Running title: Etanercept-methotrexate therapy for RA

Patient-reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: the TEMPO trial

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ABSTRACT

Objective: To compare patient-reported measures of function, health-related quality of life (QoL), and satisfaction with medication among rheumatoid arthritis patients treated with methotrexate (MTX), etanercept or both for up to one year.

Methods: In a 52-week double-blind clinical trial, patients with active RA were randomised to receive etanercept 25 mg twice weekly, methotrexate up to 20 mg weekly, or combination therapy. The Health Assessment Questionnaire disability index (HAQ), EuroQoL health status visual analogue scale (EQ-5D VAS), patient global assessment and patient general health VAS were administered at baseline and weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48 and 52. Satisfaction with medication was compared at 52 weeks.

Results: Of 682 enrolled patients, 522 completed 52 weeks of treatment. Mean improvement from baseline in HAQ score was 0.65, 0.70, and 1.0 for MTX, etanercept and combination, respectively. The mean percentage and absolute improvement in HAQ was significantly higher (P<0.01) for combination therapy than either monotherapy. Combination therapy produced significantly more rapid achievement of HAQ ≤ 0.5 and sustained for 6 months than either monotherapy (P<0.01). Compared with monotherapy recipients, patients receiving combination therapy achieved significantly better (P<0.05) health state as measured by EQ-5D VAS (63.7±3.2, 66.8±3.2, 72.7±3.1 for MTX, etanercept, and combination, respectively). Results were similar for other assessments (P<0.01). Patients in combination and etanercept groups were significantly more likely (P<0.0001 and P=0.0009, respectively) to report satisfaction with medication.

Conclusions: Combination therapy with etanercept and methotrexate improved function, QoL and satisfaction with medication significantly better than monotherapy.

Key words: rheumatoid arthritis, etanercept, methotrexate, functional status, disability, patient outcomes assessment, quality of life
INTRODUCTION
Clinical practice guidelines for rheumatoid arthritis (RA) recommend initiation of therapy with disease-modifying antirheumatic drugs (DMARDs) within three months of diagnosis to preserve function and retard joint damage.[1] Although guidelines recommend methotrexate (MTX) as standard therapy, alone or in combination with another DMARD,[1] recent studies comparing the human soluble tumour necrosis factor (TNF) receptor etanercept with MTX have reported significantly greater clinical improvement and fewer adverse events for etanercept therapy.[2,3] Furthermore, in a double-blind, randomised trial in patients with active RA despite MTX therapy, addition of etanercept to MTX improved function and disease activity measures.[4]

No controlled and randomised study, however, has included all three treatments (MTX, etanercept and combination therapy) to allow direct comparison of treatment efficacy in matched patient groups. The TEMPO study (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) was designed to compare efficacy and safety of the monotherapies with combination therapy in patients with active RA. Primary clinical and radiographic outcomes of TEMPO have been reported separately.[5] Combination therapy was significantly more efficacious than monotherapy as measured by American College of Rheumatology (ACR) response and radiographic evidence of joint damage.

This paper reports a comprehensive set of patient-reported outcomes (PROs), including satisfaction with study medication, which were included in the TEMPO study, distinct from the objective clinical and biological measures previously reported.[5] There is increasing recognition of the importance of how RA patients feel about their disease and treatment,[6] and the Bone and Joint Decade advocates greater incorporation of patient views.[7] With no cure for RA yet available, a primary goal of therapy is to restore functioning in activities of daily living and improve the health-related quality of life (QoL) of patients. Even in its early stages, RA significantly impairs physical and social functioning, emotional well-being and vitality. To help assess disease progression and response to treatment, clinical practice guidelines recommend using measures of functional status and quality of life.[1] Thus, although traditional measures such as ACR response and radiographic evidence of joint damage remain core clinical endpoints in RA outcomes studies,[8] it is increasingly recognised that PRO assessments are important in defining overall therapeutic effectiveness.[9] No single tool exists for measuring all relevant PROs in RA, so a combination of instruments is recommended.[9] It is also useful to measure patient satisfaction with treatment, which is influenced by convenience, efficacy and side effects.[6]

