Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial

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See Comment page 884

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Summary

Background Clinical remission and low disease activity are essential treatment targets in patients with rheumatoid arthritis. Although moderately active rheumatoid arthritis is common, treatment effects in moderate disease have not been well studied. Additionally, optimum use of biologics needs further investigation, including the use of induction, maintenance, and withdrawal treatment strategies. The aim of the PRESERVE trial was to assess whether low disease activity would be sustained with reduced doses or withdrawal of etanercept in patients with moderately active disease.

Methods In a randomised controlled trial, patients aged between 18 and 70 years with moderately active rheumatoid arthritis (disease activity score in 28 joints [DAS28] >3·2 and ≤5·1) despite treatment with methotrexate were enrolled at 80 centres in Europe, Latin America, Asia, and Australia between March 6, 2008, and Sept 9, 2009. To be eligible, patients had to have been receiving 15–25 mg of methotrexate every week for at least 8 weeks. In an open-label period of 36 weeks, all patients were given 50 mg etanercept plus methotrexate every week. To be eligible for a subsequent double-blind period of 52 weeks, participants had to have achieved sustained low disease activity. These patients were randomly assigned (1:1:1) by an interactive voice-response system to one of three treatment groups: 50 mg etanercept plus methotrexate, 25 mg etanercept plus methotrexate, or placebo plus methotrexate. Patients were stratified in blocks of three by DAS28 response (low disease activity or remission) at week 36. Patients, investigators, data analysts, and study staff were all masked to treatment allocation. The primary endpoint was the proportion of patients with low disease activity at week 88 in the groups given 50 mg etanercept or placebo in the double-blind period. A conditional primary endpoint was the proportion of patients receiving 25 mg etanercept who achieved low disease activity. Modified intention-to-treat populations were used for analyses. This trial is registered with ClinicalTrials.gov, number NCT00565409.

Findings 604 (72·4%) of 834 enrolled patients were eligible for the double-blind period, of whom 202 were assigned to 50 mg etanercept plus methotrexate, 202 to 25 mg etanercept plus methotrexate, and 200 to placebo plus methotrexate. At week 88, 166 (82·6%) of 201 patients who had received at least one dose of 50 mg etanercept and one or more DAS28 evaluations had low disease activity, compared with 84 (42·6%) of 197 who had received placebo (mean difference 40·8%, 95% CI 32·5–49·1%; p<0·0001). Additionally, 159 (79·1%) of 201 patients given 25 mg etanercept had low disease activity at week 88 (mean difference from placebo 35·9%, 27·0–44·8%; p<0·0001).

Interpretation Conventional or reduced doses of etanercept with methotrexate in patients with moderately active rheumatoid arthritis more effectively maintain low disease activity than does methotrexate alone after withdrawal of etanercept.

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Introduction

In individuals with rheumatoid arthritis, high disease activity is associated with joint destruction and functional disability.[1–4] The ultimate goals of treatment of rheumatoid arthritis are to slow or stop joint damage and maximally reduce disability, by attaining long-term clinical remission or at least low disease activity.[5] Whether these goals are achieved in patients with moderate disease activity—a large proportion of the overall population of individuals with rheumatoid arthritis[6,7]—has not yet been well studied. Importantly, patients with moderate disease activity are still prone to substantial progression of joint damage and therefore have serious disability.[4,8]

Although biologics such as inhibitors of tumour necrosis factor have been essential for increasing the likelihood of disease remission and low disease activity, these treatments are expensive compared with traditional disease-modifying antirheumatic drugs. Accordingly, use of biologics is restricted in some countries to

patients with high disease activity despite receiving traditional disease-modifying antirheumatic drugs.[9] Because personalised medicine is a focus in research and practice,[10] dose adjustments once a treatment target has been sustained are highly important. Although some observational data for withdrawal of biologics in early rheumatoid arthritis have been reported,[11–13] no controlled trial has yet assessed withdrawal or dose reduction. Therefore, investigation of the best possible use of biologic agents is of interest, including potential dosing alternatives and so-called induction, maintenance, and withdrawal treatment strategies. The aim of PRESERVE was to assess whether the response to treatment with conventional doses of the biologic etanercept and background methotrexate in adults with moderately active rheumatoid arthritis despite methotrexate treatment would be sustained when doses of etanercept were reduced or withdrawn.

Methods

Study design and participants

In this randomised controlled trial, patients with rheumatoid arthritis aged between 18 and 70 years with moderate disease activity at screening (4–42 days before baseline) and baseline (week 0) visits were enrolled at 80 centres in Europe, Latin America, Asia, and Australia between March 6, 2008, and Sept 9, 2009. Moderate disease activity was defined as a disease activity score in 28 joints (DAS28; on the basis of erythrocyte sedimentation rate) of more than 3·2 and 5·1 or less. Participants had to have been receiving stable doses of 15–25 mg/week of methotrexate for treatment of rheumatoid arthritis for at least 8 weeks before screening.

In an initial open-label period, patients were excluded if they had previously taken or were taking biologic treatment, any disease-modifying antirheumatic drug other than methotrexate within 28 days of baseline, or more than one non-steroidal anti-inflammatory drug at baseline. Patients taking prednisone (or equivalent) at a dose of more than 10 mg/day or at a dose that had been changed within 14 days of screening were excluded, as were those using intra-articular, intravenous, intramuscular, or subcutaneous glucocorticoids within 28 days of screening. Patients were also excluded when they had received any live vaccine within 28 days of baseline or had had tuberculosis in the previous 2 years. Individuals with latent tuberculosis infection were included only when local guidelines were followed for prophylactic treatment and if treatment was initiated before etanercept.

In the subsequent double-blind period, participants were eligible for randomisation when they had completed the open-label stage (36 weeks) and achieved sustained low disease activity (mean DAS28 ≤3·2 from weeks 12 to 36 and DAS28 ≤3·2 at week 36). Patients were excluded if the dose of non-steroidal anti-inflammatory drug or prednisone had been changed or more than 10 mg/day prednisone (or equivalent) was given within 14 days of randomisation. They were also excluded if the methotrexate dose changed within 8 weeks of randomisation (with the exception of a reduced dose because of adverse events). Patients could receive up to two intra-articular corticosteroid injections during the open-label period and up to three in the double-blind period at the investigator's discretion. The injection was to be given after a study visit; if administered within 28 days before a visit, the injected joint was excluded from assessment at the subsequent visit. Use of shortacting oral analgesic drugs (with no anti-inflammatory action) was also allowed, although it was restricted to the postassessment period on study visit days.

