

Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial



Paul Emery, Ferdinand C Breedveld, Stephen Hall, Patrick Durez, David J Chang, Deborah Robertson, Amitabh Singh, Ronald D Pedersen, Andrew S Koenig, Bruce Freundlich

Summary

Background Remission and radiographic non-progression are goals in the treatment of early rheumatoid arthritis. The aim of the combination of methotrexate and etanercept in active early rheumatoid arthritis (COMET) trial is to compare remission and radiographic non-progression in patients treated with methotrexate monotherapy or with methotrexate plus etanercept.

Methods 542 outpatients who were methotrexate-naïve and had had early moderate-to-severe rheumatoid arthritis for 3–24 months were randomly assigned to receive either methotrexate alone titrated up from 7.5 mg a week to a maximum of 20 mg a week by week 8 or methotrexate (same titration) plus etanercept 50 mg a week. Coprimary endpoints at 52 weeks were remission measured with the disease activity score in 28 joints (DAS28) and radiographic non-progression measured with modified total Sharp score. Treatment was allocated with a computerised randomisation and enrolment system, which masked both participants and carers. Analysis was done by modified intention to treat with last observation carried forward for missing data. This study is registered with ClinicalTrials.gov, number NCT00195494).

Findings 274 participants were randomly assigned to receive combined treatment and 268 methotrexate alone. 132 of 265 (50%, 95% CI 44–56%) patients who took combined treatment and were available for assessment achieved clinical remission compared with 73 of 263 (28%, 23–33%) taking methotrexate alone (effect difference 22.05%, 95%CI 13.96–30.15%, $p < 0.0001$). 487 evaluable patients had severe disease (DAS28 > 5.1). 196 of 246 (80%, 75–85%) and 135 of 230 (59%, 53–65%), respectively, achieved radiographic non-progression (20.98%, 12.97–29.09%, $p < 0.0001$). Serious adverse events were similar between groups.

Interpretation Both clinical remission and radiographic non-progression are achievable goals in patients with early severe rheumatoid arthritis within 1 year of combined treatment with etanercept plus methotrexate.

Funding Wyeth Research.

Introduction

Major consequences in rheumatoid arthritis are related to the disease itself and its associated comorbidities. Although outcomes have improved over the past few decades with the advent of new treatments and therapeutic approaches, patients still have substantial functional disability and loss of ability to work.^{1,2} Intensive but safe treatments have the potential to improve long-term outcomes.

Remission is the best outcome for early therapy. There are several definitions of remission based on clinical criteria, but disease activity score in 28 joints (DAS28) is the most commonly used validated method for the measurement of remission,^{3–5} which has been recognised in the European League Against Rheumatism working group recommendations for the management of early rheumatoid arthritis as a goal of therapy.⁶ Remission is best achieved by reducing or eliminating inflammation, thereby stopping radiographic progression at an early

stage when the disease is most destructive and before joint damage occurs.⁷ Thus, remission has become the aim of management of early rheumatoid arthritis, and this aim needs to be included in trial design.⁸

Disease-modifying antirheumatic drugs (DMARDs), alone or in combination, have been the mainstay of treatment for rheumatoid arthritis.^{9–11} Before the recent era of biological therapy, clinical remission was not commonly reported.¹² New treatment strategies advocate the use of earlier, more intensive therapy than previously applied to prevent joint damage and functional disability.¹³ In this context, remission has emerged as a realistic goal, especially in patients with early rheumatoid arthritis.^{6,14} Support for remission in disease activity and radiographic outcomes as a primary endpoint in clinical trials has grown as treatment options have improved and combined-treatment regimens have emerged.^{15–20} Recent data indicate that conventional disease modifying anti-rheumatic drugs might not halt radiographic progression,

Published Online
July 16, 2008
DOI:10.1016/S0140-6736(08)61000-4

See Online/Comment
DOI:10.1016/S0140-6736(08)61001-6

Leeds Institute of Molecular Medicine, University of Leeds, Leeds, UK (Prof P Emery MD); Leiden University Medical Centre, Leiden, Netherlands (Prof F C Breedveld MD); Cabrini Health Hospital, Malvern, VIC, Australia (S Hall MD); Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium (P Durez MD); Global Clinical Development, GlaxoSmithKline, King of Prussia, PA, USA (D J Chang MD); and Wyeth Research, Collegeville, PA, USA (D Robertson MS, A Singh PhD, R D Pedersen MS, A S Koenig DO, B Freundlich MD)

Correspondence to:
Prof Paul Emery, Leeds Institute of Molecular Medicine, University of Leeds, Leeds Teaching Hospitals Trust, Chapel Allerton Hospital, Chappeltown Road, Leeds LS7 4SA, United Kingdom, UK p.emery@leeds.ac.uk