METHODS
The PRO analyses reported here were prospectively designed secondary assessments in a 52-week, multicentre, double-blind, randomised, parallel-group, outpatient study conducted between October 2000 and July 2002 in 17 European nations, Australia and Israel. Details of the study design and primary analyses are published elsewhere.[5]

Patients
TEMPO enrolled patients at least 18 years of age who had active RA (ACR functional class I to III) with disease duration of 6 months to 20 years. Active disease was defined as having 10 or more swollen joints, 12 or more painful joints, and at least one of: erythrocyte sedimentation rate 28 mm/hour or greater, C-reactive protein 20 mg/L or greater, or morning stiffness for 45 minutes or more. Patients were also required to have experienced unsatisfactory response to at least one DMARD other than MTX. All enrolees were considered suitable candidates for MTX therapy, had never had an unsatisfactory response to MTX and had not received MTX in the six months before enrolment.

Patients were ineligible if they had been treated with any DMARD within four weeks before study baseline, or if they had ever received etanercept or another TNF antagonist. Patients were also excluded for recent treatment with investigational, immunosuppressive or corticosteroid drugs, and for significant concurrent disease.

Subjects gave written informed consent at enrolment. The protocol received independent ethics committee approval at each participating centre. The trial was carried out in accordance with the
Declaration of Helsinki, and conformed to local regulations and principles of the International Conference on Harmonisation guidelines for Good Clinical Practice (1996 revision) in the European Community.

**Treatment groups**

Subjects were randomly assigned to one of three treatment groups: MTX, etanercept or combination. Patients in the MTX group received oral MTX capsules once weekly (initially 7.5 mg, escalated over 8 weeks to a maximum of 20 mg if patients still had any painful or swollen joints) and placebo subcutaneous injections twice weekly. Patients in the etanercept group received 25 mg etanercept by subcutaneous injection twice weekly and oral placebo capsules once weekly. Patients in the combination group received 25 mg etanercept subcutaneous injections twice weekly and oral MTX capsules once weekly (dosed as in the MTX group). All patients received 5 mg folic acid supplementation twice weekly.

**Outcomes**

Principal PRO measures were the Health Assessment Questionnaire (HAQ) disability index and EuroQoL health status visual analogue scale (EQ-5D VAS). The HAQ disability index is derived from a questionnaire comprising eight subscales: dressing, arising, eating, walking, reaching, gripping, hygiene and carrying out common activities.[10] The disability index and individual subscale scores range from 0 (without any difficulty) to 3 (unable to do). The EQ-5D VAS measures current health state on a thermometer scale ranging from 0 (worst state of health imaginable) to 100 (best state of health imaginable).[11]

Additional PRO measures were a patient global assessment of overall RA activity (PGAD) and a patient general health assessment (GHVAS). A numeric rating scale ranging from 0 (none) to 10 (extreme) was used for PGAD. For GHVAS, patients reported how they felt concerning their arthritis on a 10-cm horizontal VAS anchored on the left at “very well” and on the right at “extremely bad”.

Patient satisfaction with study medication was measured using a five-point scale ranging from “very satisfied” to “very unsatisfied”. Responses of “very unsatisfied”, “unsatisfied” and “neutral” were considered to indicate patient dissatisfaction, while “satisfied” and “very satisfied” indicated patient satisfaction.

This study also assessed relationships between PROs and two clinical measures of disease activity: Disease Activity Score (DAS) and DAS28. DAS is an index of disease activity that combines the Ritchie Articular Index, total number of swollen joints, erythrocyte sedimentation rate, and GHVAS.[12] DAS28 is a modified version of the DAS that includes counts of painful and swollen joints for 28 joints.[13]

All four patient-reported outcome measures were administered at baseline and weeks 2 and 4, then every four weeks to week 24, then every eight weeks to week 48, with final follow-up at week 52. Patient satisfaction was measured at baseline, weeks 2 and 12, and final follow-up. DAS and DAS28 were calculated after study completion.