This study was done in accordance with the International Conference on Harmonisation guideline for good clinical practice and the ethical principles of the Declaration of Helsinki. All patients gave written informed consent, which was reviewed and approved by an independent ethics committee or institutional review board.

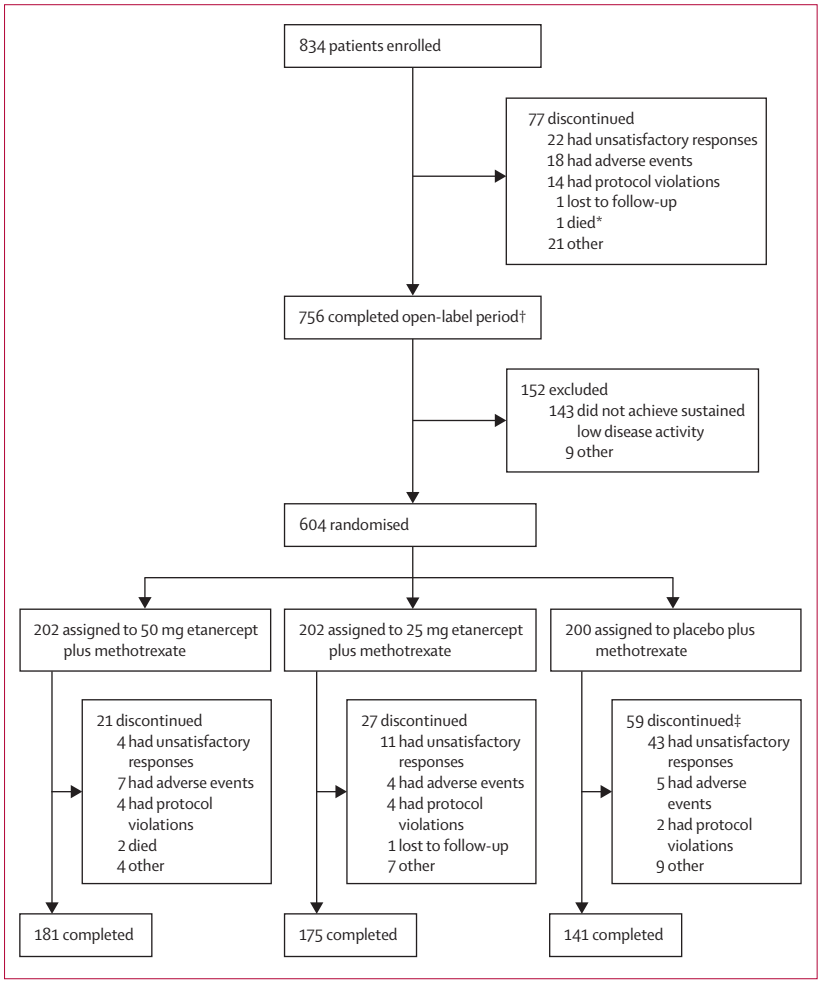

Figure 1: **Trial profile**

*Two patients died in the open-label period (both in Mexico); one is listed as having discontinued because of adverse events. †One patient was not included because of data discrepancy. ‡Significantly more patients discontinued in group given placebo than in 50 mg and 25 mg groups (p≤0·001 for both comparisons).

Randomisation and masking

Patients who achieved sustained low disease activity at the end of the open-label period and hence were eligible for the double-blind stage were randomly assigned by a centralised system in a 1:1:1 ratio to one of three treatment groups: weekly subcutaneous injections of 50 mg etanercept plus methotrexate, 25 mg etanercept plus methotrexate, or etanercept placebo (same formulation as etanercept drug product, but without active ingredient) plus methotrexate. Patients were stratified in blocks of three by DAS28 response (low disease activity or remission) at week 36. Allocation of patients to treatment groups was done with the ICOPhone interactive voice response system on the basis of information supplied by the investigator or the study staff. The etanercept packages for each patient were identical and were labelled with a unique coded number that was linked with the randomisation schedule table. Patients, investigators, data analysts, and study staff were all masked to treatment allocation.

Procedures

In the initial open-label period, enrolled patients were given subcutaneous injections of 50 mg etanercept plus oral methotrexate every week for 36 weeks. Participants were given the dose of methotrexate they had been receiving at screening; a dose increase (maximum 25 mg/week) was allowed up to week 28 at the investigator's discretion. In patients who experienced adverse events, methotrexate was withheld for up to two doses or reduced by 2·5 or 5·0 mg weekly, or both, until tolerated. A minimum dose of methotrexate of 10 mg/week was necessary for continuation in the study.

In the double-blind period, patients received their assigned weekly subcutaneous injections and the dose of methotrexate they had received in the last 8 weeks of the open-label stage. Methotrexate was supplied as open-label, repackaged commercial blisters of 2·5 mg tablets during both stages.

The primary endpoint was the proportion of patients in the groups given 50 mg etanercept or placebo in the double-blind period with DAS28 of 3·2 or less (ie, low disease activity) at week 88. If low disease activity was maintained significantly more frequently when 50 mg etanercept was continued than with placebo, a conditional primary endpoint was the proportion of patients receiving 25 mg etanercept who achieved low disease activity.

