%-years [13.5–16.0]) compared with methotrexate (12.2%-years [11.0–13.4]). The mean difference in ACR-N AUC between combination and methotrexate alone was 6.1 (95% CI 4.5–7.8, $p < 0.0001$) and between etanercept and methotrexate was 2.5 (0.8–4.2, $p = 0.0034$). Additionally, ACR-N AUC was greater for the combination group than for the etanercept group ($p < 0.0001$).

The proportion of patients achieving ACR20 in the combination group was higher than in the methotrexate group (figure 2). At week 52, mean 85% (95% CI 80–89) of patients in the combination group achieved ACR20 compared with 75% (69–80) and 76% (70–81) in the methotrexate and etanercept groups, respectively ($p = 0.0091$ for combination *vs* methotrexate; $p = 0.0151$ for combination *vs* etanercept). The proportions of patients achieving ACR50 and ACR70 were consistently higher for the combination group than for either the etanercept or methotrexate treatment group throughout the study. At week 52, 69% (95% CI 63–75) of patients in the combination group achieved ACR50 compared with 43% (36–49) and 48% (42–55) in the methotrexate and etanercept groups, respectively ($p < 0.0001$ for combination *vs* methotrexate; $p < 0.0001$ for combination *vs* etanercept). At week 52, 43% (95% CI 36–50) of patients in the combination group achieved ACR70 compared with 19% (14–25) in the methotrexate group and 24% (19–30) in the etanercept group ($p < 0.0001$ for combination *vs* methotrexate; $p < 0.0001$ for combination *vs* etanercept). The overall level of response seen with the ACR criteria was indicated by all components of this composite score (data available from authors).

At baseline, patients in all three groups had a high degree of disease activity as measured by the disease activity score (table 1). Values declined quickly after the start of both the combination and etanercept treatments and slowly with methotrexate. After 52 weeks, the mean disease activity score was lower for the combination than for the methotrexate or etanercept groups (2.3 [95% CI 2.1–2.5], 3.0 [2.8–3.2], and 3.0 [2.8–3.1], respectively; $p < 0.0001$ for combination *vs* methotrexate; $p < 0.0001$ for combination *vs* etanercept). The proportion of patients achieving remission (disease activity score < 1.6) at week 52 was mean 35% (95% CI 29–41), 13% (9–18), and 16% (11–21) for the combination, methotrexate, and etanercept groups, respectively ($p < 0.0001$ for combination *vs* methotrexate; $p < 0.0001$ for combination *vs* etanercept; $p = 0.5031$ for

etanercept *vs* methotrexate). Of 80 patients in the combination group in remission at week 52, 57 were also in remission at week 40, compared with 20 of 30 patients in the methotrexate group and 20 of 35 in the etanercept group.

The results of the health-assessment questionnaire indicated improvement over baseline values in disability for patients allocated to combination treatment compared with methotrexate alone or etanercept alone. Mean scores fell from baseline levels of 1.8 (95% CI 1.7–1.8), 1.7 (1.6–1.8), and 1.7 (1.7–1.8) to 0.8 (0.7–0.9), 1.1 (1.0–1.1), and 1.0 (1.0–1.1) at 1 year in the combination, methotrexate, and etanercept treatment groups, respectively ($p < 0.0001$ for combination *vs* methotrexate; $p < 0.0001$ for combination *vs* etanercept; $p = 0.3751$ for etanercept *vs* methotrexate).

With respect to the radiographic primary outcome, the mean change in total Sharp score for the combination group was lower than for the methotrexate and etanercept treatments at week 52 (table 2; mean difference between combination and methotrexate -3.34 [95% CI -4.86 to -1.81], $p < 0.0001$) Etanercept-treated patients had less change in total Sharp score than did methotrexate-treated patients at both timepoints (-2.27 [-3.81 to -0.74], $p = 0.0469$; figure 3). Patients receiving combination treatment had less change in erosion score than did methotrexate-treated patients at 52 weeks (table 2). The change in erosion score for etanercept-treated patients was lower than for methotrexate at 52 weeks (figure 3). Patients receiving combination treatment had less change in joint-space narrowing compared with either methotrexate-treated or etanercept-treated patients at 52 weeks (table 2). Changes in joint-space narrowing, although smaller for etanercept than for methotrexate, did not differ significantly (figure 3).