**Data analysis**

Analyses were conducted for the entire enrolled population; to reduce bias and loss of statistical power, missing data due to study drop-out or other reasons were imputed using the last observation carried forward (LOCF) method.[14] All PRO measures (HAQ disability index, eight HAQ subscale scores, EQ5D VAS, GHVAS, PGAD) were compared between treatment groups using mean change from baseline and area under the curve (AUC). Using the AUC approach, more information about the rapidity and consistency of response can be evaluated.[15,16] Additionally, the AUC approach is appropriate when within-patient measurements are highly correlated over time and when changes are larger at earlier assessments. AUC endpoint treatment comparisons used an analysis of covariance (ANCOVA) model that included factors for study centre, treatment and prior MTX use, with baseline HAQ score as a covariate.

Comparisons between treatment groups were also performed using least squares means (means adjusted for potential imbalance in baseline values using a model fitted by the least-squares method[17]) and 95% confidence intervals (CI) for EQ-5D VAS, PGAD and GHVAS. These comparisons used an
ANCOVA model that included baseline score as a covariate and factors for study centre, treatment, and prior MTX use.

The proportion of patients within different clinically meaningful HAQ disability index categories at week 52 was compared between treatment groups using chi-square analysis. Categories compared were percent of patients with decrease from baseline of at least 0.22 (a clinically meaningful improvement[18,19]), percent of patients with decrease from baseline of at least 0.8 (a major improvement), and a change of 0.5 as used in other studies.[3,20] In addition, treatments were compared by percent of patients with HAQ scores of 0.5 or below at the end of the trial, representative of scores seen in the general population.[21] Treatments were also compared by percent of patients with EQ-5D VAS scores above 82, representing population norms.[22]

Rapidity of onset of action was assessed using life-table statistical analysis. Kaplan-Meier methods were used to estimate the proportion of subjects with HAQ scores of 0.5 or below, sustained for six months, by time since randomisation. Log-rank statistics were used to compare differences in survival plots among treatment groups.

The percentage of patients satisfied with study medication at final follow-up was compared between treatment groups using chi-square analysis. Predictors of patient satisfaction were evaluated using a logistic regression model that included treatment group, age, sex, race and satisfaction with current (pre-trial) medication at baseline. Using a backward elimination stepwise process, only variables with \( P<0.20 \) were retained in the final model.

Pearson correlation analysis was used to assess pairwise correlations between DAS and HAQ Disability Score, EQ-5D VAS, GHVAS and PGAD at week 52. Similar correlation analyses were also implemented for DAS28 scores. Significance for all comparisons was defined as \( P<0.05 \). Statistical analyses were performed using SAS version 8.2.

RESULTS

All but four of 686 patients (99%) randomised to treatment groups received study medication and were included in these analyses, and 522 (76% of those randomised) completed 52 weeks of treatment. Most patients were white and female, and their baseline characteristics did not differ significantly between treatment groups (Table 1).

Table 1. Baseline patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Methotrexate (n=228)</th>
<th>Etanercept (n=223)</th>
<th>Combination (n=231)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SD)</td>
<td>53.0 (12.8)</td>
<td>53.2 (13.8)</td>
<td>52.5 (12.4)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>180 (79)</td>
<td>171 (77)</td>
<td>171 (74)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>224 (98)</td>
<td>220 (99)</td>
<td>227 (98)</td>
</tr>
<tr>
<td>Disease duration, years (SD)</td>
<td>6.8 (5.5)</td>
<td>6.5 (5.1)</td>
<td>6.8 (5.4)</td>
</tr>
<tr>
<td>Number of prior DMARDs (SD)</td>
<td>2.3 (1.6)</td>
<td>2.3 (1.4)</td>
<td>2.3 (1.4)</td>
</tr>
<tr>
<td>Prior methotrex or use, n (%)</td>
<td>96 (42)</td>
<td>93 (42)</td>
<td>101 (44)</td>
</tr>
<tr>
<td>HAQ score* (SD)</td>
<td>1.7 (0.7)</td>
<td>1.8 (0.7)</td>
<td>1.8 (0.6)</td>
</tr>
<tr>
<td>EQ-5D VAS score</td>
<td>38.2 (20.3)</td>
<td>42.1 (21.7)</td>
<td>40.3 (22.4)</td>
</tr>
<tr>
<td>Patient general health VAS, mm (SD)</td>
<td>68.0 (20.5)</td>
<td>68.2 (19.8)</td>
<td>69.4 (19.3)</td>
</tr>
<tr>
<td>Patient global assessment score (SD)</td>
<td>6.9 (1.7)</td>
<td>6.9 (1.7)</td>
<td>7.2 (1.7)</td>
</tr>
<tr>
<td>Satisfied with previous medication, n (%)</td>
<td>7 (3.1)</td>
<td>2 (0.9)</td>
<td>7 (3.0)</td>
</tr>
</tbody>
</table>