Secondary endpoints were remission based on DAS28 (<2·6) and remission based on simplified disease activity index criteria (≤3·3). A post-hoc endpoint was added to assess remission according to the Boolean definition of the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR): tender joint count of 1 or less; swollen joint count of 1 or less; concentration of C-reactive protein of 1 mg/dL or less; and patient global assessment score of 1 or less (0–10 scale). The proportions of patients achieving low disease activity (simplified disease activity index ≤11), a 20% improvement in tender and swollen joints and in three other ACR core set variables (ACR20), a 50% improvement in tender and swollen joints and in three other ACR core set variables (ACR50), a 70% improvement in tender and swollen joints and in three other ACR core set variables (ACR70), EULAR good or moderate responses, and normal score on health assessment questionnaire disability index (≤0·5) were also assessed. Changes from baseline in DAS28, simplified disease activity index, clinical disease activity index, swollen and tender joint counts (between no and 28 joints), duration of morning stiffness, concentration of C-reactive protein, erythrocyte sedimentation rate (0–100 mm/h; Westergren method), physician and patient global assessments (0–10 numerical rating scale), and patient-assessed general health and pain (visual analogue scales; 100 mm) were investigated. For joint counts with missing measurements (not <80%), total swollen and tender joint counts were assessed by multiplying the counts by a factor of 28 and then dividing by the number of non-missing swollen or tender joints. Time to loss of efficacy (defined as time to loss of both DAS28 low disease activity and a change in DAS28 ≥0·6 or discontinuation due to poor efficacy, protocol violation, or another reason) during the double-blind period was calculated. Patient-reported outcomes were also assessed with the total health assessment questionnaire disability index; EuroQol-5 total index; medical outcomes study sleep scale; functional

	Overall population in open-label period (n=834)	Randomised population		
		50 mg etanercept plus methotrexate (n=202)	25 mg etanercept plus methotrexate (n=202)	Placebo plus methotrexate (n=200)
Demographic characteristics				
Age (years)	48·4 (11·9)	48·1 (12·0)	46·4 (12·2)	48·3 (12·2)
Women	694 (83%)	164 (81%)	157 (78%)	167 (84%)
White ethnic origin	619 (74%)	158 (78%)	145 (72%)	151 (76%)
Disease characteristics				
Disease duration (years)	6·9 (7·0)	6·8 (7·2)	6·4 (7·1)	7·3 (6·7)
Rheumatoid factor positive*	603 (72%)	147 (73%)	142 (71%)	147 (74%)
Positive for anticyclic citrullinated peptide antibody*	642 (77%)	161 (80%)	156 (78%)	156 (79%)
Previous treatment				
Disease-modifying antirheumatic agents (not including methotrexate)†	221 (26%)	48 (24%)	53 (26%)	50 (25%)
Glucocorticoids‡	494 (59%)	122 (60%)	119 (59%)	121 (61%)
Non-steroidal anti-inflammatory drugs§	619 (74%)	155 (77%)	147 (73%)	152 (76%)

Data are mean (SD) or n (%). *201 patients assigned to 50 mg etanercept plus methotrexate, 201 assigned to 25 mg etanercept plus methotrexate, and 198 assigned to placebo plus methotrexate provided samples for testing of rheumatoid factor and anticyclic citrullinated peptide antibody. †Within 6 months of screening. ‡Within 28 days of screening or baseline. §Concurrent treatment with at least one non-steroidal anti-inflammatory drug at baseline.

Table 1: **Baseline characteristics**

assessment of chronic illness therapy measurement; brief pain inventory; and work productivity and activity impairment scale for rheumatoid arthritis (percentage activity impairment due to rheumatoid arthritis).

Radiographic assessments of hands, wrists, and feet were done at baseline and weeks 36 and 88, or at the time of early withdrawal when occurring in weeks 40 to 88. Radiographs were not obtained for patients who discontinued participation in the study less than 1 month after the start of the double-blind period. In patients who discontinued after 1 month (ie, after week 40), radiographs were obtained and scores were linearly extrapolated to week 88. Scores were also extrapolated to day 365 in patients who completed the study before this timepoint. Images were assessed with the van der Heijde modified total Sharp score (mTSS), which quantifies erosions and joint space narrowing. Two qualified radiologists (Synarc, Hamburg, Germany) who were masked to the treatment regimens viewed and scored the digitised radiographic images in random visit order with masking of the chronological sequence. The proportions of patients achieving an mTSS progression rate of up to 0·5 units per year (ie, non-progression) and a smallest detectable difference of 2·0 units per year were calculated.

