Efficacy, safety, and patient-reported outcomes of combination etanercept
and sulfasalazine versus etanercept alone in patients with rheumatoid
arthritis: a double-blind randomized two-year study

B. Combe,1 C. Codreanu,2 U. Fiocco,3 M. Gaubitz,4 P.P. Geusens,5 T.K. Kvien,6
K. Pavelka,7 P.N. Sambrook,8 J.S. Smolen,9 R. Khandker,10 A. Singh,10 J.
Wajdula,10* and S. Fatenejad10 for the Etanercept European Investigators
Network (The Etanercept Study 309 Investigators†)

1Service d’Immuno-Rhumatologie, Hopital Lapeyronie, Montpellier, France;
2Centrul Metodologic de Reumatologie, Bucuresti, Romania; 3Cattedra e
Divisione di Reumatologia, Policlinico Universitario, Padova, Italy; 4Medical Clinic
B Westfalian-Wilhelms-Univ, Munster, Germany; 5Biomedical Research Center,
University Hasselt, Belgium and Department of Internal Medicine/Rheumatology,
University Maastricht, Netherlands; 6Department of Rheumatology,
Diakonhjemmets Hospital, Oslo, Norway; 7Institute of Rheumatology, Praha,
Czech Republic; 8Kolling Institute, University of Sydney, Sydney, Australia; 92nd
Department of Medicine, Krankenhaus Lainz, and Department of Rheumatology,
Internal Medicine III, Medical University of Vienna, Vienna, Austria; 10Wyeth
Research, Collegeville, Pennsylvania, USA.

*The Corresponding Author has the right to grant on behalf of all authors and
does grant on behalf of all authors, an exclusive license (or non exclusive for
government employees) on a worldwide basis to the BMJ Publishing Group Ltd
to permit this article (if accepted) to be published in ARD and any other BMJPGGL
products and sublicenses such use and exploit all subsidiary rights, as set out in

†Study Investigators listed at the end of the article.

Acknowledgment: Supported by Wyeth Research, Collegeville, PA (study drug
and grants to investigational sites). The authors would like to acknowledge Ruth
Pereira and J. Maitland Young in the Publications and External Communications
Group at Wyeth for their writing support and S. Sun of Wyeth Research for
contributions to statistical analyses of the study.


Address for Correspondence: Joseph Wajdula, PhD, Clinical Research and
Development, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, USA.
E-mail: wajdulj@wyeth.com
ABSTRACT

Objective: To determine efficacy and safety of etanercept and etanercept+sulfasalazine versus sulfasalazine in patients with rheumatoid arthritis (RA) despite sulfasalazine therapy.

Methods: Patients were randomly assigned to etanercept (25 mg twice weekly; sulfasalazine was discontinued at baseline), etanercept+sulfasalazine (unchanged regimen of 2-3 g/day) or sulfasalazine in a double-blind, randomised, 2-year study in adult patients with active RA despite sulfasalazine therapy. Efficacy was assessed using the American College of Rheumatology (ACR) criteria, disease activity scores (DAS), and patient-reported outcomes (PROs).

Results: Demographic variables and baseline disease characteristics were comparable among treatment groups; mean DAS was 5.1, 5.2 and 5.1, for etanercept (n=103), etanercept+sulfasalazine (n=101), and sulfasalazine (n=50) respectively. Withdrawal due to lack of efficacy was highest with sulfasalazine (26 [52%] versus 6 [6%] for either etanercept group, p<0.001). Patients receiving etanercept or etanercept+sulfasalazine had a more rapid initial response, which was sustained at 2 years, than those receiving sulfasalazine: mean DAS was 2.8, 2.5, versus 4.5 respectively (p<0.05); ACR 20 response was achieved by 67%, 77%, versus 34% of patients respectively (p<0.01). Overall, PROs followed a similar pattern; clinically significant improvement in Health Assessment Questionnaire was achieved by 76%, 78%, versus 40% of patients respectively (p<0.01). Commonly reported adverse events occurring in the etanercept groups were injection site reactions and pharyngitis/laryngitis (p<0.01).

