The safety and efficacy of adding etanercept to methotrexate or methotrexate to etanercept in moderately active rheumatoid arthritis patients previously treated with monotherapy

D van der Heijde, G Burmester, J Melo-Gomes, C Codreanu, E Martin Mola, R Pedersen, B Freundlich, D J Chang and for the Etanercept Study 400 Investigators

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ABSTRACT

Objective: To determine if adding etanercept (ETN) to methotrexate (MTX) or MTX to ETN for 52 weeks in rheumatoid arthritis (RA) patients with moderate disease activity provides higher efficacy.

Methods: All patients (n = 227) received open-label ETN 25 mg subcutaneously twice-weekly and MTX orally up to 20 mg weekly for 52 weeks and had completed a 3-year study in which patients received MTX, ETN or combination therapy. Endpoints were based on Disease Activity Score (DAS) and European League Against Rheumatism (EULAR) responses.

Results: Patients previously receiving combination therapy (Combination group; n = 96) had a lower disease activity at baseline. The mean DAS for those previously receiving MTX (MTX-added group; n = 55) and previously receiving ETN (ETN-added group; n = 76) were in the moderate disease activity range at baseline; Combination patients had a low disease activity. The greatest increase in DAS remission rates from baseline to week 52 was in the ETN-added group (23.6% to 41.8%, p = 0.01), although Combination (37.6% to 50.0%, p < 0.01) and MTX-added (26.7% to 36.8%, p = NS) also demonstrated improvements. DAS low disease activity and EULAR responses showed similar results. No new safety issues were identified.

Conclusion: RA patients who were partial responders to long-term MTX or etanercept monotherapy obtained a higher efficacy with combination therapy. Responses achieved by patients with combination therapy after 3 years in the previous study were sustained or improved during the fourth year of treatment. This trial supports the higher therapeutic effect of combination treatment with etanercept and MTX in RA patients with moderate disease activity despite monotherapy with one of the two agents.

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disease affecting up to 1–3% of the population in Western countries. RA may result in joint destruction, permanent deformity and loss of function. Therefore, long-term efficacy, as well as safety of therapy, is critical in the treatment of this chronic disease.

Goals for treatment include preventing or controlling joint damage, limiting functional loss and achieving remission of disease activity. Therapy should begin early with disease-modifying antirheumatic drugs (DMARDs). Among DMARDs, methotrexate (MTX) is one of the most effective agents. Drugs that block tumour necrosis factor (TNF), a key cytokine in the pathogenesis of RA, have also become important therapeutic options. Successful treatment of clinical signs and symptoms of RA have been reported for all three TNF inhibitors approved in the United States and Europe.

The 3-year Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO) established the combination of etanercept and MTX as a very effective therapy for RA. After 1 year of therapy in patients with active RA for whom previous treatment with a DMARD other than MTX had failed, the combination of etanercept and MTX was demonstrated to be superior in clinical efficacy and in the prevention of radiographic progression compared with either etanercept monotherapy or MTX monotherapy. The 1-year results of TEMPO were sustained during the 2nd and 3rd years of treatment.

We report here the results of a 52-week open-label study in which patients who completed 3 years of the original double-blinded TEMPO study could enrol in a 52-week open-label extension study and receive treatment with the combination of etanercept and MTX. Since most of the patients on monotherapy were not in remission at the end of 3 years, it was clinically appropriate to add another therapy to provide all patients with the combination of etanercept and MTX. Furthermore, even for patients with relatively good control of clinical signs and symptoms of RA, radiographic progression with structural damage may still be occurring. The purpose of this study was to determine whether patients who had been maintained for 3 years on monotherapy and with moderate disease activity would benefit further from the addition of etanercept to MTX or the addition of MTX to etanercept. Unlike other studies, patients in this trial generally had at least partial response to MTX or etanercept monotherapy as they had maintained their treatment for 3 years and had attained a moderate disease activity state. In addition, this study investigated the ability of the combination etanercept and MTX to sustain the clinical efficacy achieved in the previous study for a 4th year in a clinical trial.