	Overall population in open-label period (n=834; week 0)	Randomised population					
		50 mg etanercept plus methotrexate (n=201)		25 mg etanercept plus methotrexate (n=201)		Placebo plus methotrexate (n=197)	
		Week 0	Week 36	Week 0	Week 36	Week 0	Week 36
Clinical characteristics							
Disease activity score in 28 joints	4·4 (0·4)	4·3 (0·5)	2·0 (0·6)	4·4 (0·4)	2·1 (0·6)	4·3 (0·4)	2·1 (0·6)
Simplified disease activity index	19·1 (5·1)	18·7 (4·8)	4·7 (3·6)	19·2 (5·1)	4·8 (3·2)	18·8 (5·4)	4·8 (3·2)
Clinical disease activity index	17·8 (5·0)	17·5 (4·6)	4·1 (3·5)	17·9 (5·0)	4·2 (3·2)	17·8 (5·3)	4·3 (3·2)
Tender joint count (0–28 scale)	5·1 (2·9)	4·7 (2·7)	0·6 (1·2)	5·2 (2·9)	0·7 (1·3)	5·1 (2·9)	0·7 (1·2)
Swollen joint count (0–28 scale)	3·8 (2·6)	3·9 (2·7)	0·6 (1·5)	3·8 (2·6)	0·6 (1·2)	4·0 (2·7)	0·6 (1·1)
Duration of morning stiffness (min)	177·0 (333·5)	188·1 (358·4)	34·5 (146·1)	172·8 (339·3)	36·5 (115·2)	182·9 (364·3)	38·0 (151·8)
C-reactive protein (mg/L)	12·3 (16·4)	11·9 (13·9)	5·9 (5·9)	12·8 (18·0)	6·0 (6·5)	10·4 (13·1)	5·2 (3·3)
Erythrocyte sedimentation rate (0–100 mm/h)	22·2 (13·1)	22·2 (12·9)	9·9 (7·2)	21·7 (13·4)	10·7 (8·6)	20·4 (12·1)	9·6 (6·0)
Physician global assessment (0–10 scale)	4·1 (1·3)	4·0 (1·3)	1·1 (0·9)	4·0 (1·3)	1·2 (1·1)	4·2 (1·3)	1·1 (0·8)
Patient global assessment (0–10 scale)	4·9 (1·7)	4·9 (1·8)	1·8 (1·7)	4·8 (1·7)	1·8 (1·5)	4·6 (1·7)	1·9 (1·6)
General health visual analogue scales (0–100 mm)	43·4 (17·0)	43·2 (17·3)	14·1 (15·8)	41·5 (15·5)	14·8 (15·0)	40·9 (15·6)	15·1 (15·5)
Pain visual analogue scales (0–100 mm)	45·5 (17·4)	46·1 (17·8)	12·8 (15·5)	43·1 (16·1)	13·8 (14·8)	44·1 (16·3)	14·2 (15·6)
Patient-reported characteristics							
Total health assessment questionnaire disability index (0–3 scale*)	1·1 (0·6)	1·1 (0·6)	0·5 (0·5)	1·1 (0·6)	0·5 (0·5)	1·1 (0·6)	0·5 (0·4)
EuroQol-5 total index (0–1 scale†)	0·6 (0·2)	0·6 (0·2)	0·8 (0·2)	0·6 (0·2)	0·8 (0·2)	0·6 (0·2)	0·8 (0·2)
Medical outcomes study sleep scale problem I index (0–100 scale‡)	35·1 (17·4)	34·5 (17·2)	21·3 (17·2)	33·0 (16·8)	18·9 (16·5)	34·6 (16·8)	20·9 (17·7)
Functional assessment of chronic illness therapy: fatigue (0–52 scale§)	32·5 (9·7)	32·8 (9·5)	41·9 (8·9)	34·5 (8·8)	43·3 (8·0)	33·3 (9·5)	42·6 (7·9)
Brief pain inventory interference (0–10 scale¶)	4·0 (2·0)	4·1 (2·0)	1·3 (1·8)	3·7 (2·0)	1·3 (1·5)	3·8 (1·9)	1·3 (1·6)
Brief pain inventory severity (0–10 scale¶)	4·2 (1·7)	4·1 (1·6)	1·5 (1·6)	4·1 (1·6)	1·6 (1·5)	4·0 (1·6)	1·6 (1·4)
Activity impairment because of rheumatoid arthritis (0–100%‖)	44·4% (20·4%)	43·7% (20·0%)	16·3% (17·9%)	42·2% (19·4%)	17·3% (18·6%)	41·3% (20·5%)	17·4% (17·7%)
Radiographic characteristics**							
Modified total Sharp score (0–448 scale)	39·3 (55·3)	42·6 (58·8)	42·7 (58·8)	39·1 (60·3)	38·9 (59·8)	42·3 (47·5)	42·4 (47·6)
Erosion score (0–280 scale)	24·8 (33·2)	25·8 (34·6)	25·8 (34·6)	24·7 (36·8)	24·7 (36·5)	26·2 (28·1)	26·1 (28·1)
Joint space narrowing score (0–168 scale)	14·5 (23·6)	16·8 (25·3)	16·9 (25·4)	14·4 (24·8)	14·2 (24·6)	16·1 (21·1)	16·1 (21·2)
Rate of progression in modified total Sharp score†† (units/year)	9·0 (22·1)	7·5 (9·4)	0·1 (2·2)	10·3 (21·9)	0·1 (1·9)	11·0 (35·2)	0·2 (1·6)

Data are mean (SD). *Lower score denotes less functional disability. †Higher score indicates better quality of life. ‡Lower score indicates better sleep. §Higher score denotes less fatigue. ¶Higher score denotes worse pain. ‖Lower percentage denotes less activity impairment (one component of work productivity and activity impairment assessment). **Data for the radiographic variables were derived from the radiographic population (open-label period: n=709; double-blind period: 50 mg etanercept plus methotrexate n=184, 25 mg etanercept plus methotrexate n=184, and placebo plus methotrexate n=167). ††The values at baseline are the historical rates of progression (rate of progression from date of diagnosis); the values for the randomised populations at week 36 have been extrapolated to 1 year.

Table 2: **Characteristics at baseline of the overall modified intention-to-treat population in the open-label period and at baseline and week 36 for the modified intention-to-treat subpopulations in the double-blind period**