Conclusion: Etanercept and etanercept+sulfasalazine are efficacious for the long-term management of patients with RA. Therefore, addition of etanercept or substitution with etanercept should be considered as treatment options for patients not adequately responding to sulfasalazine.
INTRODUCTION

Several options including disease-modifying antirheumatic drugs (DMARDs), such as methotrexate and sulfasalazine, and anti-tumour necrosis factor (anti-TNF) agents such as etanercept, infliximab and adalimumab, are available for the treatment of patients with rheumatoid arthritis (RA). For patients with an inadequate response to DMARD therapy, one recommended therapeutic option is anti-TNF therapy either added to or as a replacement for the existing regimen.[1, 2]

In clinical studies, anti-TNF agents are highly effective and generally well tolerated when added to existing treatment regimens for patients with active RA who had not responded to a DMARD such as methotrexate [3-8] or sulfasalazine, another frequently prescribed DMARD. However, there are very few studies assessing the benefits and risks of adding an anti-TNF agent to existing sulfasalazine therapy for patients with RA inadequately responding to sulfasalazine.[9-11] (http://www.fda.gov/cder/biologics/products/adalabb123102.htm). Combe et al [10] previously reported on the 6-month interim results from the current study; the 6-month results showed that etanercept, in combination with or in place of sulfasalazine, resulted in substantial improvements in RA.[10] Both etanercept regimens were well tolerated.[10]

This 2-year report provides data on the long-term therapeutic response including patient reported outcomes and safety of etanercept, added to or in place of sulfasalazine, versus sulfasalazine alone in patients with active RA, despite stable sulfasalazine therapy.

PATIENTS AND METHODS

Study Design and Patients

This was a 2-year randomised, double-blind, double-dummy, multicenter study in patients with active RA who had an inadequate response to sulfasalazine.

Eligible patients were >18 years of age with disease duration ≤20 years with active adult-onset RA (functional class I-III), defined as ≥6 swollen and ≥10 tender joints, and ≥1 of the following: erythrocyte sedimentation rate (Westergren) ≥28 mm at the end of the first hour, serum C-reactive protein ≥20 mg/l, and morning stiffness >45 minutes. Patients must have received stable doses of sulfasalazine (2-3 g daily) for ≥4 months before screening. Details of the exclusion/inclusion criteria have been published previously.[10]

This study was conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice in the European Community and the Declaration of Helsinki. Ethics committees of the participating centres
approved the study protocol. Patients gave written informed consent before participating in the study.

**Treatment**

Patients were randomly assigned to 1 of 3 treatment groups (in a 2:1:2 ratio): etanercept (etanercept 25 mg by subcutaneous injection twice weekly + placebo), sulfasalazine (sulfasalazine 2, 2.5, or 3 grams daily + placebo), or combination (etanercept + sulfasalazine) therapy. Patients in the etanercept group discontinued sulfasalazine at baseline.

**Clinical Assessment**

Response to therapy was assessed at baseline and at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 56, 68, 80, 92, and 104. The primary efficacy endpoint, percentage of patients achieving ≥20% improvement, as defined by American College of Rheumatology (ACR) 20 criteria [12], at week 24, was reported previously.

Key efficacy assessments included ACR response rates (ACR 20, ACR 50, and ACR 70), disease activity score (DAS), and morning stiffness in minutes. Assessments were based on ACR criteria and DAS as previously reported.[10]

Patient-reported outcome measures included the HAQ disability index [13, 14], EQ-5D VAS [15], global assessment of overall RA activity (PGAD) and GHVAS. The PGAD, an assessment of overall RA activity as experienced by the patient, is recorded on an 11-point numeric rating scale where a score of zero means no disease activity and a score of 10 means extreme disease activity. For the GHVAS, patients responded to the question “How do you feel concerning your arthritis?” by marking the appropriate position on a 100-mm VAS ranging from “very well” to “extremely bad.” For both PGAD and GHVAS, lower scores imply better health.

To determine whether patient-reported outcomes (PROs) closely reflected clinical improvements, the study examined the relationship between changes in health status measures or disability and changes in disease activity. Pearson correlation analysis was performed between the 4 PRO measures (HAQ, EQ-5D VAS, PGAD, and GHVAS) and a measure of disease activity, DAS.[16]

**Safety Assessments**

Safety assessments were based on reports of adverse events (AEs) and results of routine physical examinations and laboratory determinations. An event was considered to be a treatment-emergent adverse event (TEAE), if it occurred during the study or if the severity or frequency of a preexisting event increased during the study. A serious adverse event (SAE) included any event resulting in
death, hospitalisation or cancer. An infection was a serious infection if reported as an SAE.