PATIENTS AND METHODS

Patients

All patients who completed 3 years of treatment in the TEMPO study were eligible for enrolment into...
the 52-week extension study. The TEMPO study design has been previously described in detail. In brief, patients with active RA were randomised to treatment with etanercept monotherapy (25 mg twice weekly), MTX monotherapy (up to 20 mg/week) or the combination of etanercept and MTX (in the same doses as the monotherapy groups). To enrol in the current study, patients required a negative pregnancy test for women, use of a medically accepted method of contraception, no significantly abnormal laboratory values, no dose of prednisone >10 mg/d or change in dosage within 2 weeks of extension study initiation and no clinically relevant concurrent medical condition or event.

Study protocol
All patients received both open-label etanercept 25 mg subcutaneously twice weekly and oral MTX at individualised doses up to 20 mg/week. Patients who had previously been treated with 3 years of MTX monotherapy added etanercept 25 mg twice weekly to their regimen, while those who had previously been treated with 3 years of etanercept monotherapy added MTX, following a rapid dose escalation starting with 7.5 mg weekly up to 20 mg weekly by week 8. Patients previously treated with the combination of etanercept and MTX continued with their regimen. For patients in the original MTX monotherapy group or the original combination group, the dose of MTX was initially maintained at the same stable dose from the blinded part of the original TEMPO study. However, investigators were permitted to increase or decrease MTX dosages up to 5 mg/month, if required, as long as the dosage remained between 10 mg/week and 20 mg/week. Oral corticosteroids of up to prednisone 10 mg per day or equivalent were allowed; intramuscular injections were not permitted. Intrarticular corticosteroids were limited to one injection every 3 months, but given at least 2 weeks before assessments. Assessments were performed at baseline and at weeks 4, 8, 12, 26, 39 and 52. The protocol and amendments received Independent Ethics Committee/Institutional Review Board approval before initiation of study centres, and all participating patients gave written informed consent.

Study end points
The Disease Activity Score (DAS) was used to determine the proportion of patients in remission (<1.6) and low disease activity (<2.4) at 52 weeks. The European League Against Rheumatism (EULAR) response criteria of moderate or good response were based on the DAS28.

Safety assessments were based on reports of adverse events (AEs) and results of routine physical examinations and laboratory measurements. A serious adverse event was any AE that resulted in death, was life-threatening, required or prolonged inpatient hospitalisation, led to a persistent or significant disability or incapacity, resulted in cancer, or resulted in a congenital anomaly or birth defect. An infection requiring treatment with parenteral antibiotics or inpatient hospital admission was reported as a serious infection.

Statistical analysis
Efficacy and safety analyses utilised a modified intention-to-treat approach in which all patients who were randomised were included. The last-observation-carried-forward approach was used to account for missing data.

The statistical analysis focused on the within-group comparisons of change from baseline, using McNemar’s test for difference in proportional responses and paired t test for continuous or ordinal endpoints, as patients were not re-randomised at study entry. Between-group analysis was performed across the 3 treatment groups only for baseline comparisons using an analysis of variance (ANOVA) model with treatment as factor. All tests and confidence intervals were 2-sided at an alpha of 0.05.

The primary clinical endpoint was DAS remission at 52 weeks. For continuous and ordinal efficacy variables with baseline values, including DAS, DAS28, number of tender joints, number of swollen joints, physician global assessment, patient global assessment, general health visual analogue scale (VAS), pain VAS, Health Assessment Questionnaire (HAQ), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), both the mean absolute value and mean percentage change from baseline were summarised. Additional analyses were conducted for the EULAR response criteria, comparing week 52 results with the baseline of the study.

For patients not in low disease activity or remission at baseline, post hoc analyses were conducted to determine the proportions and the odds ratios of achieving these improved clinical disease states at week 52 based on treatment group.

RESULTS
Patients and study completion
In the original TEMPO study, 686 patients were randomised, of which 327 completed at least 3 years. Eighty-one (81) patients were treated at sites that did not continue participation in the extension study for non-medical reasons, the most common reasons including investigator non-interest and regulatory document submission delays. None of the sites listed ethical concerns as the primary reason for non-participation. Of the 246 patients who had an opportunity to participate in the study, 227 of those patients (92.3%) were enrolled in this study. Seventy-six (76) of the patients had been treated previously with etanercept (MTX-added), 55 with MTX (ETN-added) and 96 with the combination etanercept and MTX (Combination) (fig 1).