	Open-label period (week 36; n=834)	Double-blind period (week 88)						
		Placebo plus methotrexate (n=200)	50 mg etanercept plus methotrexate (n=202)	Mean difference between 50 mg etanercept and placebo groups		25 mg etanercept plus methotrexate (n=202)	Mean difference between 25 mg etanercept and placebo groups	
				Mean difference (95% CI)	p value		Mean difference (95% CI)	p value
Clinical and functional endpoints								
DAS28 low disease activity (≤3·2)	677/826 (82·0%)	84/197 (42·6%)	166/201 (82·6%)	40·8% (32·5 to 49·1%)	<0·0001	159/201 (79·1%)	35·9% (27·0 to 44·8%)	<0·0001
DAS28 remission (<2·6)	525/826 (63·6%)	58/197 (29·4%)	134/201 (66·7%)	37·1% (28·0 to 46·2%)	<0·0001	121/201 (60·2%)	31·1% (21·9 to 40·3%)	<0·0001
Low disease activity on simplified disease activity index (≤11)	672/826 (81·3%)	107/197 (54·3%)	168/201 (83·6%)	29·4% (21·2 to 37·6%)	<0·0001	165/201 (82·1%)	26·7% (18·0 to 35·5%)	<0·0001
Remission on simplified disease activity index (≤3·3; ACR/EULAR index-based remission)	196/826 (23·7%)	23/197 (11·7%)	76/201 (37·8%)	27·2% (19·3 to 35·0%)	<0·0001	63/201 (31·3%)	18·7% (10·7 to 26·8%)	<0·0001
ACR/EULAR Boolean remission	262/829 (31·6%)	21/197 (10·7%)	73/201 (36·3%)	27·1% (19·3 to 34·8%)	<0·0001	66/201 (32·8%)	22·2% (14·2 to 30·2%)	<0·0001
ACR20	600/824 (72·8%)	96/197 (48·7%)	151/200 (75·5%)	27·5% (18·4 to 36·5%)	<0·0001	150/201 (74·6%)	26·0% (17·0 to 35·1%)	<0·0001
ACR50	493/824 (59·8%)	51/197 (25·9%)	125/200 (62·5%)	36·4% (27·4 to 45·4%)	<0·0001	115/201 (57·2%)	31·4% (22·4 to 40·5%)	<0·0001
ACR70	229/824 (27·8%)	22/197 (11·2%)	71/200 (35·5%)	24·9% (16·7 to 33·0%)	<0·0001	63/201 (31·3%)	20·1% (12·5 to 27·7%)	<0·0001
EULAR good or moderate response	724/823 (88·0%)	122/197 (61·9%)	181/200 (90·5%)	28·3% (18·7 to 38·0%)	<0·0001	177/201 (88·1%)	25·1% (16·9 to 33·4%)	<0·0001
Normal health assessment questionnaire disability index (≤0·5)	450/829 (54·3%)	82/197 (41·6%)	120/201 (59·7%)	18·4% (8·7 to 28·0%)	0·0002	107/201 (53·2%)	12·0% (2·4 to 21·6%)	0·015
Total improvement on health assessment questionnaire disability index ≥0·22	594/829 (71·7%)	100/196 (51·0%)	144/199 (72·4%)	21·2% (11·9 to 30·6%)	<0·0001	145/200 (72·5%)	21·3% (12·2 to 30·4%)	<0·0001
Clinical outcomes								
DAS28	2·5 (1·1)	3·5 (1·4)	2·4 (1·0)	−1·0 (−1·3 to −0·8)	<0·0001	2·5 (1·1)	−0·9 (−1·2 to −0·7)	<0·0001
Simplified disease activity index	7·4 (7·3)	13·5 (11·3)	6·3 (6·8)	−7·2 (−8·9 to −5·6)	<0·0001	7·0 (7·2)	−6·5 (−8·1 to −4·9)	<0·0001
Clinical disease activity index	6·7 (7·1)	12·7 (11·0)	5·6 (6·6)	−7·0 (−8·6 to −5·5)	<0·0001	6·3 (7·0)	−6·3 (−7·8 to −4·7)	<0·0001
Tender joint count (0–28 scale)	1·6 (3·0)	3·8 (4·7)	1·4 (3·0)	−2·4 (−3·1 to −1·7)	<0·0001	1·4 (2·4)	−2·4 (−3·0 to −1·7)	<0·0001
Swollen joint count (0–28 scale)	1·2 (2·3)	2·5 (3·6)	0·8 (1·8)	−1·8 (−2·3 to −1·2)	<0·0001	1·0 (2·4)	−1·4 (−1·9 to −0·9)	<0·0001
Duration of morning stiffness (min)	66·7 (215·7)	132·4 (316·9)	62·3 (226·5)	−71·6 (−116·9 to −26·3)	0·0020	48·0 (153·9)	−83·9 (−129·2 to −38·7)	0·0003
C-reactive protein (mg/L)	6·7 (8·4)	10·2 (14·6)	7·0 (10·2)	−3·6 (−5·7 to −1·5)	0·0007	6·7 (7·7)	−4·0 (−6·1 to −1·9)	0·0002
Erythrocyte sedimentation rate (mm/h)	13·2 (12·5)	21·0 (19·3)	14·0 (10·0)	−7·2 (−9·8 to −4·6)	<0·0001	14·5 (11·7)	−7·2 (−9·8 to −4·7)	<0·0001
Physician global assessment (0–10 scale)	1·6 (1·5)	2·8 (2·2)	1·3 (1·5)	−1·4 (−1·8 to −1·1)	<0·0001	1·5 (1·6)	−1·3 (−1·6 to −1·0)	<0·0001
Patient global assessment (0–10 scale)	2·4 (2·0)	3·7 (2·4)	2·1 (1·8)	−1·5 (−1·9 to −1·2)	<0·0001	2·4 (2·0)	−1·2 (−1·6 to −0·9)	<0·0001
General health visual analogue scales (0–100 mm)	20·8 (20·5)	31·7 (23·3)	18·1 (18·9)	−13·2 (−16·9 to −9·5)	<0·0001	20·6 (19·6)	−10·8 (−14·5 to −7·1)	<0·0001
Pain visual analogue scales (0–100 mm)	19·7 (20·2)	32·3 (24·6)	16·9 (18·3)	−14·7 (−18·5 to −10·9)	<0·0001	19·7 (20·5)	−12·3 (−16·1 to −8·5)	<0·0001
Patient-reported outcomes								
Total health assessment questionnaire disability index (0–3 scale*)	0·6 (0·6)	0·8 (0·6)	0·5 (0·5)	−0·3 (−0·4 to −0·2)	<0·0001	0·6 (0·5)	−0·3 (−0·4 to −0·2)	<0·0001
EuroQol-5 total index (0–1 scale†)	0·8 (0·2)	0·7 (0·3)	0·8 (0·2)	0·1 (0·1 to 0·1)	<0·0001	0·8 (0·2)	0·1 (0·1 to 0·1)	<0·0001
Medical outcomes study sleep scale problem I index (0–100 scale‡)	23·1 (18·7)	31·1 (20·6)	23·7 (16·9)	−7·5 (−10·6 to −4·4)	<0·0001	24·6 (17·8)	−5·6 (−8·8 to −2·5)	0·0004
Functional assessment of chronic illness therapy: fatigue (0–52 scale§)	40·6 (9·4)	36·9 (11·0)	39·5 (9·3)	4·5 (2·9 to 6·1)	<0·0001	40·4 (0·9)	3·4 (1·8 to 5·0)	<0·0001
Brief pain inventory interference (0–10 scale¶)	1·8 (1·9)	2·7 (2·4)	1·6 (1·8)	−1·1 (−1·5 to −0·8)	<0·0001	1·8 (1·8)	−0·9 (−1·3 to −0·5)	<0·0001
Brief pain inventory severity (0–10 scale¶)	2·0 (1·8)	3·0 (2·1)	1·9 (1·7)	−1·1 (−1·4 to −0·7)	<0·0001	2·1 (1·8)	−0·9 (−1·3 to −0·6)	<0·0001
Activity impairment because of rheumatoid arthritis (0–100%‖)	22·1 (21·2)	31·7 (24·8)	20·2 (20·4)	−11·0 (−15·0 to −7·0)	<0·0001	21·3 (21·0)	−10·3 (−14·2 to −6·3)	<0·0001

(Continues on next page)