Testing for anti-nuclear, anti-double stranded DNA (anti-dsDNA), anti- etanercept, and anti-cardiolipin antibodies was done at screening and at specified visits.

Incidence of malignancies in this study was compared with the incidence estimated from the United States National Cancer Institute’s (NCI) Surveillance, Epidemiology, and End Results (SEER) database.[16] The age- and sex-specific incidence rates for cancer from the SEER database were applied to the exposure in this study.

Statistical Analysis

The ACR 20, ACR 50, and ACR 70 response rates were analysed using the Mantel-Haenszel Chi-square test, stratified by study centre. Changes from baseline in components of the ACR and patient-reported outcomes (HAQ disability index, EQ-5D, GHVAS, and PGAD) were analysed with a 2-way analysis of covariance with treatments and center as factors and the baseline as a covariate. Efficacy analyses were based on a modified intent-to-treat population, including patients who received any test article and provided efficacy data at baseline and at any subsequent visit. The proportions of patients with clinically meaningful changes in HAQ disability index at week 104 were compared between treatment groups using Chi-square analyses. Pearson correlation analyses were used to assess correlations between DAS and PROs over 104 weeks. The last-observation-carried-forward (LOCF) approach was used to account for missing data points. LOCF imputation was also applied to patients who discontinued for unsatisfactory response. AEs were summarised and compared among treatment groups, using Chi-square or Fisher exact test. The sample sizes, 100 for the etanercept alone group and sulfasalazine plus etanercept group versus 50 for the sulfasalazine alone group, gave ~90% power to detect pairwise differences in ACR 20% response of 33% versus 66% between the monotherapies.

RESULTS

Efficacy

Of the 260 patients who were randomly assigned in the study, 254 patients received ≥1 test article (etanercept=103, sulfasalazine=50, and combination=101).[10] The population was predominantly white, female, and had a mean age of 51 years (consistent with the typical RA population). As previously reported, there were no significant differences among the groups in the baseline characteristics with the exception of the percentage of patients receiving prior corticosteroids and the mean number of prior DMARDs.[10]
A total of 96 patients discontinued the study: 38 receiving etanercept, 34 receiving sulfasalazine, and 24 receiving combination therapy. Overall, a significantly greater number of the patients who continued on sulfasalazine monotherapy (68%) withdrew from the study compared with those receiving etanercept, either as combination (24%) or replacement (37%) therapy (p<0.001); the difference between etanercept and the combination was also significant (p<0.05). The most common primary reason for discontinuation, lack of efficacy, led to a significantly higher number of withdrawals in patients receiving sulfasalazine (52%) compared with those receiving either etanercept regimen (6% for each; p<0.001). Discontinuations because of AEs were not significantly different among the groups (8%, 19%, and 10%, for the sulfasalazine, etanercept, and combination, respectively) and there was no trend in the types of AEs that led to discontinuation in any of the groups.

Times to discontinuation were estimated using the Kaplan-Meier method (Figure 1): the combination group had the longest times to discontinuation. Based on the log-rank test, the differences among the 3 groups were statistically significant (p<0.001 for sulfasalazine versus etanercept or combination and p=0.06 for etanercept versus the combination).

Disease activity, as assessed by mean DAS, was significantly lower in the groups receiving etanercept than in the group receiving sulfasalazine from week 2 to week 104 (p<0.01, Figure 2). Significantly lower mean DAS values were observed during weeks 68-104 for the combination group compared with the etanercept alone group (p<0.05). A significantly higher proportion of patients receiving the combination or etanercept had a low level of disease activity (as assessed by DAS <2.4) compared with those receiving sulfasalazine after 6 months, which was maintained throughout 2 years (p<0.01): at 2 years, 57.0% of patients receiving combination, 45.6% receiving etanercept, and 4.0% receiving sulfasalazine. Likewise, the proportion of patients achieving disease remission was significantly higher with the etanercept groups compared with the sulfasalazine group (p<0.01).

Treatment response as assessed by ACR 20 was achieved by a significantly higher percentage of patients receiving etanercept, added to or in place of sulfasalazine, compared with those receiving sulfasalazine (p<0.01; Figure 3A). Similarly, these significant differences in treatment response among the groups were also seen using ACR 50 (p<0.01) and ACR 70 (p<0.01; Figure 3B, 3C) criteria. For ACR 20 responses, the differences were significant beginning at week 2; for ACR 50 and ACR 70, the differences were significant beginning at week 8 and 12, respectively. Response rates were not significantly different between the 2 groups receiving etanercept.