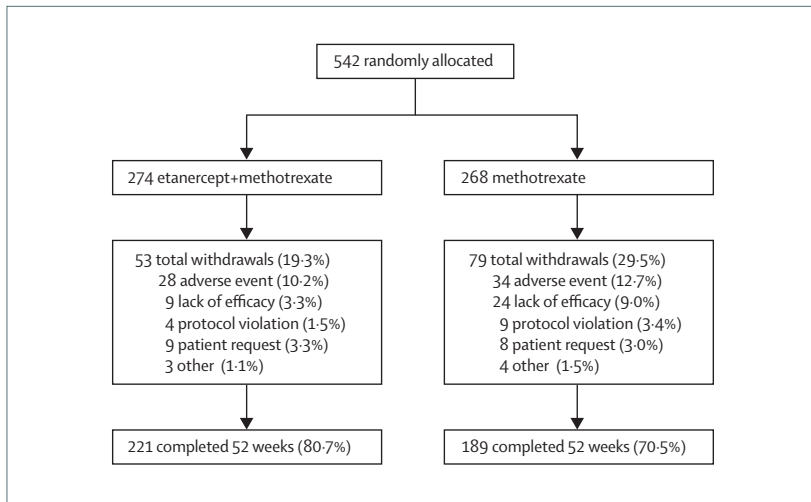


Figure 1: Trial profile

More patients in the combined-treatment group than in the methotrexate monotherapy group completed period 1, largely because of a larger number of withdrawals due to lack of efficacy in the monotherapy group.

even when they produce clinical remission, which could be attributed to incomplete suppression of synovitis.^{16,18,21} Combination therapy with methotrexate and an anti-tumour-necrosis-factor (TNF) agent seems to be best in this respect, nearly halting structural progression and producing clinically relevant responses.^{15,22}

The combination of methotrexate and etanercept in early rheumatoid arthritis (COMET) trial investigates clinical remission, radiographic non-progression, and restoration of function in a continuing 2-year study comparing the effects of combined etanercept (a fully human TNF soluble receptor) and methotrexate with those of methotrexate alone in patients with moderate-to-severe, active, early rheumatoid arthritis. The aim of this study was to investigate aggressive therapy for early disease with combined treatment as the regimen of choice to achieve clinical and radiographic treatment targets and normalisation of function. The results in this report are for the first year (period 1).

Methods

Patients

Participants were enrolled at 70 sites in Europe, Latin America, Asia, and Australia from October, 2004, to February, 2006. Patients were age 18 years or older with diagnosis of adult-onset rheumatoid arthritis, disease duration of at least 3 months but not more than 2 years, DAS28 of 3.2 or more, and either Westergren ESR of 28 mm/h or more or C-reactive protein of 20 mg/L or more. Patients were ineligible if they had received previous treatment with methotrexate, etanercept, or another TNF antagonist at any time or had received treatment with other DMARDs or corticosteroid injections in the 4 weeks before baseline visits. Individuals with important concurrent medical diseases were

ineligible, as were those with other relevant comorbidities. Participants were randomly assigned with a computerised randomisation and enrolment (CORE) system to generate and implement allocation sequence, manage assignment to treatment groups, and maintain blinding. Data were unblinded only if needed for medical management of patients. Masking was removed for one sponsor biostatistical programmer to do the 52-week primary analysis for this report. The study remains blinded throughout period 2, up to week 104.

This study was done in accordance with the ethical principles of the Declaration of Helsinki. The protocol and its amendments received independent ethics committee or institutional review-board approval and regulatory review and approval before site initiation and recruitment of patients. All elements of informed consent were explained to eligible patients and adequate time was allowed for questions and for patients to make voluntary decisions. No patient underwent procedures specific to the protocol until he or she had signed and dated an approved informed consent form.

Procedures

COMET is a 24-month, double-blind, randomised, parallel-group, multicentre, outpatient study with two periods. In period 1, patients were randomly assigned to one of two initial treatment groups, one receiving combination etanercept plus methotrexate and another receiving methotrexate alone. Participants received either etanercept 50 mg by subcutaneous injection or etanercept-matching placebo injections once a week for 52 weeks. Etanercept was given as two separate injections of 25 mg on the same day, once a week. All participants received oral methotrexate, starting at 7.5 mg once a week. In patients with tender or swollen joints, the dose was titrated up over 8 weeks to a maximum of 20 mg a week (figure 1).

Stable doses of oral corticosteroids (≤ 10 mg per day of prednisone or an equivalent agent) or a single non-steroidal anti-inflammatory drug were permitted if started at least 4 weeks before baseline and kept constant throughout the first 24 weeks of the study. After completion of 24 weeks of treatment, reductions in dose of prednisone or other oral corticosteroid by 1 mg per day or less were allowed every week. Oral corticosteroids were tapered to 3 mg per day or less before the dose of non-steroidal anti-inflammatory drug was decreased. All patients received folic acid supplementation of 5 mg twice weekly (not given on the same day as methotrexate) to reduce side-effects associated with methotrexate.

Coprimary endpoints were the proportion of patients achieving remission (DAS28 < 2.6) at week 52 and the change in van der Heijde modified total Sharp score^{23,24} (mTSS; joint erosion score plus joint space narrowing score) from baseline to week 52.

Radiographs of hands, wrists, and feet were taken at baseline and week 52 (mTSS range 0–448).²⁵ Two separate

physicians who were masked to the treatment regimens and sequence of films read the digitised radiographic images (BioImaging Technologies Inc, Newtown, Pennsylvania, USA) for all participants in a randomised sequence (inter-rater correlation was 0·935–0·961).

Functional status was assessed as a secondary endpoint with the health assessment questionnaire disability index, one of the most widely used measures of functional status in rheumatology.²⁶ The mean normal population-based score for this index is 0·49.^{27,28} An employment questionnaire was administered at weeks 12, 24, 36, and 52, asking participants whether they had stopped working since the last visit. Those who reported that they stopped working more than once in the first year of study were counted only once in this analysis (ie, at the first time they stopped working).