* n=227 and 230 for methotrexate and combination, respectively

DMARDs: disease-modifying antirheumatic drugs; HAQ: Health Assessment Questionnaire disability index; EQ-5D VAS: EuroQoL health status visual analogue scale

HAQ

As shown in Figure 1, subjects receiving combination therapy achieved significantly greater improvement in functional status than did those receiving MTX alone from week 2 onwards, and than those receiving etanercept alone from week 4 onwards (Figure 1). Superior response to combination therapy was
sustained for the 52-week study duration. AUC analysis confirmed these findings. At week 52, combination therapy yielded significantly greater functional status improvements compared to either monotherapy (Figure 2).

Results for the eight HAQ subscales were consistent with those for the composite HAQ disability index. Figure 2 shows that by final follow-up combination therapy recipients achieved greater improvements than did MTX recipients for all HAQ subscales except grip. There were significant differences between combination therapy and etanercept in eating, hygiene, reach, and walking scores. No significant difference between etanercept and MTX was noted for any HAQ subscale.

Table 2 shows that by 52 weeks, combination therapy recipients were significantly more likely to attain HAQ disability index scores similar to population norms (0.5 or lower[21]) than were monotherapy recipients ($P<0.05$). A majority of patients in all three groups experienced a clinically meaningful improvement ($\geq 0.22$), but a significantly higher proportion of combination therapy recipients than monotherapy recipients achieved this degree of improvement ($P<0.05$). Combination therapy and etanercept recipients were significantly more likely than MTX recipients to achieve a major HAQ disability index score improvement of 0.8 or greater ($P<0.05$). However, only subjects in the combination group were significantly more likely than subjects in the MTX group to achieve an improvement of 0.5 or more (45% vs 36%, respectively; $P<0.05$).

Table 2. Percent distribution of Health Assessment Questionnaire (HAQ) disability index score and EQ-5D VAS scores, by treatment group

<table>
<thead>
<tr>
<th></th>
<th>Methotrexate (n=228)</th>
<th>Etanercept (n=223)</th>
<th>Combination (n=231)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with HAQ score $\leq 0.5$ at follow-up</td>
<td>34</td>
<td>34</td>
<td>44*†</td>
</tr>
<tr>
<td>Patients with EQ-5D Score at or above population norms at follow-up</td>
<td>24</td>
<td>31</td>
<td>41*†</td>
</tr>
<tr>
<td>Patients with HAQ improvement $\geq 0.22$§</td>
<td>77</td>
<td>77</td>
<td>86*†</td>
</tr>
<tr>
<td>Patients with HAQ improvement $\geq 0.5$§</td>
<td>53</td>
<td>55</td>
<td>72*†</td>
</tr>
<tr>
<td>Patients with HAQ improvement $\geq 0.8$§</td>
<td>36</td>
<td>45†</td>
<td>58*†</td>
</tr>
</tbody>
</table>

* $P<0.05$ for combination versus methotrexate
† $P<0.05$ for combination versus etanercept
‡ $P<0.05$ for etanercept versus methotrexate
§ From baseline to follow-up

As shown in Figure 3, 27%, 26%, and 39% of patients in the MTX, etanercept and combination groups, respectively, reached a HAQ score of 0.5 or lower and sustained it for six months. The overall log-rank test for equality over treatment groups was highly significant ($P=0.003$). Pairwise comparisons revealed that the combination treatment strategy provided significantly faster onset in achieving sustained HAQ scores of 0.5 or lower compared to either monotherapies ($P=0.003$ for combination versus etanercept; $P=0.005$ for combination versus methotrexate).