The early and sustained response pattern was also seen with components of the ACR response criteria. Significant differences (p<0.01) were seen for combination therapy or etanercept alone compared with sulfasalazine alone.
Comparing the etanercept groups, the combination group separated from the etanercept monotherapy group for a short period (week 8 to 20) as demonstrated by the lower erythrocyte sedimentation rate (ESR) levels (p<0.05). No significant difference between these groups was seen for other ACR components before week 68 (total swollen joints) or week 92 (patient global assessment and physician global assessment), after which time the combination group showed better responses (p<0.05).

**Patient-reported Outcomes**

Mean HAQ values for the etanercept and combination groups were significantly lower than those for the sulfasalazine group from week 2 (p<0.01, sulfasalazine versus etanercept or combination) and these differences were sustained for the remainder of the 2-year study [10] (p<0.01) (Figure 4).

Three health status measures using least squares means at week 104 are presented in Figure 5. Patients who received etanercept or combination therapy showed significantly lower GHVAS scores, indicative of better general health, than patients who received sulfasalazine at week 104. Likewise, recipients of etanercept or combination therapy reported significantly better health state, as indicated by lower RA activity (PGAD) and higher EQ-5D scores than patients receiving sulfasalazine.

Our analyses also found that a significantly higher proportion of patients receiving etanercept or the combination attained the threshold of HAQ improvement $\geq 0.22$ by week 104 compared with those receiving sulfasalazine (p<0.01 compared with sulfasalazine alone). Similarly, a significantly higher proportion of patients receiving etanercept or the combination achieved EQ-5D VAS scores above population norms[17] at week 104 compared with those receiving sulfasalazine (p<0.01 compared with sulfasalazine alone).

Further analyses revealed that changes in disease activity from baseline through 104 weeks correlated with changes in disability as measured by the HAQ disability index and with changes in health status measures. Pearson correlations between change from baseline in DAS and HAQ (0.57), PGAD (0.69), EQ-5D VAS (–0.61), or GHVAS (0.67) were all significant (p<0.001).

**Safety**

The pattern of AEs reported during the 2 years of the study was not different from that reported during the first 6 months of the study.[10] There were no significant differences between the combination and either monotherapy groups in the overall incidence of noninfectious AEs (Table 1). However, there were significantly more treatment-emergent infections in patients receiving etanercept than in those receiving sulfasalazine (p<0.001).
Table 1. Number (%) of Patients With the Most Common Treatment-Emergent Adverse Events (≥10% in Any Treatment Group)

<table>
<thead>
<tr>
<th>Body System TEAE</th>
<th>ETN (n=103)</th>
<th>ETN+SSZ (n=101)</th>
<th>SSZ (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Noninfectious Adverse Events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any TEAE (excluding infection)</td>
<td>90 (87.4)</td>
<td>80 (79.2)</td>
<td>32 (64.0)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>34 (33.0)</td>
<td>21 (20.8)</td>
<td>2 (4.0)†‡</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (10.7)</td>
<td>25 (24.8)†</td>
<td>4 (8.0)‡</td>
</tr>
<tr>
<td>Back pain</td>
<td>9 (8.7)</td>
<td>20 (19.8)</td>
<td>5 (10.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (6.8)</td>
<td>19 (18.8)†</td>
<td>5 (10.0)</td>
</tr>
<tr>
<td>Accidental injury</td>
<td>16 (15.5)</td>
<td>17 (16.8)</td>
<td>1 (2.0)‡</td>
</tr>
<tr>
<td>Asthenia</td>
<td>5 (4.9)</td>
<td>16 (15.8)†</td>
<td>1 (2.0)‡</td>
</tr>
<tr>
<td>Rash</td>
<td>15 (14.6)</td>
<td>8 (7.9)</td>
<td>3 (6.0)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>14 (13.6)</td>
<td>12 (11.9)</td>
<td>2 (4.0)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14 (13.6)</td>
<td>12 (11.9)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Injection site haemorrhage</td>
<td>9 (8.7)</td>
<td>14 (13.9)</td>
<td>3 (6.0)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>8 (7.8)</td>
<td>14 (13.9)</td>
<td>7 (14.0)</td>
</tr>
<tr>
<td>RA</td>
<td>10 (9.7)</td>
<td>12 (11.9)</td>
<td>5 (10.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11 (10.7)</td>
<td>6 (5.9)</td>
<td>0.0*</td>
</tr>
<tr>
<td>Cough increased</td>
<td>7 (6.8)</td>
<td>12 (11.9)</td>
<td>4 (8.0)</td>
</tr>
<tr>
<td>Parasthesia</td>
<td>4 (3.9)</td>
<td>11 (10.9)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td><strong>Infectious Adverse Events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any TEAE Infection</td>
<td>76 (73.8)</td>
<td>60 (59.4)†</td>
<td>21 (42.0)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>29 (28.2)</td>
<td>29 (28.7)</td>
<td>10 (20.0)</td>
</tr>
<tr>
<td>Pharyngitis/laryngitis</td>
<td>24 (23.3)</td>
<td>10 (9.9)</td>
<td>3 (6.0)‡</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>21 (20.4)</td>
<td>12 (11.9)</td>
<td>4 (8.0)</td>
</tr>
<tr>
<td>Condition</td>
<td>ETN (18)</td>
<td>SSZ (12)</td>
<td>Combination (2)</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>----------</td>
<td>----------</td>
<td>----------------</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>18 (17.5)</td>
<td>12 (11.9)</td>
<td>2 (4.0)</td>
</tr>
<tr>
<td>Gingival/dental infection</td>
<td>7 (6.8)</td>
<td>12 (11.9)</td>
<td>2 (4.0)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>12 (11.7)</td>
<td>3 (3.0)</td>
<td>0.0</td>
</tr>
<tr>
<td>Miscellaneous skin infections†‡</td>
<td>19 (18.4)</td>
<td>12 (11.9)</td>
<td>0.0‡</td>
</tr>
</tbody>
</table>