During the 52-week study period, 93.8% of the patients (213/227) completed the study (fig 1). Of the 14 patients who discontinued from the study, 3 patients were in the Combination group, 3 patients were in the ETN-added group, and 8 patients were in the MTX-added group. Baseline demographics were similar across the 3 groups and to the original TEMPO baseline. Overall, patients were predominantly female (78.4%), white (99.1%) and rheumatoid factor positive (71.8%). The mean age at baseline was 55.1 years, and the mean disease duration was 9.8 years. The original TEMPO baseline demographics and disease characteristics across the 3 groups for the 227 patients enrolled in the extension study were similar (table 1). At the baseline of this extension study (the end of the 3 year double-blinded TEMPO study), however, the disease activity was generally lower for the Combination group. The mean DAS for the Combination group of 2.1 was significantly lower than for the other two groups and in the low disease activity range, whereas the DAS for the ETN-added group and MTX-added group were in the moderate disease activity range at 2.5 and 2.6, respectively (table 1). The DAS28 baseline results showed similar disease activity patterns. During the study, the mean weekly MTX doses taken by patients in Combination, ETN-added, and MTX-added groups were 16.8 mg, 17.8 mg and
Clinical efficacy

DAS remission

The proportion of patients achieving DAS remission (DAS < 1.6) increased for all treatment groups. The remission rate in the ETN-added group significantly increased from 23.6% at extension study baseline to 41.8% (p = 0.01) at week 52 (fig. 2). The Combination group significantly increased the remission rate from 37.6% to 50.0% (p = 0.01). The change in remission rate was not significant in the MTX-added group (26.7% to 36.8%; p = 0.06).

Of the patients not in remission at baseline, an additional 28.6% of patients in the ETN-added group achieved remission at week 52. In the MTX-added group and Combination group, 23.6% and 24.1% more patients reached remission, respectively.

Compared with the Combination group, the odds ratio for remission was significantly higher in the ETN-added group (odds ratio = 2.2, 95% CI = 1.3 to 3.6, p = 0.002) and the MTX-added group (odds ratio = 2.2, 95% CI = 1.3 to 3.7, p = 0.002).

Table 1: Patient demographics and disease characteristics at original TEMPO baseline, extension study baseline, and Week 52 of the extension study

<table>
<thead>
<tr>
<th></th>
<th>TEMPO baseline</th>
<th>Baseline</th>
<th>Week 52</th>
<th>TEMPO baseline</th>
<th>Baseline</th>
<th>Week 52</th>
<th>TEMPO baseline</th>
<th>Baseline</th>
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<td></td>
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<td>80.0</td>
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<td>73.7</td>
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<td>Disease duration (years)</td>
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<td></td>
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<td>8.8</td>
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<td>DAS</td>
<td></td>
<td>5.6</td>
<td>2.1**</td>
<td>1.9 (11.3)**</td>
<td>5.9</td>
<td>2.5</td>
<td>1.9 (23.6)**</td>
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<td>DAS28</td>
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<td>3.1</td>
<td>2.9 (9.4)</td>
<td>6.9</td>
<td>3.9</td>
<td>3.0 (21.4)**</td>
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<td>Tender joint count (0–71)</td>
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<td>5.6 (13.3)</td>
<td>35.0</td>
<td>9.1</td>
<td>5.7 (39.2)**</td>
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<td>Swollen joint count (0–68)</td>
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<td>2.6</td>
<td>1.6 (41.1)*</td>
<td>24.0</td>
<td>4.7</td>
<td>2.3 (46.9)**</td>
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<td>5.0</td>
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<td>15.8</td>
<td>3.4</td>
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<td>1.6 (28.1)**</td>
<td>6.6</td>
<td>2.4</td>
<td>1.7 (27.9)**</td>
<td>6.5</td>
<td>2.3</td>
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<td>Patient global assessment (0–10)</td>
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<td>2.5</td>
<td>2.2 (11.7)</td>
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<td>2.8</td>
<td>2.7 (4.3)</td>
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<td>2.8</td>
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<td>19.0 (16.8)</td>
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<td>27.7</td>
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<td>HAQ (0–3)</td>
<td></td>
<td>1.7</td>
<td>0.6</td>
<td>0.6 (9.5)</td>
<td>1.6</td>
<td>0.7</td>
<td>0.7 (4.0)</td>
<td>1.7</td>
<td>0.8</td>
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<tr>
<td>ESR (mm/h)</td>
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<td>20.2</td>
<td>20.8 (5.3)</td>
<td>41.8</td>
<td>28.6</td>
<td>21.4 (21.7)**</td>
<td>43.1</td>
<td>26.1</td>
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<td>CRP (mg/l)</td>
<td></td>
<td>24.3</td>
<td>6.8</td>
<td>6.6 (20.3)</td>
<td>27.9</td>
<td>10.4</td>
<td>8.0 (14.9)</td>
<td>27.4</td>
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*p<0.05 and **p<0.01, week 52 compared with baseline, paired t test; †p<0.05 combination compared with ETN-added; ‡p<0.05 combination compared with MTX-added, ANOVA model with factors for treatment and prior MTX use as covariate.