	Open-label period (week 36; n=709)	Double-blind period (week 88)						
		Placebo plus methotrexate (n=167)	50 mg etanercept plus methotrexate (n=184)	Mean difference between 50 mg etanercept and placebo groups		25 mg etanercept plus methotrexate (n=184)	Mean difference between 25 mg etanercept and placebo groups	
				Mean difference (95% CI)	p value		Mean difference (95% CI)	p value
(Continued from previous page)								
Radiographic outcomes**								
Modified total Sharp score (0–448 scale)	39·7 (55·5)	42·8 (48·3)	42·6 (58·8)	..	..	38·9 (59·8)	..	..
Rate of progression (units per year)	..	0·60 (0·13)	−0·06 (0·13)	−0·7 (−1·0 to −0·3)	0·026	0·05 (0·13)	−0·6 (−0·9 to −0·2)	0·070
Erosion score (0–280 scale)	25·0 (33·3)	26·4 (28·6)	25·7 (34·6)	..	..	24·7 (36·4)	..	..
Rate of progression (units per year)	..	0·33 (0·11)	−0·05 (0·10)	−0·4 (−0·7 to −0·1)	0·031	0·02 (0·10)	−0·3 (−0·6 to −0·0)	0·030
Joint space narrowing score (0–168 scale)	14·7 (23·7)	16·4 (21·5)	16·9 (25·4)	..	..	14·2 (24·6)	..	..
Rate of progression (units per year)	..	0·27 (0·07)	−0·01 (0·07)	−0·3 (−0·5 to −0·1)	0·055	0·02 (0·07)	−0·2 (−0·4 to −0·1)	0·070
Radiographic endpoints**								
Progression rate in modified total Sharp score ≤0·5 (units per year)††	584/709 (82)	138/167 (83)	164/184 (89)	6·8 (−0·6 to 14·2)	0·117	163/184 (89)	7·3 (0·5 to 14·1)	0·118
Progression rate in modified total Sharp score ≤2·0 (units per year)††	663/709 (94)	149/167 (89)	179/184 (97)	7·9 (0·0 to 15·7)	0·007	176/184 (96)	7·1 (−1·7 to 16·0)	0·026

Data are n/N (%) or mean (SD), unless otherwise stated. Clinical assessments (except DAS28 low disease activity) done with last-observation-carried-forward method. DAS28 low disease activity at week 88 done by modified non-responder imputation (patients who discontinued early because of poor efficacy were imputed as non-responders for all timepoints). DAS28=disease activity score in 28 joints. ACR=American College of Rheumatology. EULAR=European League Against Rheumatism. ACR20=20% improvement in tender or swollen joints and three other ACR core set variables. ACR50=50% improvement in tender or swollen joints and three other ACR core set variables. ACR70=70% improvement in tender or swollen joints and three other ACR core set variables. *Lower score denotes less functional disability. †Higher score indicates better quality of life. ‡Lower score indicates better sleep. §Higher score denotes less fatigue. ¶Higher score denotes worse pain. ||Lower percentage denotes less activity impairment (one component of work productivity and activity impairment assessment). **Data for the radiographic variables were derived from the radiographic population (open-label period n=709; 50 mg etanercept plus methotrexate n=184; 25 mg etanercept plus methotrexate n=182; and placebo plus methotrexate n=167). ††Extrapolated linearly in double-blind period to 1 year.

Table 3: **Treatment efficacy at week 36 for the modified intention-to-treat population in the open-label period and at week 88 for the modified intention-to-treat subpopulations in the double-blind period**

Statistical analysis

A sample size of 900 patients was estimated for the open-label period. With the assumption that 60% of patients would achieve DAS28 low disease activity or remission at the end of this stage (on the basis of the TEMPO trial[14]), a sample size of 175 patients per treatment group for the double-blind period was calculated to be necessary for more than 90% power to reject the null hypothesis of no difference between the treatment groups with an α of 0·05. Because PRESERVE included patients with moderate disease activity and used a withdrawal design, the proportion of participants who would maintain DAS28 low disease activity or remission was conservatively estimated to be 85% in the groups receiving etanercept versus 70% of patients receiving methotrexate monotherapy.

In the open-label period, the modified intention-to-treat and safety populations included all patients who received at least one dose of etanercept. The radiographic population included all those who received at least one dose of study drug and had assessable baseline and postbaseline radiographs. In the double-blind period, the modified intention-to-treat population was made up of patients who had received at least one dose of study drug and had one or more DAS28 evaluations. The safety population included all patients given at least one dose of the assigned treatment. The radiographic intention-to-treat population included all those who received at least one dose of study drug and had both a week-36 and postrandomisation radiograph assessment.

Demographic and baseline disease characteristics were summarised with descriptive statistics and analysed with one-way ANOVA for continuous variables and χ^2 tests for categorical variables. For the randomised, double-blind period, all analyses of proportions were analysed for treatment differences with two approaches: the χ^2 test, stratified by geographical region and DAS28 status at week 36; and a generalised linear model, adjusted for geographical region and DAS28 status at week 36. Models with treatment-group proportions close to 0% or 100% should be interpreted with caution. The DAS28 strata were removed only for DAS28 analyses. The primary endpoint was analysed with the Cochran-Mantel-Haenszel test of general association. A modified non-responder imputation analysis was done, in which patients who discontinued early because of poor efficacy were imputed as non-responders for all timepoints; all other patients were analysed with the last-observation-carried-forward