ETN=etanercept; SSZ=sulfasalazine; TEAE=treatment emergent adverse event.
Fisher exact pairwise comparisons: *p<0.05 etanercept versus sulfasalazine; †p <0.05 etanercept versus combination; and ‡p<0.05 combination versus sulfasalazine.
†The types of skin infections included commonly reported events such as acne, phlebitis, fungal infections, and nail disorders.

Treatment-emergent infections per patient year were significantly higher with etanercept (1.72) than etanercept and sulfasalazine (1.11) or with sulfasalazine (0.86; p<0.001 overall). There were significant differences between the etanercept group and both the sulfasalazine and combination groups (p<0.001). Medically important infections occurred in more patients receiving etanercept (11; 10.7%) than in those receiving combination (5; 5%, p not significant) or sulfasalazine (0; p<0.05). After 352 days receiving combination therapy, 1 patient was hospitalized and withdrawn from the study, and treated with anti-tuberculous drugs following a histological determination of tuberculous lymphadenitis.

There was no clustering of SAEs. In the 2 years of the study, 23 patients receiving the combination, 27 receiving etanercept, and 2 receiving sulfasalazine had ≥1 SAEs. Noninfectious SAEs were significantly higher in patients receiving etanercept (20.8% for the combination and 20.4% for etanercept alone) versus 4% for patients receiving sulfasalazine (p<0.01).

At all scheduled visits, patients receiving the combination had a significantly greater reduction in white blood cell (WBC) counts (mean change from baseline) than those receiving sulfasalazine alone (p<0.001). In contrast, there was no significant difference in this laboratory parameter between the ETN and SSZ groups. Across all treatment groups, no subjects developed any NCI grade 3 or 4 WBC abnormalities, except for 1 subject who had a transient grade 4 WBC abnormality that normalized. All mean WBC counts were within normal limits at all visits.

Leucopenia was reported as a TEAE in 8 (7.9%) patients in the combination group, 2 (1.9%) in the etanercept group, and none in the sulfasalazine group (p not significant). None of the events of leucopenia were associated with NCI Grade 3 or 4 levels of neutrophils or other NCI Grade 3 or 4 laboratory abnormalities. No patients withdrew from the study because of TEAEs of leucopenia; all events were resolved during the study.

Malignancy was diagnosed in 2 patients receiving etanercept. One patient with a history of skin cancer developed actinic squamous cell carcinoma of the lower lip.
The second patient, whose diagnosis was myelodysplastic syndrome after 12 weeks of etanercept, then developed myelocytic leukaemia and subsequently died.