Values are means (% improvement from extension study baseline) unless stated otherwise. DAS, Disease Activity Score; VAS, visual analogue scale; HAQ, Health Assessment Questionnaire; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein. The per cent improvement is 100–(adjusted mean change/adjusted mean baseline).
achieving remission in the ETN-added group was 1.26 (95% CI: 0.51, 3.09) and 0.97 (95% CI: 0.41, 2.31) in the MTX-added group. The odds ratio for the ETN-added group versus the MTX-added group was 1.29 (95% CI: 0.52, 3.22).

DAS low disease activity
At baseline, the proportion of patients with low disease activity (<2.4) in the ETN-added group activity was 49.1% and increased to 72.7% (p<0.01) at week 52 (fig 5). The MTX-added group (46.7% to 57.9%, p<0.05) and Combination group (64.5% to 74.0%, p<0.05) showed improvements as well. Of the patients not in low disease activity at baseline, an additional 53.6% achieved low disease at week 52. In the MTX-added group and Combination group, 52.8% and 42.4% more patients reached a low disease activity, respectively. Compared with the Combination group, the odds ratio for achieving low disease activity in the ETN-added group was 1.57 (95% CI: 0.57, 3.43) and 0.65 (95% CI: 0.25, 1.70) in the MTX-added group. The odds ratio for the ETN-added group versus the MTX-added group was 2.40 (95% CI: 0.89, 6.47).

DAS
The mean DAS at baseline was significantly lower for patients in Combination group compared with patients in the other 2 groups (table 1). All treatment groups demonstrated significant improvement in the mean DAS during the extension study, with the ETN-added group improving from 2.5 to 1.9 (p<0.01), MTX-added group improving from 2.6 to 2.2 (p<0.05), and the Combination group improving from 2.1 to 1.9 (p<0.05) (table 1).

EULAR responses
All three groups demonstrated significant improvements at week 52 in the good/moderate and good EULAR response criteria from the baseline of the extension study. Similar to other endpoints, the improvements appeared greatest for the group that added etanercept (fig 4).

Other efficacy endpoints
Other efficacy endpoints, including DAS components and American College of Rheumatology core measures, are shown in table 1. The results generally showed the same pattern as described for DAS-derived endpoints with improvement in all groups, but most consistent in the ETN-added group.

Safety
The proportion of patients reporting one or more AE during the 52 weeks was similar across treatment groups (table 2).

Five patients withdrew from the study due to one or more AEs (fig 1): 1 in the Combination group (rheumatoid arthritis flare), 1 in the ETN-added group (carcinoma/hernia/aneurysm), and 3 in the MTX-added group (neutropenia, bacteraemia/pneumonia and mucositis/nausea). Five (5) patients experienced serious infections: in the Combination group, 1 patient had infectious diarrhoea; in the ETN-added group, 1 patient had an upper-respiratory infection; in the MTX-added group, 1 patient had an upper-respiratory infection, 1 patient had pyelonephritis, and 1 patient had bacteraemia and pneumonia. No cases of tuberculosis, opportunistic infections, systemic lupus erythematosus, multiple sclerosis or other central demyelinating disease were reported. Of the 2 deaths in the study, one patient who added MTX developed interstitial pneumonitis that led to multi-organ failure and the other patient, in the Combination group
group, experienced an accidental injury with a hip fracture, followed by a fatal pulmonary embolus after surgery.