**EQ-5D VAS**

Table 3 shows EQ-5D scores improved in all three treatment groups. However, combination therapy recipients achieved significantly higher EQ-5D VAS scores (indicative of better health state) at week 52 than did patients who received either monotherapy. By week 52, combination therapy was significantly more likely than either monotherapy to yield EQ-5D scores above population norms. Comparison of AUC scores also revealed that combination therapy recipients had significantly greater improvement in EQ-5D VAS score than MTX patients (data not presented).
Table 3. Health status at baseline and 52 weeks of patients with rheumatoid arthritis receiving methotrexate, etanercept or combination therapy with methotrexate and etanercept, as measured by least squares mean (95% CI) for EuroQoL health status visual analogue scale, patient global assessment and patient general health visual analogue scale (LOCF analyses)

<table>
<thead>
<tr>
<th></th>
<th>Methotrexate (n=228)</th>
<th>Etanercept (n=223)</th>
<th>Combination (n=231)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 52</td>
<td>Baseline</td>
</tr>
<tr>
<td>EQ-5D VAS</td>
<td>38.74 (35.74–41.73)</td>
<td>63.66 (60.48–66.84)</td>
<td>43.12 (40.07–46.17)</td>
</tr>
<tr>
<td>PGAD</td>
<td>6.85 (6.61–7.09)</td>
<td>3.95 (3.63–4.27)</td>
<td>6.86 (6.61–7.10)</td>
</tr>
<tr>
<td>GHVAS</td>
<td>68.88 (66.15–71.61)</td>
<td>36.28 (33.09–39.46)</td>
<td>68.96 (66.19–71.74)</td>
</tr>
</tbody>
</table>

EQ-5D VAS: EuroQoL health status visual analogue scale; PGAD: patient global assessment; GHVAS: patient general health visual analogue scale

† P<0.01 for combination versus methotrexate
‡‡ P<0.01 and P<0.05, respectively, for combination versus etanercept
**Patient global assessment**

As shown in Table 3, combination therapy recipients reported significantly lower RA disease activity at week-52 PGAD than did subjects receiving either monotherapy. Combination therapy recipients had significantly greater improvement in PGAD than MTX recipients from week 2 onwards, and than etanercept patients from week 12 onwards. Results from AUC analysis at week 52 were similar (data not presented).

**Patient General Health VAS**

Table 3 shows that patients who received combination therapy attained significantly lower GHVAS scores (indicating better general health) at week 52 than did patients who received either monotherapy. Comparison of change from baseline (%) over time revealed that combination therapy recipients had significantly greater improvement in GHVAS score than MTX recipients from week 2 onwards, and than etanercept patients from week 8 onwards.

**Patient satisfaction with treatment**

A significantly higher percentage of patients in the combination and etanercept groups were satisfied with their medication than in the MTX group (Table 4). There was no significant difference in satisfaction with treatment between combination and etanercept groups. Logistic regression analysis revealed that etanercept and combination-therapy recipients were more than twice as likely to be satisfied with treatment as MTX recipients (Table 5). There was no significant association between satisfaction with treatment at week 52 and patient sex, disease duration, or baseline satisfaction. Age and race were non-significant and were eliminated from the final model.

Table 4. Patient satisfaction with rheumatoid arthritis medication by treatment group at study endpoint, as measured on a five-point scale

<table>
<thead>
<tr>
<th>Response</th>
<th>Methotrexate (n = 228)</th>
<th>Etanercept (n = 221)</th>
<th>Combination (n = 230)</th>
<th>Overall P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Not satisfied§</td>
<td>64</td>
<td>28.1</td>
<td>32</td>
<td>14.5*</td>
</tr>
<tr>
<td>Satisfied¶</td>
<td>164</td>
<td>71.9</td>
<td>189</td>
<td>85.5</td>
</tr>
</tbody>
</table>

* P<0.0005 for etanercept vs methotrexate  
† P<0.0001 for combination vs methotrexate  
‡ P=0.4716 for combination vs etanercept  
§ Satisfaction response of very dissatisfied, somewhat dissatisfied or neutral  
¶ Satisfaction response of satisfied or very satisfied

Table 5. Multiple logistic regression analysis of predictors of patient satisfaction with medication