The incidence of malignancy observed in this study was compared with expected incidence based on the United States SEER programme. The observed number (one) of malignancies in etanercept- or combination-treated patients during the entire study was lower than the expected numbers (2.7) based on SEER, which excludes nonmelanoma skin cancers.[16]

The second reported death was a patient with interstitial pneumonitis, who had a history of smoking, coronary obstructive pulmonary disease, and childhood pneumonia.

No patients developed systemic lupus erythematosus or a lupus-like syndrome, glomerulonephritis, pleuritis, peritonitis, or seizure. There were no reports of central demyelinating diseases in this study. Occurrences of auto-antibodies were not significantly different among groups at baseline and at last visit.

DISCUSSION

The results from this 2-year double-blind, randomised study in patients with active RA despite sulfasalazine therapy provide further evidence that etanercept, either alone or when added to existing DMARD therapy, has a favourable long-term safety and efficacy profile. The addition of or switching to etanercept resulted in a rapid and sustained improvement of all clinical efficacy endpoints compared with sulfasalazine alone. The efficacy results were similar in both etanercept groups, indicating that patients inadequately responding to sulphasalazine would benefit by either the addition of etanercept to their existing (sulfasalazine) treatment or by switching from sulfasalazine to etanercept. Treatment with etanercept, sulfasalazine, or the combination did not result in any unexpected safety findings. The combination of etanercept and sulfasalazine was not associated with greater toxicity than either therapy alone.

Modifications to a less than adequate treatment regimen, such as the addition of another agent or substitution of a “failing” drug with another agent are a standard approach. Clinical studies in patients with RA have shown that adding or substituting an anti-TNF agent to the existing methotrexate therapy [3, 4, 7, 18, 19], results in a significant improvement in the therapeutic response. The addition of an anti-TNF agent to (or in place of) inadequate sulfasalazine has not been extensively evaluated in clinical trials. In the only other placebo-controlled trial in RA patients not adequately treated with sulfasalazine, adalimumab was added to the existing treatment,[9] (http://www.fda.gov/cder/biologics/products/adalabb123102.htm). In that study, patients receiving the combination showed a greater degree of improvement than those receiving sulfasalazine alone. However, modest sample sizes
(sulfasalazine alone, n=33; sulfasalazine plus adalimumab, n=29) make it difficult to compare the efficacy results among the treatment arms. In a larger open-label study evaluating adalimumab alone and in patients inadequately responding to at least one traditional DMARD, the number of ACR20 responders was similar for adalimumab + sulfasalazine and adalimumab alone.[11]

Patients who received ETN monotherapy or ETN+SSZ combination achieved significantly higher ACR response rates than patients in the SSZ monotherapy group (p<0.01). For all three treatment groups, the core components generally followed the pattern of the ACR composite response. Mean ESR values in both the ETN+SSZ combination and ETN monotherapy groups were significantly lower than in the SSZ monotherapy group from week 2 (p<0.01) through week 104 (p<0.01). For a short period (week 8 to wk 20) the combination group had significantly lower ESR levels than the ETN alone group (p<0.05), but the difference was not significant from wk 24 to wk 104.

Physical function scores were significantly improved in the groups receiving etanercept, either alone or in combination with sulfasalazine, compared with sulfasalazine alone using several previously defined thresholds.[20, 21] In patients with RA, a change of ≥0.22 units in the HAQ score has been used to estimate the number of patients with a clinically significant improvement in physical function.[21] In this study, by week 104, 3 in every 4 patients receiving etanercept, either alone or as add-on therapy, achieved a HAQ improvement of ≥0.22, compared with less than 1 in 2 patients continuing on sulfasalazine therapy.

Etanercept and combination therapy resulted in significantly greater improvements in all measured PROs than the modest improvements seen with sulfasalazine therapy. Furthermore, there was a significant correlation between disease activity, as assessed by the DAS, and physical function, as assessed by the HAQ. Significant correlation was also observed between disease activity and other PROs, including the EQ-5D VAS, and PGAD.

The study was originally designed as a 6-month trial, which is not long enough to detect radiographic changes, but was subsequently extended to 2 years. However, because both disease activity and radiographically assessed joint damage have been shown to be major contributors to the physical functioning of the patient with RA,[22-25] the significant improvements in disease activity and physical functioning would suggest that radiographic progression was inhibited in these patients.