**DISCUSSION**

This study was designed to address a clinically relevant question: Can partial responders to long-term MTX monotherapy with moderate disease activity gain a higher efficacy with combination therapy? In this trial, RA patients who had completed the 3-year double-blinded TEMPO study added etanercept to MTX monotherapy, added MTX to etanercept monotherapy or continued the combination of both agents. The results show data that combination therapy, especially adding etanercept to MTX, can provide further clinical improvements for RA patients with moderate disease activity after 3 years of monotherapy. Furthermore, the study demonstrates the sustained efficacy of the combination of etanercept and MTX therapy over a 4-year period, including a remission rate of 50% and a low disease activity of 74%. Importantly, it also reaffirms the safety profile of combination therapy during the 52 weeks of the study.

This open-label 52-week extension study represents a 4th year of participation by RA patients in clinical trials, the initial 3-yr study being blinded. Consequently, the number of patients continuing in the extension study was smaller than the original study population and was not based on a specific sample-size power calculation; however, almost 94% of the patients completed the study. The patients who continued in this extension study represent a subgroup of patients from TEMPO who, as a group, were sufficiently satisfied with their therapy, since they had not withdrawn from the original study. This makes the additional clinical improvement achieved by switching from monotherapy to combination therapy all the more noteworthy, especially as the treatment goal for the extension study was remission. As the patients in this extension study were not re-randomised at baseline after receiving 3 years of 3 different treatments, patients exhibited some differences in the baseline disease characteristics, with the combination group generally demonstrating lower clinical disease activity. Therefore, comparisons across the 3 groups were not the focus of this report.

RA treatment guidelines typically require an inadequate response to MTX prior to initiating treatment with TNF-inhibitors. Previous studies have demonstrated the efficacy of etanercept in such patients. In a double-blind, placebo-controlled study by Weinblatt et al, RA patients with persistently active disease despite treatment with MTX who added etanercept achieved significantly better clinical outcomes than patients who added placebo. Van Riel confirmed the findings in an open-label study, in which active RA patients with an inadequate response to MTX demonstrated additional clinical improvements when etanercept was either added to MTX or substituted for MTX. Although these studies allowed RA patients with both moderate and severe disease to enrol, most of the patients had severe disease. In the Weinblatt study, the median swollen joint count was 17 for the placebo group and 20 for the etanercept group (out of 68 assessed), and the tender joint count was 28 for both groups (out of 71 assessed); DAS was not reported, however. In the van Riel study, the reported mean DAS28 at baseline was 6.2 for the group treated with etanercept alone and 6.3 for the group treated with the combination of etanercept and MTX.

In contrast to previous studies, this trial involved groups of patients whose mean disease activity demonstrated moderate disease while on either MTX or etanercept monotherapy. The mean DAS28 at baseline of the 52-week extension for the ETN-added group was 3.9 and in the moderate disease activity range; the mean tender and swollen joint counts were 9.1 and 4.7, respectively. Despite one-quarter of the patients already being in remission at baseline, adding etanercept to MTX in this extension study not only significantly increased the proportion of patients achieving remission and low disease activity at week 52, but also significantly improved the DAS and increased the EULAR good/moderate and good responder rates. Significant clinical benefits were also achieved in the other 2 groups on some endpoints, but the ETN-added group generally demonstrated the largest numerical improvements and on the most endpoints.

RA patients with moderate disease activity represent a large portion of the RA population. A recent publication has estimated that 41% to 45% of the RA population has moderate disease activity. However, these patients may be undertreated...
because they are not eligible to receive TNF inhibitors in some regions as their disease is not considered sufficiently severe.

Even with the open-label study design, objective parameters of disease activity also improved when monotherapy was switched to combination therapy. Most notably, the ESR was significantly lowered in the ETN-added group after 52 weeks of combination therapy with a similar trend in the CRP levels.

Another important finding of this study was the sustained efficacy of the combination of etanercept and MTX over 4 years of therapy. Patients who had received 3 years of combination therapy in TEMPO had a low disease activity on DAS and DAS28 at baseline. After continued therapy with etanercept and MTX for 52 weeks in the extension study, the clinical response was largely sustained for most endpoints, and the DAS remission rate significantly improved to 50%.