Statistical analysis

Power determinations for period 1 assumed two-sided testing at the 0·025 significance level. On the basis of proportions achieving DAS remission in the TEMPO trial,²² 37% with combined therapy and 23% with methotrexate alone, the sample size allowed for 90% power to show a significant difference in remission. On the assumption of a difference in mTSS between groups of 1·5 to 2 and a standard deviation of 4·5, there was 94% power to detect a significant difference in radiographic progression.

For the two coprimary endpoints, Hochberg's step-up procedure was used to adjust for multiple comparisons. The change in mTSS was compared between treatment groups with ANCOVA on the rank of the change scores, averaged over readers, with the rank of baseline scores as the covariate. The proportions of participants achieving remission as measured with DAS28 were compared with Fisher's exact test. Hochberg's step-up procedure controls the type-1 error for the two primary endpoint comparisons. According to this procedure, if both coprimary endpoints are significant at the α 0·05 level, both are declared statistically significant. However, if one primary endpoint is not significant at the 0·05 level, the other must be significant at the α 0·025 level to be statistically significant.

The modified intention-to-treat efficacy population, was defined as all patients who received at least one dose and reported both baseline and at least one on-treatment DAS28 result; for radiographic analyses, only patients with valid baseline and follow-up radiographs were included. Missing values were assumed to be missing at random and imputed with the last observation carried forward (LOCF) for clinical endpoints. For radiographic analyses, annualised progression rates were used for radiographs obtained before the 52-week visit. For patients who did not complete 52 weeks, this value was imputed by linear extrapolation from the time of final on-treatment assessment, unless the final radiograph was obtained

	Methotrexate (n=263)	Etanercept plus methotrexate (n=265)	Total (N=528)
Demographic characteristics			
Age (years)*	52·3 (0·8)	50·5 (0·9)	51·4 (0·6)
Female	191 (73%)	196 (74%)	387 (73%)
White	232 (88%)	231 (87%)	463 (88%)
Previous DMARDs †	65 (24%)	48 (18%)	113 (21%)
Previous corticosteroids †	131 (50%)	135 (49%)	266 (49%)
Previous NSAIDs †	205 (76%)	197 (72%)	402 (74%)
Disease characteristics			
Disease duration (months)*	9·3 (0·4)	8·8 (0·4)	9·0 (0·3)
DAS28	6·5 (1·0)	6·5 (1·0)	6·5 (1·0)
Swollen joint count (0–68 possible joints)	17·6 (10·0)	17·1 (10·5)	17·3 (10·2)
Tender joint count (0–71 possible joints)	24·8 (14·5)	25·1 (14·6)	25·0 (14·5)
Health assessment questionnaire (0–3 range)	1·6 (0·7)	1·7 (0·7)	1·7 (0·7)
ESR (mm/h)	49·3 (24·1)	47·8 (23·9)	48·5 (24·0)
Anti-CCP positive	179 (70%)	174 (67%)	353 (69%)
C-reactive protein (mg/L)	36·5 (33·5)	37·0 (38·5)	36·7 (36·1)
Data are mean (SD) or number (%) unless otherwise indicated. No significant differences between groups for any characteristic. SE=standard error of the mean, DMARDs=disease-modifying antirheumatic drugs. NSAIDs=non-steroidal anti-inflammatory drugs. DAS(28)=disease activity scale (based on 28 joints). VAS=visual analogue scale. Anti-CCP=antibodies against cyclic citrullinated peptide. *Mean (SE). †Based on randomised patients: combined treatment n=274, methotrexate alone n=268; total N=542.			
Table 1: Demographics and baseline disease characteristics, modified intention-to-treat population by treatment group			

during the first 3 months of study. All values were adjusted by linear extrapolation before analysis to represent the change at 52 weeks: $365 \times (\text{observed change} \div \text{days between readings})$.

Clinical secondary endpoints include the proportion of participants who achieved DAS44 remission (DAS44 <1·6) and American Academy of Rheumatology (ACR) 20%, 50%, and 70% responses. The secondary endpoints health assessment questionnaire disability index and stopping work were analysed as change from baseline by use of ANCOVA, with baseline value as the covariate. Additional outcomes reported by patients and economic data obtained in the trial will be presented separately. For participants who were working full-time or part-time at baseline, cumulative numbers and proportions of those who stopped working were assessed. The proportions of patients in each group who reported they had stopped working by week 52 were compared by Fisher's exact test with LOCF.

Role of the funding source

Wyeth Research sponsored this clinical trial and was responsible for the collection and analysis of data. The authors and the sponsor were involved with study design, interpretation of data, manuscript preparation, and decision to publish. All statistical analyses were done by the biostatistical group at Wyeth. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the report for publication.

Results

542 patients from 22 countries participated in this trial; 472 (87%) were from Europe and Australia, and the remainder were from Latin America and Asia. 528 patients (263 on methotrexate alone and 265 on combined treatment) were available for clinical efficacy analysis; all 542 were included in the safety analysis. 230 in the methotrexate group and 246 in the combined-treatment group had data that were valid for radiographic analysis. At baseline, 487 (92%) of 528 patients had DAS28 >5.1, indicating severe disease. Demographics and baseline disease characteristics are presented in table 1.