See Online for appendix

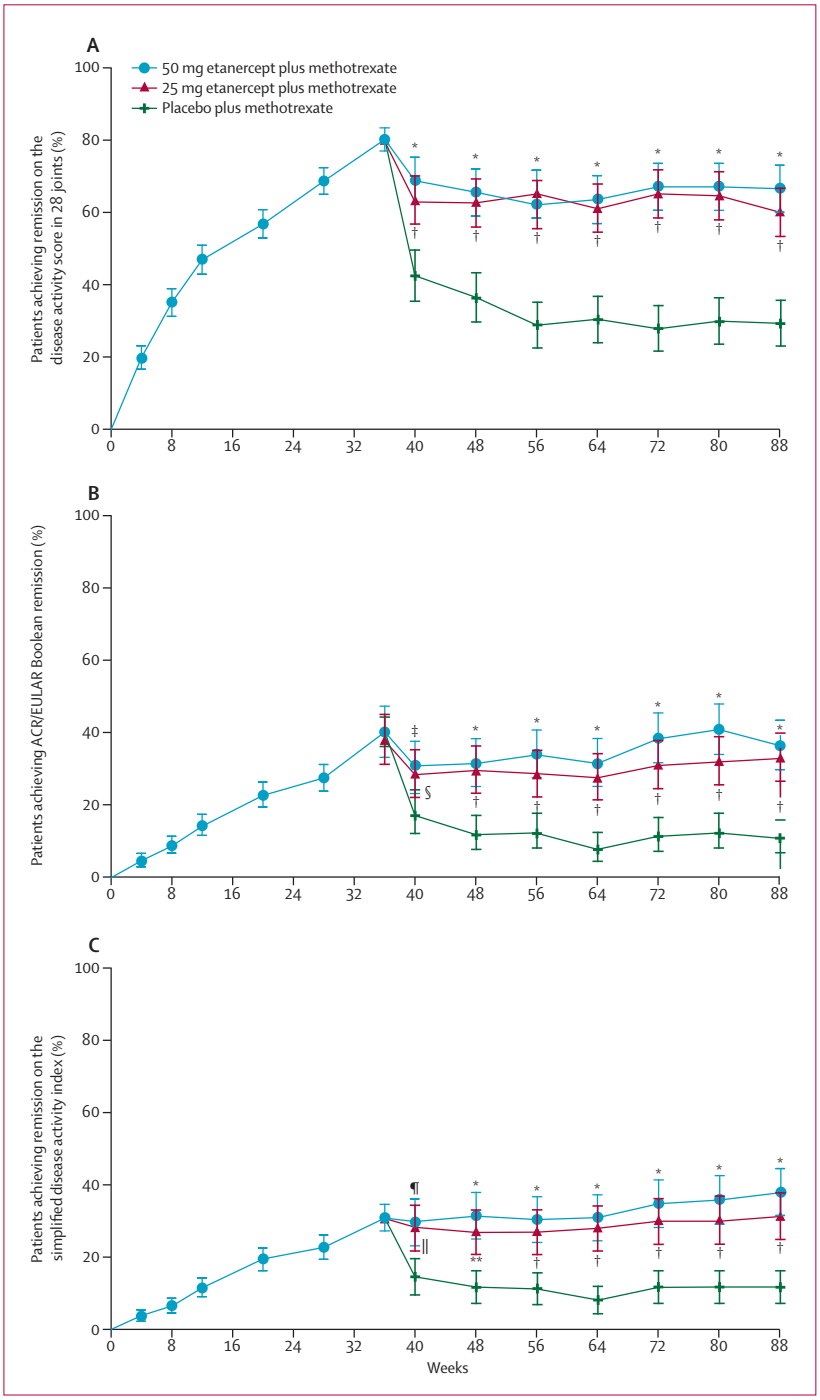

Figure 2: **Proportions of patients achieving remission based on the (A) disease activity score in 28 joints, (B) ACR/EULAR Boolean, and (C) simplified disease activity index definitions by treatment group**
Patients from the modified intention-to-treat population in the double-blind period included. Last-observation-carried-forward analysis. Bars show 95% CIs. ACR/EULAR=American College of Rheumatology/European League Against Rheumatology criteria.*50 mg etanercept plus methotrexate versus placebo plus methotrexate p<0·0001. †25 mg etanercept plus methotrexate versus placebo plus methotrexate p<0·0001. ‡50 mg etanercept plus methotrexate versus placebo plus methotrexate p=0·0019. §25 mg etanercept plus methotrexate versus placebo plus methotrexate p=0·0078. ¶50 mg etanercept plus methotrexate versus placebo plus methotrexate p=0·0007. ||25 mg etanercept plus methotrexate versus placebo plus methotrexate p=0·0019. **25 mg etanercept plus methotrexate versus placebo plus methotrexate p=0·0001.

method. All other postbaseline analyses were based on the last-observation-carried-forward approach, except radiographic endpoints (which were extrapolated to week 88). The analysis of time to loss of efficacy also assessed reported cases; the Kaplan-Meier approach was used for survival estimation and the log-rank test for statistical testing, with censoring at day 372. Continuous endpoints were analysed in ANCOVA models in SAS (version 9.2) with week-36 baseline values of endpoints, geographical region, and week-36 DAS28 low disease activity or remission as covariates; baseline and change values for radiographic endpoints were rank transformed before analysis (ie, rank ANCOVA).

PRESERVE is registered with ClinicalTrials.gov, number NCT00565409.

Role of the funding source

PRESERVE was sponsored by Wyeth, which was acquired by Pfizer in October, 2009. Pfizer was responsible for data collection and analysis. The academic authors and sponsor representatives were involved in the study design, data analyses, data interpretation, writing of the report, and the final decision to submit for publication. Biostatisticians at Pfizer did and verified all data analyses. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. In the open-label period, all patients achieved at least 80% compliance with injection and oral treatment. In the double-blind period, 199 (98·5%) of 202 patients given 50 mg etanercept, 199 (98·5%) of 202 given 25 mg etanercept, and 199 (99·5%) of 200 given placebo achieved 80% compliance. The proportion of patients who were eligible to continue to the double-blind period (604 [72%] of 834) was higher than had been predicted; therefore, the sample size for the second stage was larger than had been specified in the study protocol. Demographic and disease characteristics were similar in all three groups at baseline (table 1) and at the start of the double-blind period (table 2).

In the modified intention-to-treat population, significantly more patients given 50 mg or 25 mg etanercept had DAS28 low disease activity at week 88 than did those given placebo (table 3; appendix). The proportion of patients with remission fell rapidly after week 36 in the group given placebo (figure 2). The difference between proportions of patients in the 50 mg or 25 mg etanercept groups and the placebo group who achieved DAS28 remission grew with time (p<0·0001). Significantly fewer patients in the withdrawal group than in the two etanercept groups attained low disease activity and remission states, ACR20, ACR50, ACR70, EULAR good or moderate responses, and a normal total score on the health assessment questionnaire disability index (table 3). Mean DAS28 and simplified disease activity index

deteriorated significantly in the placebo group compared with the etanercept groups from week 40 onwards (table 3, figure 3). Patients assigned to receive 50 mg or 25 mg etanercept continued to have low disease activity in the double-blind period, whereas those who received placebo had mean scores in the range of moderate disease activity (figure 3). The groups given etanercept showed similar patterns of loss of response, and maintained efficacy better than did the group given placebo (for both comparisons log-rank p<0·0001; figure 4).