Although this study demonstrated that RA patients treated with MTX for 3 years gained additional clinical benefits by adding etanercept to their regimen, it is unlikely that the radiographic damage incurred over the 3 years on MTX monotherapy can be completely reversed. By the end of 2 years of therapy in the original TEMPO study, MTX-treated patients had progressed 3.54 points on the modified total Sharp score compared with a change of –0.56 for the group treated with combination therapy.22 By the end of 3 years, the radiographic progression for patients receiving MTX monotherapy had increased to 5.95 while the combination group had a change of –0.14.22 Consequently, not only is earlier combination therapy likely to provide substantial improvement in clinical efficacy, but also the treatment may result in better radiographic outcomes than delayed introduction of etanercept in combination with MTX.

Finally, the results of this study reaffirm that the combination of etanercept and MTX does not lead to new unexpected safety signals or toxicities over 52 weeks of therapy. There were no cases of tuberculosis, opportunistic infections, systemic lupus erythematosus, or multiple sclerosis or other central demyelinating diseases in any of the patients during the study. Serious infections were uncommon and occurred in less than 5% of the patients receiving combination therapy, which is similar to the rates reported during each of the previous 3 years of TEMPO. The overall favourable safety profile of combination treatment over the 3-year duration of TEMPO was also observed for an additional year in this study.

In summary, the results from this 52-week study demonstrate the higher efficacy of combination therapy for RA patients who were partial responders to long-term MTX or etanercept monotherapy, as evidenced by the significant improvement in various clinical parameters such as DAS remission, DAS low disease activity and EULAR response criteria. These benefits with combination therapy had the greatest impact in the ETN-added group. Furthermore, the clinical improvements achieved by patients treated with combination therapy for 3 years in the original TEMPO study were sustained or improved during the 4th year of treatment in this extension study. No new safety signals were identified, although the risk–benefit ratio should always be considered when adding a new treatment to an existing regimen. This trial supports the higher therapeutic effect of combination therapy with etanercept and MTX in RA patients experiencing moderate disease activity despite monotherapy with one of the 2 agents.

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Competing interests: DvdH, GB, JMG, CC, and EMM participated as investigators, consultants, or both to Wyeth. DvdH was reimbursed by Wyeth, the manufacturer of etanercept, for attending several conferences and for running educational programmes. EMM has received fees as a consultant of Abbott, Centocor, Schering Plough, and Bristol Myers Squibb. RP, BF and DC are employed by and have stock options with Wyeth Pharmaceuticals.

REFERENCES


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**FUNDING AVAILABLE FOR RESEARCH PROJECTS**

The Committee on Publication Ethics (COPE) has established a Grant Scheme to fund research in the field of publication ethics. The Scheme is designed to provide financial support to any member of COPE for a defined research project that is in the broad area of the organisation’s interests, and specifically in the area of ethical standards and practice in biomedical publishing. The project should have a specific goal and be intended to form the kernel of a future publication.

A maximum sum of £5000 will be allocated to any one project, but applications for smaller sums are welcomed.

The terms and conditions of the Grant are as follows:

- At least one of the applicants must be a member of COPE.
- Calls for applications will be made twice a year with closing dates of 1 December and 1 June. An electronic version of the application form must be sent to the Administrator no later than 12 pm (noon GMT) on the closing date for consideration by COPE Council.
- The application must contain a lay summary of the project, a definition of the question to be posed, sufficient methodological detail to allow assessment of the viability of the project, a clear timeline and a definition of the likely deliverables. A full justification for the sum requested must accompany the application.
- A report on the progress of the research should be presented within one year of the award and at the end of the project. The grant must be used within two years from the date of award, and balance sheets must be forwarded annually. These should be sent to the Administrator. Any remaining funds after two years must be returned.
- It is anticipated that the work stemming from the project will be presented at one of COPE’s annual seminar meetings within 2–3 years of the award. Such data may also be published in peer-reviewed journals. Any publications or related presentations at meetings by the recipient emanating in part or whole from COPE’s support should be duly acknowledged and copies sent to the Administrator.

Applications are reviewed by a COPE sub-committee. Applicants will be advised of a decision as soon as practicable after the deadline date.

An application form can be obtained by contacting Linda Gough, COPE administrator, at LGough@bmj.com or 020 7383 6602. For more information on COPE, see http://www.publicationethics.org.uk/

The closing date for receipt of applications is 1 December 2007 or 1 June 2008.