At 52 weeks, the proportion of participants who achieved DAS28 remission (DAS28 <2.6) was significantly greater in the combined-treatment group than in the monotherapy group (132 [50%] of 265, 95% CI

44–56% vs 73 [28%] of 263, 23–33%; effect difference 22.05%, 95% CI 13.96–30.15%, $p < 0.0001$). The observed analysis corroborates the LOCF analysis (119 [56%] of 212 vs 64 [36%] of 176; 19.77%, 10.02–29.52%, $p < 0.0001$). At all time points and as early as week 2, the proportion of patients who achieved DAS28 remission was significantly greater in the combined-treatment group than in the monotherapy group (figure 2).

Radiographic non-progression was defined as mTSS of 0.5 or less.²⁵ 135 of 230 (59%, 53–65%) participants in the methotrexate group and 196 of 246 (80%, 75–85%) in the combined-treatment group showed no progression of joint damage at 52 weeks (effect difference 20.98%, 12.97–29.09%, $p < 0.0001$). A definition of non-progression as mTSS ≤ 0 produced similar results (figure 3).

Normal health assessment questionnaire disability index was defined as 0.5 or less.²⁸ 140 (55%) of 256 patients achieved an index of 0.5 or less in the combined-treatment group compared with 93 (39%) of 241 in the methotrexate group (effect difference 16.10%, 7.44–24.76%, $p = 0.0004$) at week 52. Improvement in health assessment questionnaire disability index from baseline to week 52 was greater in the combined-treatment group (61%; from 1.7 to 0.7) than in the methotrexate group (44%; from 1.6 to 0.9; $p < 0.0001$).

The cumulative proportion of patients who were working full-time or part-time at baseline but stopped working since the previous study visit at all four assessment time points was lower in the combined-treatment than in the monotherapy group. By week 52, 24 of 100 patients in the methotrexate group who were working full-time or part-time at baseline reported that they had stopped working at least once, compared with nine (9%) of 105 of those in the combined-treatment group ($p = 0.004$).

The proportion achieving DAS44 remission (DAS44 <1.6) was significantly greater in the combined-treatment group than in the monotherapy group from week 4 (effect difference 9.07%, 95% CI 4.84–13.31%, $p < 0.0001$) and at all timepoints thereafter, with 136 of 265 (51%, 45–57%) and 73 of 263 (28%, 23–33%), respectively, achieving DAS44 remission at week 52 (23.56%, 15.47–31.66%, $p < 0.0001$). The proportions of patients achieving low disease activity defined as DAS28 of 3.2 or less were much the same (170 [64%] of 265, 58–70%, in the combined-treatment group vs 109 [41%] of 263, 35–47% in the monotherapy group; 22.71%, 14.41–31.00%, $p < 0.0001$) and DAS44 <2.4 (194 [73%] of 265, 67–79% vs 128 [49%] of 263, 43–55%; 24.54%, 16.48–32.60%, $p < 0.0001$). The proportions of patients achieving ACR responses were also greater in the combined-treatment group with 220 (86%, 82–90%), 181 (71%, 66–76%), and 124 (48%, 41–55%) of 256 in this group reaching ACR20, ACR50, and ACR70, respectively, compared with 163 (67%, 61–73%), 119 (49%, 43–55%), and 69 (28%, 22–34%) of 243 in the methotrexate group ($p < 0.0001$). Patients in the

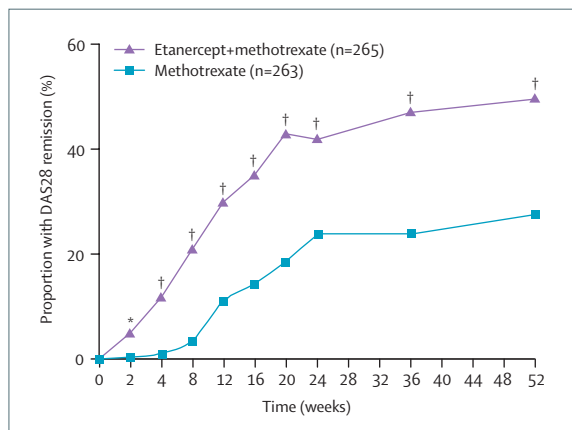


Figure 2: DAS28 remission over 52 weeks of treatment
A significant difference in the proportion of patients in DAS28 remission was seen in week 2 and persisted for the study period. * $p < 0.002$. † $p < 0.0001$.

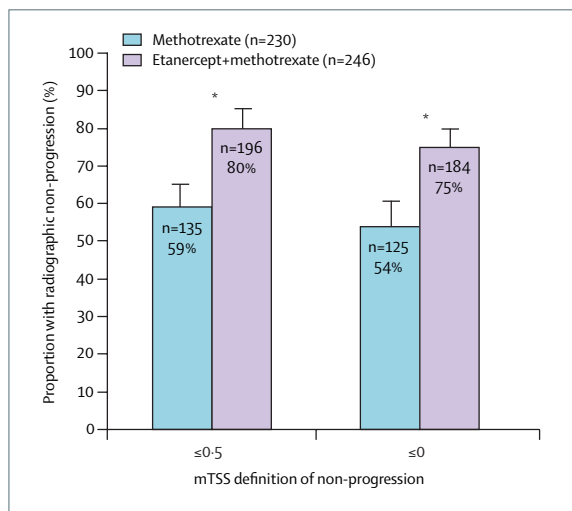


Figure 3: Proportions of patients (95% CI) achieving radiographic non-progression at week 52
* $p < 0.0001$.

methotrexate group had a higher median weekly dose of methotrexate than those in the combined-treatment group (19.6 mg per week, 95% CI 7.5–25.5 vs 16.8 mg per week, 6.1–20.0) after dose titration at 8 weeks.