Treatment with etanercept, sulfasalazine, or the combination did not result in any unexpected safety findings: however, the comparison of TEAEs among treatment groups in this study has bias. Generally, with any drug patients report AE(s) at a higher frequency during the first few weeks or months after the start of treatment and patients who cannot tolerate the drug are withdrawn. As a protocol-inclusion
criterion, patients in the sulfasalazine group were required to have tolerated sulfasalazine well; hence, these patients were expected to report AEs at a lower rate than patients receiving a “new” treatment.

Use of anti-TNF agents has also been associated with the increased frequency of autoantibodies, which could result in autoimmune diseases such as systemic lupus erythematosus.[26-28] Although the number of patients who tested positive for anti-dsDNA increased by the end of our study, there were no relevant clinical symptoms associated with the positive anti-dsDNA test results in any of the treatment groups.

Leucopenia, neutropenia, thrombocytopenia, and pancytopenia have also been reported in patients receiving anti-TNF therapies. In this study, the incidence of TEAEs of leucopenia was greater in the combination group (7.9%) than in the etanercept group (1.9%) or the sulfasalazine group (0%), but between group differences were not statistically significant. Investigators categorized the severity of all 8 events in the combination group as mild: none of the TEAEs of leukopenia were associated with NCI Grade 3 or 4 values of neutrophils or with other NCI Grade 3 or 4 laboratory abnormalities. No patients withdrew from the study because of leucopenia. Thus, the lower WBC counts did not seem to be clinically relevant. Furthermore, there were no reports of aplastic anaemia or pancytopenia.

This study shows that the addition of etanercept to sulfasalazine, a DMARD other than methotrexate, can provide significant long-term improvement in efficacy. Specifically, it shows that etanercept provides benefit when added to or switched with sulfasalazine in patients who show an inadequate response to sulfasalazine. The reported findings are especially relevant in view of the recent reports regarding monotherapy failures, which discourage the choice for both MTX + SSZ and leflunomide + SSZ combination therapy.[29, 30] Generally, the combination treatment was not associated with an increased incidence of AEs. Etanercept either alone or added to existing sulfasalazine therapy is associated with a favorable risk benefit profile, thus broadening the range of options for the treatment of patients with active RA.

**Competing Interests:** B Combe was a consultant and a speaker for Wyeth. C Codreanu received investigator fees for carrying out Wyeth trials. U Fiocco received reimbursement from Wyeth Italia for running educational programmes. M Gaubitz was reimbursed by Wyeth for attending several conferences and was paid for giving educational talks. PP Geusens received support for clinical studies from Wyeth Research. TK Kvien was a consultant and a speaker for Wyeth and received funds for research. J Wajdula, R Khandker, A Singh, and S Fatenejad are employees of Wyeth Research.
List of the Etanercept Study 309 Investigators in Europe and Australia (Other than the Authors)

Prof Maxime Dougados, Hopital Cochin, Paris, France
Prof Joël Dehais, Hopital Pellegrin, Bordeaux France
Prof Philippe Goupille, Hopital Trousseau, Tours, France
Prof Pierre Miossec, Hopital E Herriot, Lyon, France
Dr Anett Grässler, University Hospital, Dresden, Germany
Prof Umberto Ambanelli Universita di Parma, Parma, Italy
Prof Silvano Todesco, Policlinico Universitario, Padova, Italy
Dr Hillary Capell, Glasgow Royal Infirmary, Glasgow, United Kingdom
Dr Ian Griffiths, Freeman Hospital, Newcastle upon Tyne, United Kingdom
Dr Richard Hull, Queen Alexandra Hospital, Portsmouth, Hampshire, United Kingdom
Dr George Kitas, Corbett Hospital, Stourbridge, West Midlands, United Kingdom
Dr Robert Moots, Fazakerley Hospital, Liverpool, United Kingdom
Prof David G.I. Scott, Norfolk and Norwich Hospital, Norwich, United Kingdom
Prof David L. Scott, Dulwich Hospital, London, United Kingdom
Dr Peter Shelton, Leicester Royal Infirmary, Leicester, United Kingdom
Dr Bryan Williams, University Hospital of Wales, Cardiff, South Wales, United Kingdom;
Dr Gary Wright, Musgrave Park Hospital, Belfast, United Kingdom
Dr Paresh Jobanputra, University of Birmingham, Birmingham, United Kingdom
Dr Knut Mikkelsen, Lillemanners sanitetsfæroyning, Lillehammer, Norway
Dr Olav Bjorneboe, Martina Hansens Hospital, Gjetterm, Norway
Dr Petr Vitek, Centrum Rehabilitace, Zlin, Czech Republic
Dr Ladislav Bortlik, NZZ Bormed, Ostrava, Czech Republic
Dr Marie Sedlackova, Thomayer University Hospital, Praha, Czech Republic
Dr Sevda Augustinova, Medipont, (Jerzy Lech) Ceske Budejovice, Czech Republic
Dr. Peter Nash, Sixth Avenue Specialist Centre, Maroochydore, Australia
Dr Stephen Hall, Cabrini Medical Centre, Malvern, Australia
Dr Florin Radulescu, Ambulatoriu Centrului Metodologic de Reumatologie, Bucuresti, Romania
D. Coman Tanasescu, Institutul de Medicina Interna, Bucuresti, Romania
Dr Horatiu Bolosiu, Spitalul Clinic Judetean Cluj, Cluj-Napoca, Romania
REFERENCES