The proportion of patients without progression (total Sharp score ≤ 0.5) was higher in the combination group compared with etanercept and methotrexate groups at week 52 (mean 80% [95% CI 74–85] *vs* 68% [61–74] and 57% [50–64], respectively; $p < 0.0001$ for combination *vs* methotrexate; $p = 0.0043$ for combination *vs* etanercept). Additionally, the proportion without progression at week 52 was higher in the etanercept alone group compared with methotrexate alone ($p = 0.0213$). The proportion of patients who had a radiographic progression of more than the smallest detectable difference (6.2) at 52 weeks was mean 2.8% (95% CI 1.0–5.9), 11.8% (7.8–16.9), and 4.2% (2.0–7.9) in the combination, methotrexate, and etanercept groups, respectively ($p = 0.0015$ for combination *vs* methotrexate; $p = 0.5733$ for combination *vs* etanercept; $p = 0.0070$ for etanercept *vs* methotrexate).²²

We investigated whether previous use of methotrexate might affect response to treatment in any of the three arms.

	Methotrexate (n=228)	Etanercept (n=223)	Etanercept and methotrexate (n=231)
Any adverse event	185 (81%)	192 (86%)	187 (81%)
Abdominal pain	40 (18%)	26 (12%)	42 (18%)
Accidental injury	25 (11%)	19 (9%)	21 (9%)
Asthenia	20 (9%)	23 (10%)	24 (10%)
Back pain	20 (9%)	28 (13%)	24 (10%)
Cough increased	17 (7%)	14 (6%)	25 (11%)
Diarrhoea	20 (9%)	23 (10%)	19 (8%)
Headache	32 (14%)	34 (15%)	34 (15%)
Injection site reaction*	4 (2%)	46 (21%)	23 (10%)
Nausea†	73 (32%)	22 (10%)	55 (24%)
Rash	21 (9%)	16 (7%)	23 (10%)
Vomiting‡	26 (11%)	7 (3%)	12 (5%)
Infections			
All	147 (64%)	131 (59%)	154 (67%)
Serious	10 (4%)	10 (4%)	10 (4%)

Data are number of events (%). * $p < 0.0001$ etanercept *vs* methotrexate, $p = 0.0002$ combination *vs* methotrexate, $p = 0.0017$ combination *vs* etanercept. † $p < 0.0001$ etanercept *vs* methotrexate, $p < 0.0001$ combination *vs* etanercept. ‡ $p = 0.0009$ etanercept *vs* methotrexate, $p = 0.0177$ combination *vs* methotrexate.

Table 3: Treatment-emergent adverse events

For the primary endpoints ACR-N AUC and total Sharp score, and for other key endpoints of ACR20, ACR50, ACR70, and disease activity score remission, no significant interaction was observed.

Etanercept was generally well tolerated as monotherapy and in combination with methotrexate. Table 3 shows infections and treatment-emergent adverse events that arose in at least 10% of patients. The number of patients reporting infections and serious infections was similar in all treatment groups. No cases of tuberculosis or opportunistic infections were reported.

No significant differences were recorded in the number of patients who withdrew from the study because of adverse events including infections. Three deaths were reported: one patient on methotrexate with suspected sepsis died of pulmonary embolism; one on etanercept died of heart failure and suspected sepsis; and one on combination withdrew from the study because of stroke and died 10 weeks later of pneumonia. 19 (8%) patients in the combination group had a serious adverse event other than infection compared with 27 patients (12%) and 25 patients (11%) in the methotrexate and etanercept groups, respectively.

Six malignant diseases were noted: three basal-cell carcinomas of the skin (one in each group) and one case each of breast cancer, rectal cancer, and melanoma in the etanercept group. Five patients in the methotrexate group had National Cancer Institute grade 3 or 4 abnormalities of hepatic enzymes compared with two patients each in the etanercept and combination groups. No cases of multiple sclerosis, other central demyelinating diseases, or serious blood dyscrasias were reported.

Discussion

We have shown that combination treatment was more efficacious than methotrexate or etanercept alone for control of rheumatoid arthritis disease activity. Additionally, just over a third of patients treated with the combination achieved remission at 52 weeks compared with an eighth of those given methotrexate and about a sixth of those given etanercept. These observations were lent support by changes in health-assessment questionnaire scores. The combination was also more efficient than methotrexate or etanercept alone in slowing or retarding joint damage, as assessed by radiography. Notably, combination therapy resulted in mean negative radiographic progression scores with the entire 95% CI below zero.