There was a significant reduction in the mean DAS28 swollen-joint count in both groups, with 85% improvement from baseline to week 52 in the combined-treatment group (from 12.4 to 1.8) and 65% improvement in the methotrexate group (from 12.3 to 4.3). The differences between groups were significant from week 2 (effect difference 5.36%, 1.29–9.43%, $p=0.0108$). The proportions of patients in the combined-treatment and monotherapy groups with no swollen joints at 52 weeks were 156 (59%) of 265 and 99 (38%) of 263, respectively (21.33%, 12.90–29.56%, $p<0.0001$).

Joint-space narrowing and joint erosion were assessed, and mTSS was calculated from these for both groups.²⁹ The mTSS change from baseline was 2.44 (95% CI 1.45–3.43) for the methotrexate group and 0.27 (–0.13 to 0.68) for the combined-treatment group at week 52. Change in mTSS seemed to be driven by joint erosion rather than by joint-space narrowing.

Post-hoc analysis showed that 78 (35.3) of 221 patients achieved clinical remission, radiographic non-progression, and normal function after period 1 compared with 39 (20.6%) of 189 patients in the methotrexate group. By contrast, only 18 patients (8.1%) in the combined-treatment group achieved none of these criteria compared with 53 (28.0%) in the methotrexate group.

246 (91.8%) patients in the methotrexate group and 247 (90.2%) in the combined-treatment group reported adverse events: the most common were nausea (50 [19%] in the methotrexate group and 53 [19%] in the combined-treatment group) and nasopharyngitis (44 [16%] and 45 [16%]). Serious adverse events were recorded for 34 (12.7%) patients and 33 (12.0%). Serious adverse events occurring in more than one patient overall were worsening of rheumatoid arthritis (five patients in the methotrexate group and two in the combined-treatment group); breast cancer (three in the methotrexate group); chest pain (one in each group); pneumonia (one in each group); cholelithiasis (two in the combined-treatment group); intervertebral disc protrusion (two in the combined-treatment group); osteoarthritis (two in the methotrexate group); interstitial lung disease (two in the combined-treatment group); and hip arthroplasty (two in the methotrexate group).

One patient died during the study because of acute respiratory failure (group remains blinded). Eight patients in the methotrexate group and five in the combined-treatment group had serious infections. One patient in the methotrexate group had opportunistic herpes zoster infection. No patients had tuberculosis or demyelinating diseases. Eight malignant diseases were reported: three cases of breast cancer and one case of prostate cancer in the methotrexate group; and one each of chronic lymphocytic leukaemia, epidermoid

	Methotrexate (n=268)	Etanercept plus methotrexate (n=274)	Total (N=542)
Any adverse event	246 (92%)	247 (90%)	493 (91%)
Serious adverse events*	34 (13%)	33 (12%)	67 (12%)†
Cardiac	2 (1%)	2 (1%)	4 (1%)
Ear and labyrinth	0	1	1
Eye	1	0	1
Gastrointestinal	4 (1%)	1	5 (1%)
General and administration site	1	2 (1%)	3 (1%)
Hepatobiliary	0	3 (1%)	3 (1%)
Infection	8 (3%)	5 (2%)	13 (2%)
Injury, poisoning, and procedural complications	4 (1%)	3 (1%)	7 (1%)
Laboratory values	1	1	2
Metabolic and nutritional	0	2 (1%)	2
Musculoskeletal and connective tissue	9 (3%)	4 (1%)	13 (2%)
Nervous system	1	4 (1%)	5 (1%)
Psychiatric	1	1	2
Renal and urinary	1	1	2
Respiratory, thoracic, and mediastinal	1	3 (1%)	4 (1%)
Skin and subcutaneous tissue	0	1	1
Surgical and medical procedures	2 (1%)	1	3 (1%)
Vascular	2 (1%)	1	3 (1%)
Malignant disease	4 (1%)	4 (1%)	8 (1%)

Data are number (%). *Body system totals are not necessarily the sum of the individual adverse events because a patient can report two or more different adverse events in the same system organ class. †One patient died during the first 52 weeks of this study, cause of death being reported as acute respiratory failure. The patient's drug allocation remains masked until the end of period 2.

Table 2: Safety summary by treatment group

cancer of the tongue, basal-cell carcinoma, and Bowen's disease in the combined-treatment group. No malignant diseases were thought by the investigator or the medical monitor to be related to treatment with study drugs (table 2).

Discussion

Half the patients on combination therapy with etanercept and methotrexate successfully achieved clinical remission (as judged with DAS28), significantly more than those receiving conventional methotrexate monotherapy. The primary outcome had a higher threshold of clinical response than in previous large randomised, double blind, controlled clinical trials for rheumatoid arthritis.^{9,11,16,30} Almost two-thirds of patients in the combination group achieved low disease activity (DAS28 ≤ 3.2), which is also a stringent criterion for efficacy in a study population that began the trial with severe disease. Furthermore, results indicate near halting of radiographic progression in 80% of this group compared with 59% of the group that received methotrexate alone.