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>χ²</th>
<th>P</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.9978</td>
<td>0.2047</td>
<td>23.7725</td>
<td>&lt;0.0001</td>
<td>2.236</td>
<td>1.389–3.600</td>
</tr>
<tr>
<td>Etanercept</td>
<td>0.8046</td>
<td>0.243</td>
<td>10.9643</td>
<td>0.0009</td>
<td>2.236</td>
<td>1.389–3.600</td>
</tr>
<tr>
<td>Combination</td>
<td>1.0165</td>
<td>0.2511</td>
<td>16.3862</td>
<td>&lt;0.0001</td>
<td>2.764</td>
<td>1.689–4.521</td>
</tr>
<tr>
<td>Disease duration</td>
<td>-0.0227</td>
<td>0.0185</td>
<td>1.5138</td>
<td>0.2186</td>
<td>0.978</td>
<td>0.943–1.014</td>
</tr>
<tr>
<td>Male</td>
<td>0.3353</td>
<td>0.2604</td>
<td>1.6585</td>
<td>0.1978</td>
<td>1.398</td>
<td>0.839–2.329</td>
</tr>
<tr>
<td>Satisfaction at baseline</td>
<td>1.6801</td>
<td>1.0296</td>
<td>2.6625</td>
<td>0.1027</td>
<td>5.366</td>
<td>0.713–40.373</td>
</tr>
</tbody>
</table>

**Correlation between patient reported outcomes and disease activity measures**

Table 6 shows that severity of disease activity correlated significantly with greater disability as measured by the HAQ disability index, and with lower health status as measured by the EQ-5D VAS, PGAD and GHVAS. These correlations were comparable for the DAS and DAS28 indices of disease activity.
Table 6. Correlation between patient-reported health status measures and measures of disease activity at week 52 (LOCF analysis)

<table>
<thead>
<tr>
<th>Measure</th>
<th>DAS score</th>
<th>DAS28 score</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAQ score</td>
<td>0.65</td>
<td>0.64</td>
</tr>
<tr>
<td>EQ-5D VAS score</td>
<td>-0.63</td>
<td>-0.64</td>
</tr>
<tr>
<td>Patient global assessment</td>
<td>0.66</td>
<td>0.67</td>
</tr>
<tr>
<td>Patient general health VAS</td>
<td>0.71</td>
<td>0.73</td>
</tr>
</tbody>
</table>

All correlation coefficients were statistically significant at \( P < 0.0001 \)

DISCUSSION

Combination therapy in TEMPO resulted in significantly greater improvements than did monotherapy on all measures of PRO: functional status, QoL and treatment satisfaction. The mean improvement in functional status among combination therapy recipients of 1.0 was significantly larger than in either methotrexate or etanercept groups. Kosinski et al suggest that a decrease in HAQ disability index of 0.13 to 0.24 may be considered clinically significant.[18] This is consistent with the 0.22 unit change that Wells et al determined is perceived by RA patients as meaningful improvement.[19] The difference in HAQ disability index score at 52 weeks between combination therapy and monotherapy is therefore clinically as well as statistically significant. More importantly, by week 52, 58% in the combination group achieved improvement in functional status score of 0.8 or more, and 44% of subjects in the group had HAQ disability scores of less than or equal to 0.5. Further, at week 52 patients in the combination group were significantly more likely to attain EQ-5D VAS scores comparable to population norms.

Patient satisfaction with medication is expected to predict drug preferences and adherence to prescription regimens,[23] both of which are components of real-world treatment effectiveness. Patients in TEMPO who received combination therapy or etanercept were significantly more likely than MTX recipients to report satisfaction with medication.

Response to combination therapy separated from MTX and etanercept early in treatment and the difference was sustained for 52 weeks. Kaplan-Meier survival plots for time to occurrence of HAQ scores less than 0.5 and sustained for six months confirmed the faster onset of action in the combination group compared to etanercept or MTX alone. Similar trends in improvement over time were found for the EQ-5D VAS, PGAD and GHVAS.