Methotrexate was chosen as a comparator in this study because it is usually used as the first-line antirheumatic drug and has a well-described safety and efficacy profile.²³ We included only patients who were deemed to be appropriate candidates for methotrexate treatment at the time of enrolment in the study and therefore allowed fair comparison of the effects of the drug with etanercept. Additionally, an aggressive dose-escalation scheme for methotrexate was used to assure that therapeutic doses of the drug were used in the study.²⁴ To account for the possibility of a differential response in patients treated in the past with methotrexate, previous use was included as a factor in all the clinical efficacy and radiographic analyses. Although the study was not designed to assess sub-populations, we recorded no significant effects of previous methotrexate treatment on clinical efficacy and radiographic endpoints.

ACR-N AUC was designated the primary endpoint. This measure provides a direct comparison with another study¹² in which etanercept and methotrexate were investigated in patients with early rheumatoid arthritis. Our results with the two monotherapies are closely similar to those reported in

this study,¹² underlining the robustness of our findings and further lending support to the observation that the combination was more efficacious in reduction of disease activity than either etanercept or methotrexate alone. This idea has also been lent support by findings of an observational study in clinical practice²⁵ in which combination treatment with etanercept and methotrexate gave a more favourable clinical response than etanercept alone.

Remission has been described as the goal of treatment for rheumatoid arthritis, yet published reports of success in achieving this goal are scarce.^{18,26} Almost three times as many patients in the combination group were in remission at two consecutive timepoints compared with either monotherapy. This finding shows that the goal of sustained remission is reachable in many patients with established rheumatoid arthritis.

The health-assessment questionnaire disability index is most usually used to assess functional status.²⁷ Similar to the disease activity results, combination treatment was more efficient in reduction of disability as measured by the questionnaire than either two monotherapies.

Radiographic data at 24 and 52 weeks indicated that patients in the combination and etanercept treatment groups had significantly less progression of disease for all measured radiographic endpoints compared with patients in the methotrexate group. Furthermore, the combination provided a significantly better result than either monotherapy concerning changes in total Sharp score at 52 weeks of treatment. Comparison of results across trials should be done with caution, but patients' response to etanercept in terms of radiographic progression was similar to findings of another study,¹² even though patients in our study had longer disease duration than patients in that trial.

One of the most challenging results of the TEMPO trial was that the combination of etanercept and methotrexate resulted in significant lowering of total Sharp score compared with baseline, with a negative progression rate. Repair of joint damage on an individual joint level has been suggested by various investigators in case reports,²⁸ and by results of studies specifically addressing if repair is possible.^{29,30} Our results suggest that repair induced by treatment may be possible on a group level.

No new safety findings were noted in this study. Treatment with the combination did not result in increased infections or other adverse events. Specifically, no cases of tuberculosis or other opportunistic infections were reported. A significantly lower proportion of patients in the combination group withdrew from the study for all reasons compared with the methotrexate group. The safety profiles of the monotherapies accorded with other findings.^{12,13,24,31}

Concurrent initiation and use of the combination of etanercept and methotrexate brings us closer to the goals of antirheumatic treatment, specifically the achievement of clinical remission and repair of structural damage.

Contributors

All authors participated in development of the study, interpretation of data, and had access to all data and final responsibility for the decision to submit for publication. L Klareskog and D van der Heijde had main responsibility for writing the article, with input from all other authors. L Klareskog provided the clinical variables to be assessed and had responsibility for final scrutiny of the protocol. D van der Heijde provided the radiological variables to be assessed and established the radiological evaluation unit. R Pedersen advised on statistics. J Wajdula, S Fatenejad, and M Sanda were responsible for making the protocol adhere to guidelines issued by the EMEA and FDA, recruited the clinical investigators who treated the patients, and gathered data.

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Conflict of interest statement

LK, DvdH, JPDJ, AG, JK, MM, EM-M, KP, JS, and LS participated as investigators, consultants, or both to Wyeth. JW, RP, SF, and MS are employees of Wyeth Research. Furthermore, LK has served as an investigator and as a member of advisory boards for Wyeth, Schering-Plough, Abbott Immunology, Bristol Myers Squibb, and Millenium Pharmaceuticals. DvdH has been a consultant and advisory board member for Wyeth, Amgen, Abbott, Centocor, Schering-Plough, Merck, and Pfizer. JPDJ has been an advisory board member for Wyeth and Schering-Plough. AG received a travel grant from Wyeth to attend a conference. EMM has received fees as a consultant of Abbott, Centocor, Schering-Plough, and Bristol Myers Squibb.

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