In early disease, disability is probably a function of joint swelling and pain.²⁵ The COMET study showed that 50% of patients achieved DAS28 remission with few swollen or tender joints. In fact, 59% of patients on

	Design	Therapy	Population	Key endpoints	Results
COBRA ⁹	Double blind 28 week; step-down through 56 week; observed through 80 week	Combination prednisone+methotrexate+ sulfasalazine) vs sulfasalazine; followed by step-down of prednisone, then step-down of methotrexate	Early rheumatoid arthritis (<2 years); n=155	Clinical pooled index; joint damage index; ACR20, ACR50	Rapid lowering of clinical pooled index with combined therapy at 28 weeks; difference reduced after prednisone withdrawal and disappeared after methotrexate withdrawal; lower rate of radiographic progression with combination therapy at 28 weeks and 56 weeks, and lasting at 80 weeks
Dougados et al ¹¹	Double blind 52 week	Sulfasalazine, methotrexate, or sulfasalazine+ methotrexate	Early rheumatoid arthritis (≤1 year); n=205	DAS change from baseline	Early treatment seemed beneficial; however, no clinically relevant superiority of combined treatment
TEMPO ³⁰	Double blind 3 year	Etanercept vs methotrexate vs etanercept+ methotrexate	Early (≤3 years) vs late rheumatoid arthritis; n=682	ACR-N at 24 weeks; mTSS change from baseline at 52 weeks; DAS, DAS28, and mTSS at 3 years	Combined treatment better than either monotherapy; radiographic outcomes better with combined treatment
PREMIER ¹⁶	Double blind 2 year	Adalimumab vs methotrexate vs adalimumab+ methotrexate	Early rheumatoid arthritis (<3 years); n=799	ACR50 at 1 year, mTSS change from baseline at 1 year	Combined treatment better than monotherapy in ACR50 and radiographic outcomes at 1 year
BeST ³³	2 year	Sequential disease-modifying antirheumatic drug monotherapy (group 1), step-up combination therapy (group 2), initial combination therapy with tapered high-dose prednisone (group 3), and initial combination therapy with TNF antagonist infliximab (group 4).	Early rheumatoid arthritis (≤2 years); n=508	Proportion of patients with DAS ≤2.4; HAQ; mTSS	Initial combination therapy including either prednisone or infliximab resulted in earlier functional improvement and less radiographic damage after 1 year than did sequential monotherapy or step-up combination therapy
FIN-RACO ³⁰	2 year	Sulphasalazine, methotrexate, and sulphasalazine+ methotrexate; sulphasalazine monotherapy changed to methotrexate monotherapy during the trial	Early rheumatoid arthritis (<2 years); n=199	ACR50 at 1 year and 2 years, Larsen score	Combined treatment better outcomes at 1 year and 2 years
TICORA ³⁵	18 month	Sequential DMARDs—routine care vs tight control	Rheumatoid arthritis (<5 years); n=111	DAS <2.4, DAS improved >1.2 from baseline, Ritchie articular index	Tight control better than routine treatment strategy
ASPIRE ³⁴	54 week	Placebo+methotrexate, infliximab 3 mg/kg+ methotrexate, or infliximab 6 mg/kg+methotrexate	Early rheumatoid arthritis (≤3 years); n=1049	ACR-N at 54 weeks, mTSS	Combination therapy provides greater benefit

ACR20 or 50=American College of Rheumatology criteria, greater than 20% or 50% improvement. DAS=disease activity score. mTSS=modified total Sharp score. HAQ=health assessment questionnaire.

Table 3: Randomised clinical trials of early rheumatoid arthritis

combination therapy had no swollen joints at week 52. In later disease, function is posited to be affected more by joint destruction than in earlier disease.³¹ 80% of patients in the combination group had no progression, defined as mTSS change of 0.5 or less, of joint destruction over 52 weeks, and 75% had no change according to an even more stringent criterion (mTSS ≤0.0). By contrast, 41% and 46% (mTSS <0.5 and <0.0, respectively) of patients in the methotrexate monotherapy group had radiographic progression. The participants in COMET had moderate-to-severe functional disability on the basis of baseline health assessment questionnaire disability index. At 52 weeks, over half of patients on combination therapy had functional disability comparable to that in the healthy population. Therefore, besides achieving an immediate improvement in disability, longer term disability might be preventable by inhibiting radiographic progression.

These data build on the results in patients with more longstanding disease than those included in this study, further supporting the value of early intervention.¹⁸

Other randomised, controlled, double-blind clinical trials in patients with early rheumatoid arthritis have shown a similar positive effect of combined methotrexate

and anti-TNF therapy (all three available anti-TNF agents) compared with monotherapy but used less stringent endpoints than this study.^{16,18,20,32–34} These positive effects were seen in both clinical (including remission) and radiographic endpoints. Table 3 summarises some of the large randomised clinical trials relevant to the treatment of early rheumatoid arthritis, use of combination therapy, and key clinical and radiographic endpoints.