Additionally, these results support previous findings that PRO assessments are valid indicators of RA disease status. Table 6 shows that increasing disease activity (measured by DAS score) is significantly correlated with greater disability as measured by the HAQ disability index, and with lower health status as measured by the EQ-5D VAS, PGAD and GHVAS. The HAQ disability index has previously been demonstrated to correlate significantly with DAS scores.[24]

The degree of improvement in QoL with etanercept monotherapy in the TEMPO trial is consistent with previous findings. In a 26-week, double-blind study comparing etanercept 10 mg or 25 mg against placebo, both etanercept doses produced significantly greater QoL improvement as revealed by the HAQ index and all HAQ subscales except grip.[25,26] By 26 weeks, HAQ index score decreased (improved) only 2% in the placebo group, but decreased 39% in the etanercept 25 mg twice-weekly group.[25] A similar benefit was experienced by the etanercept group in TEMPO, with a 38% decrease from baseline HAQ index score at 24 weeks. On a visual analogue scale similar to the EQ-5D VAS, patients in the 26-week study receiving either etanercept dose reported greater QoL improvement from baseline than did placebo recipients: approximately 20 points vs 8 points, respectively.[26] These results are comparable to EQ-5D VAS improvements in TEMPO, in which mean score in the etanercept group increased 25 points at 24 weeks and 26 points at 52 weeks.

The finding in TEMPO of no significant difference in HAQ disability index at 52 weeks between etanercept and MTX agrees with results of a previous study in patients with early RA (diagnosed no more than three years before study entry).[27] In that study, etanercept yielded a significantly greater improvement in the HAQ eating subscale, while MTX recipients had significantly greater improvement in the dressing subscale; no significant differences were found for other subscales.
TEMPO included only patients judged to be appropriate candidates for MTX treatment at study enrolment, so these results may not be generalisable to different patient populations. A potential study limitation is that imputing missing PRO data by the LOCF method may introduce bias if scores change over time.[14] However, analysis of the on-protocol population yields results consistent with those for the LOCF population (data not presented).

Conclusions
Combination therapy with etanercept plus MTX yielded significantly greater improvements on four PRO assessments than did therapy with either agent alone. These results support findings of a previous study in which combination therapy resulted in significantly better improvement on HAQ disability index and PGAD than did monotherapy with MTX.[4]
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Competing interest statement
D. van der Heijde has received reimbursement for symposium attendance and speaking and consulting fees from Wyeth, and has acted as an expert witness for Wyeth at an EMEA meeting for radiographic results of the TEMPO study. L. Klareškog has received reimbursement for symposium attendance, speaking and consulting fees, and research funds from Wyeth. J. Tornero has received reimbursement for symposium attendance, speaking fees and research funds from Wyeth. J. Melo-Gomes and C. Codreanu declare no potential competing interests. A. Singh, R. Pedersen, B. Freundlich and S. Fatenejad are employees of Wyeth and hold stock and/or stock options in Wyeth. B. Freundlich has also received funds for research and staff members from Wyeth.
Figure 1. Mean improvement from baseline of patients to 52-week follow-up of patients with rheumatoid arthritis receiving methotrexate, etanercept or combination therapy with methotrexate and etanercept, as measured by Health Assessment Questionnaire (HAQ) score (LOCF analysis).
*:* significant difference between etanercept and methotrexate at $P<0.01$ and $P<0.05$, respectively
†:† significant difference between combination and methotrexate at $P<0.01$
‡:‡ significant difference between combination and etanercept at $P<0.01$ and $P<0.05$, respectively

Figure 2. Mean improvement from baseline to 52-week follow-up of patients with rheumatoid arthritis receiving methotrexate, etanercept or combination therapy with methotrexate and etanercept, as measured by area under the curve for the eight subscales of the Health Assessment Questionnaire (HAQ) score (LOCF analysis).
†,† significant difference between combination and methotrexate at $P<0.01$ and $P<0.05$, respectively
‡,‡ significant difference between combination and etanercept at $P<0.01$ and $P<0.05$, respectively

Figure 3. Kaplan-Meier estimation of time to HAQ disability scores $\leq 0.5$ and sustained for six months
REFERENCES


Area Under Curve for HAQ and HAQ subscales at week 52

- HAQ
- Activities
- Arising
- Dressing
- Eating
- Grip
- Hygiene
- Reaching
- Walking

Methotrexate
Etanercept
Combination

†
‡
Combination vs. MTX = 0.005
Combination vs. Etanercept = 0.002
Etanercept vs. MTX = 0.780
Patient-reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: the TEMPO trial

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