analysis of the TEMPO trial. Abstract SAT0193. In: European League Against Rheumatism (EULAR); 2006; Amsterdam. The Netherlands; 2006.


FIGURE LEGENDS

Figure 1. Percent of Patients Remaining in the Study versus Time (in weeks). Based on the log-rank test, the p values for the comparisons of the time to discontinuation are <0.001 (SSZ versus etanercept), <0.001 (SSZ versus combination), and 0.06 (etanercept versus combination).

Figure 2. Mean Disease Activity Score (DAS) Over Time (in weeks; last-observation-carried-forward, modified intent-to-treat analysis). Symbols: Etanercept plus sulfasalazine \( \nabla \); Etanercept \( \bullet \); sulfasalazine \( \blacksquare \). \( *p<0.05 \) etanercept versus combination; \( \dagger p<0.05 \) sulfasalazine versus combination; \( \ddagger p<0.05 \) sulfasalazine versus etanercept.

Figure 3. Percentage of Patients in Each Treatment Group Achieving an ACR Response (LOCF). A ACR 20, B ACR 50 and C ACR 70. Symbols: Etanercept plus sulfasalazine \( \nabla \); Etanercept \( \bullet \); sulfasalazine \( \blacksquare \). \( *p<0.01 \) etanercept versus combination; \( \dagger p<0.01 \) sulfasalazine versus combination; \( \ddagger p<0.05 \) sulfasalazine versus etanercept.

Figure 4. Mean Health Assessment Questionnaire (HAQ) scores from baseline to week 104 for patients with rheumatoid arthritis receiving sulfasalazine, etanercept, or combination therapy with sulfasalazine and etanercept (last-observation-carried-forward analysis). Symbols: etanercept plus sulfasalazine \( \Delta \); etanercept \( \bullet \); sulfasalazine \( \blacksquare \). \( *p<0.01 \) sulfasalazine versus etanercept; \( \dagger p<0.01 \) sulfasalazine versus combination.

Figure 5. Health status at baseline and week 104 for patients with rheumatoid arthritis receiving etanercept, sulfasalazine, or combination therapy as measured by least squares means for EQ-5D, GHVAS, and PGAD (LOCF analysis). A. EQ-5D; B. GHVAS; C. PGAD.
Figure 1

![Graph showing the percentage of patients over time for different treatments.](image-url)
Figure 2
Figure 3A
Figure 3B
Figure 3C
A. EQ-5D

Least squares mean

Baseline

Week 104

Etanercept
Etanercept + Sulfasalazine
Sulfasalazine
B. GHVAS

![Bar chart showing least squares mean for baseline and week 104 for Etanercept, Etanercept + Sulfasalazine, and Sulfasalazine groups.](chart.png)
C. PGAD

Least squares mean

Baseline

Etanercept

Etanercept + Sulfasalazine

Sulfasalazine

Week 104
Efficacy, safety, and patient-reported outcomes of combination etanercept and sulfasalazine versus etanercept alone in patients with rheumatoid arthritis: a double-blind randomized two-year study


Ann Rheum Dis  published online September 15, 2008

Updated information and services can be found at: http://ard.bmj.com/content/early/2008/09/15/ard.2007.087106

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Open access (595)
- Connective tissue disease (4253)
- Degenerative joint disease (4641)
- Immunology (including allergy) (5144)
- Musculoskeletal syndromes (4951)
- Rheumatoid arthritis (3258)

Notes

To request permissions go to: http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to: http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to: http://group.bmj.com/subscribe/