In the TEMPO study, which also compared etanercept plus methotrexate with methotrexate alone,¹⁸ patients had a mean disease duration of 6.8 years and 40% and 19%, respectively, were in remission. The patients in COMET had 50% and 28% rates of remission for combination and methotrexate therapies, respectively. This finding reinforces the idea that patients with earlier disease may have a distinct benefit from intensive treatment strategies.^{33,35}

Patients with rheumatoid arthritis are more likely than healthy people to have low paying jobs or be unemployed once the diagnosis has been established.^{36–39} When patients become classified as being unable to work because of disability related to rheumatoid arthritis, they are unlikely to return to work.³⁹ Treatments that can

inhibit this progressive disability are available, as are indices to measure their success. In a blinded, controlled manner, the COMET trial showed that patients who received combination therapy have a nearly three-fold reduction in work stoppage compared with those who took high-dose methotrexate alone. The ability to remain a productive member of the workforce has implications for patients, employers, and society as a whole. This effect of rheumatoid arthritis is especially significant for women aged 55–64 years, because they have a high incidence of stopping work early.³⁷ Despite the use of high dose methotrexate monotherapy (median 19.6 mg/week in weeks 8–52), nearly a quarter of patients who were in employment at baseline in the COMET trial had stopped working at least once by the end of 1 year compared with about a tenth in the combination group. Additionally, reduced risk of joint damage has the potential to reduce the need for future joint-replacement surgery.

There were no new safety signals noted during period 1 of COMET. The incidences of serious adverse events, serious infections, and malignant diseases were much the same in both groups. Early, intensive therapy seems to improve the long-term outcomes for patients with rheumatoid arthritis without sacrificing safety.

This study does have some limitations. Unlike patients treated in the real-world setting, COMET participants were not allowed to decrease the dose of their primary medication for reasons other than adverse events. Therefore, the combination regimen might have had a similar positive effect with lower doses of methotrexate. Conversely, in general practice, results may not be as robust if lower doses of methotrexate are used. Additionally, the route of administration of methotrexate was not allowed to be changed from oral to subcutaneous for higher doses, so the results might differ had subcutaneous administration been allowed.

Also, the analyses in this report are of treatment group means rather than individual patients' responses. Many patients on high-dose methotrexate had good responses, including lack of radiographic progression. The high rates of DAS28 remission and radiographic non-progression do not indicate that rheumatoid disease was completely eliminated; however, more patients remained in employment with combined treatment than with methotrexate alone.

The results of the COMET trial suggest that remission is an achievable goal in patients with early severe rheumatoid arthritis within the first year of therapy with etanercept plus methotrexate. This conclusion seems consistent for several measurable dimensions, including clinical disease, radiographic outcomes, and functional status. The positive clinical outcomes in the combination-treatment group also seem to determine the ability of patients to remain in employment. Furthermore, these outcomes appear to be achieved without exposing patients to significant additional risk.

Contributors

PE, FB, SH, and PD collected and interpreted data and wrote this report. DJC designed the trial, interpreted the data, wrote the report, and was a medical monitor during the trial. DR, AS, and BF designed the trial, interpreted the data, and wrote the report. RDP designed the trial, analysed the data and wrote the report. ASK interpreted the data, wrote the report, and served as medical monitor during the trial.

Conflict of interest statement

PE has served as a Wyeth consultant, has received Wyeth research grants, and was the primary investigator in this trial. FB has served as a Wyeth consultant and was an investigator in this trial. SH and PD were investigators in this trial. DJC was a Wyeth employee at the time of this trial. DR, RDP, AS, ASK, and BF are Wyeth employees.

Acknowledgments

We thank the COMET investigators, their staff, and their patients for participation in this clinical trial; Joanne R Foehl, Wyeth, who prepared this report and managed its submission; and Theresa Mscicz and Denise Seydor for their contributions to operational study management.

References

- 1 Symmons D, Tricker K, Harrison M, et al. Patients with stable long-standing rheumatoid arthritis continue to deteriorate despite intensified treatment with traditional disease modifying anti-rheumatic drugs—results of the British Rheumatoid Outcome Study Group randomised controlled clinical trial. *Rheumatology* 2006; **45**: 558–65.
- 2 Sokka T, Krishnan E, Häkkinen A, Hannonen P. Functional disability in rheumatoid arthritis patients compared with a community population in Finland. *Arthritis Rheum* 2003; **48**: 59–63.
- 3 Prevoo MLL, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LBA, van Riel PLCM. Modified disease activity scores that include twenty-eight-joint counts—development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995; **38**: 44–48.
- 4 Prevoo ML, van Gestel AM, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. *Br J Rheumatol* 1996; **35**: 1101–05.
- 5 van der Heijde DMPM, van 't Hof MA, van Riel PLCM, van Leeuwen MA, van Rijswijk MH, van de Putte LBA. A comparison of validity of single variables and composed indices for measuring disease activity in rheumatoid arthritis. *Ann Rheum Dis* 1992; **51**: 177–81.
- 6 Combe B, Landewé R, Lukas C, Bolosiu HD, Breedveld F. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCSIT). *Ann Rheum Dis* 2007; **66**: 34–45.
- 7 van der Heijde D. Radiographic progression in rheumatoid arthritis: does it reflect outcome? does it reflect treatment? *Ann Rheum Dis* 2001; **60** (suppl 3): iii47–50.
- 8 Emery P, Salmon M. Early rheumatoid arthritis: time to aim for remission? *Ann Rheum Dis* 1995; **54**: 944–47.
- 9 Boers M, Verhoeven AC, Markuse HM, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet* 1997; **350**: 309–18.
- 10 O'Dell JR, Haire CE, Erikson N, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. *N Engl J Med* 1996; **334**: 1287–91.
- 11 Dougados M, Combe B, Cantagrel A, et al. Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components. *Ann Rheum Dis* 1999; **58**: 220–25.
- 12 Wolfe F, Hawley DJ. Remission in rheumatoid arthritis. *J Rheumatol* 1985; **12**: 245–52.
- 13 Combe B. Early rheumatoid arthritis: strategies for prevention and management. *Best Pract Res Clin Rheumatol* 2007; **21**: 27–42.
- 14 Sokka T, Mäkinen H, Puolukka K, Möttönen T, Hannonen P. Remission as the treatment goal—the FIN-RACO trial. *Clin Exp Rheumatol* 2006; **24** (suppl 43): S74–76.

- 15 Klareskog L, van der Heijde D, de Jager JP, et al, for the TEMPO study investigators. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in subjects with rheumatoid arthritis. *Lancet* 2004; **363**: 675–81.
- 16 Breedveld FC, Weisman MH, Kavanaugh AF, et al, for the PREMIER Investigators. The PREMIER study: a multicenter, randomised, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 2006; **54**: 26–37.
- 17 van der Bijl AE, Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, et al. Infliximab and methotrexate as induction therapy in patients with early rheumatoid arthritis. *Arthritis Rheum* 2007; **56**: 2129–34.
- 18 van der Heijde D, Klareskog L, Landewé R, et al, for the TEMPO Study Investigators. Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum* 2007; **56**: 3928–39.
- 19 van der Heijde D, Burmester G, Melo-Gomes J, et al, for the Etanercept Study 400 Investigators. The safety and efficacy of adding etanercept to methotrexate or methotrexate to etanercept in moderately active rheumatoid arthritis patients previously treated with monotherapy. *Ann Rheum Dis* 2008; **67**: 182–88.
- 20 Möttönen T, Hannonen P, Leirisalo-Repo M, et al, for the Fin-RACo trial group. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. *Lancet* 1999; **353**: 1568–73.
- 21 Brown AK, Quinn MA, Karim Z, et al. Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression. *Arthritis Rheum* 2006; **54**: 3761–73.
- 22 van der Heijde D, Klareskog L, Rodriguez-Valverde V, et al, for the TEMPO Study Investigators. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis Rheum* 2006; **54**: 1063–74.
- 23 van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. *J Rheumatol* 2000; **27**: 261–63.
- 24 van der Heijde DM, van Riel PL, Nuver-Zwart IH, Gribnau FW, van de Putte LB. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. *Lancet* 1989; **1**: 1036–38.
- 25 van der Heijde D, Landewé R, Klareskog L, et al. Presentation and analysis of data on radiographic outcome in clinical trials—experience from the TEMPO study. *Arthritis Rheum* 2005; **52**: 49–60.
- 26 Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. *J Rheumatol* 2003; **30**: 167–78.
- 27 Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: dimensions of practical applications. *Health Qual Life Outcomes* 2003; **1**: 20.
- 28 Hubert HB, Bloch DA, Fries JF. Risk factors for physical disability in an aging cohort: the NHANES I epidemiologic followup study. *J Rheumatol* 1993; **20**: 480–88.
- 29 van der Heijde DMFM, van Leeuwen MA, van Riel PLCM, et al. Biannual radiographic assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis. *Arthritis Rheum* 1992; **35**: 26–34.
- 30 van der Heijde D, Klareskog L, Pedersen R, Wajdula J, Fatenejad S. Efficacy of etanercept in early versus long-term rheumatoid arthritis: posthoc analysis of 3-year TEMPO data. *Arthritis Rheum* 2007; **56** (suppl 9): S151 (abstract P265).
- 31 Kirwan JR. Conceptual issues in scoring radiographic progression in rheumatoid arthritis. *J Rheumatol* 1999; **26**: 720–25.
- 32 Genovese MC, Bathon JM, Fleischmann RM, et al. Longterm safety, efficacy, and radiographic outcome with etanercept treatment in patients with early rheumatoid arthritis. *J Rheumatol* 2005; **32**: 1232–42.
- 33 Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study)—a randomized, controlled trial. *Arthritis Rheum* 2005; **52**: 3381–90.
- 34 St Clair EW, van der Heijde DMFM, Smolen JS, et al, for the Active-Controlled Study of patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset Study Group. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum* 2004; **50**: 3432–43.
- 35 Grigor C, Capell H, Stirling A, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 2004; **364**: 263–69.
- 36 Puolakka K, Kautiainen H, Möttönen T, et al, for the FIN-RACo Trial Group. Impact of initial aggressive drug treatment with a combination of disease-modifying antirheumatic drugs on the development of work disability in early rheumatoid arthritis—a five-year randomized followup trial. *Arthritis Rheum* 2004; **50**: 55–62.
- 37 Allaire S, Wolfe F, Niu J, Lavalley M, Michaud K. Work disability and its economic effect on 55–64-year-old adults with rheumatoid arthritis. *Arthritis Rheum* 2005; **53**: 603–08.
- 38 Merkesdal S, Ruof J, Huelsemann L, et al. Indirect cost assessment in patients with rheumatoid arthritis (RA): comparison of data from the health economic patient questionnaire HEQ-RA and insurance claims data. *Arthritis Rheum* 2005; **53**: 234–40.
- 39 Verstappen SMM, Bijlsma JWJ, Verkleij H, et al, on behalf of the Utrecht Rheumatoid Arthritis Cohort Study Group. Overview of work disability in rheumatoid arthritis patients as observed in cross-sectional and longitudinal surveys. *Arthritis Rheum* 2004; **51**: 488–97.