Significantly more patients in the groups given etanercept achieved a radiographic progression rate of the smallest detectable difference or less (ie, 2·0 mTSS units per year) at week 88 than in the placebo group (table 3); no significant differences between groups were recorded for non-progression (table 3). The change in mTSS from week 36 to week 88 in the group given 50 mg etanercept (–0·06 units) was significantly different from the group given placebo (0·60 units; p=0·0259), but the change in the group given 25 mg etanercept (0·05 units) was not different from that in the placebo group (p=0·070) or from that in the group given 50 mg etanercept (p=0·67). Patients in the placebo group had higher erosion scores at week 88 than did those in etanercept groups (table 3).

No new safety signals were detected during the 88-week trial. During the open-label period, the most frequent treatment-emergent adverse events were headache (51 [6%] of 834 patients) and nasopharyngitis (45 [5%]). 38 patients (5%) had serious adverse events (table 4; appendix), of which the most frequent were pneumonia (5 [1%]), cellulitis (2 [<1%]), acute pyelonephritis (2 [<1%]), and basal-cell carcinoma (2 [<1%]).

In the double-blind period, the occurrence of adverse events was similar across the three groups (table 4). Overall, 351 (58%) of 604 patients had treatment-emergent adverse events (table 4), of which the most frequent were nasopharyngitis (17 [8%] of 202 patients given 50 mg etanercept; ten [5%] of 202 given 25 mg etanercept; and ten [5%] of 200 given placebo) and bronchitis (12 [6%] given 50 mg etanercept; 11 [5%] given 25 mg etanercept; and six [3%] given placebo). 34 patients (6%) had treatment-emergent serious adverse events (table 4), of which the most frequent were sepsis (one [1%] given 50 mg etanercept; and one [1%] given placebo), urinary tract infection (two [1%] given placebo), and malignant melanoma (one [1%] given 50 mg etanercept; and one [1%] given placebo). Two deaths occurred in the group given 50 mg etanercept: one due to pulmonary embolism and one septicaemia.

Discussion

This trial has shown that withdrawal of etanercept in patients with rheumatoid arthritis who have achieved sustained low disease activity causes disease activity to increase again. More than half of patients who stopped taking etanercept lost low disease activity compared

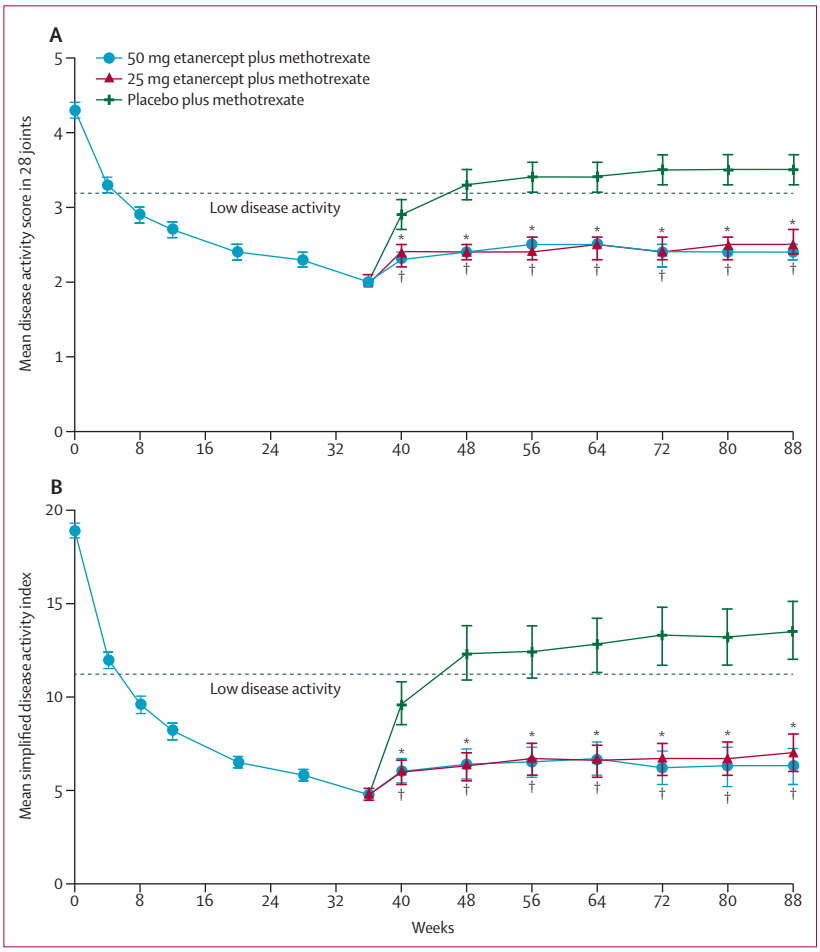

Figure 3: **Mean (A) disease activity score in 28 joints and (B) simplified disease activity index by treatment group**
Patients from the modified intention-to-treat population in the double-blind period included. Last-observation-carried-forward analysis. Bars show 95% CIs. *50 mg etanercept plus methotrexate versus placebo plus methotrexate p<0·0001. †25 mg etanercept plus methotrexate versus placebo plus methotrexate p<0·0001.

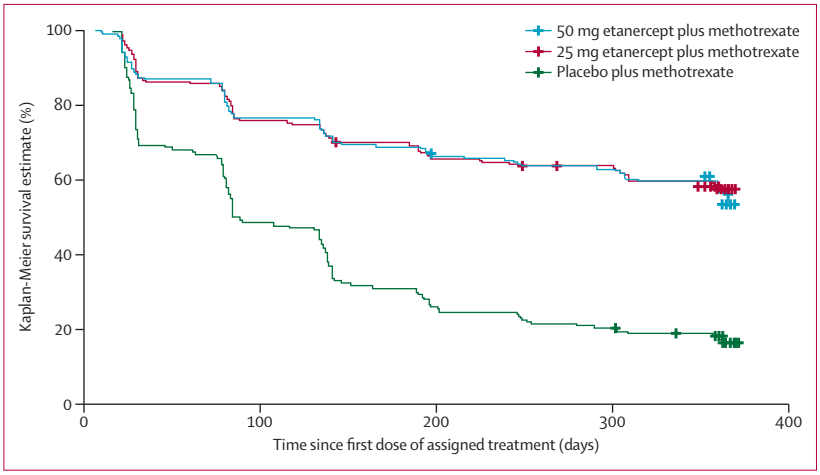

Figure 4: **Time to loss of efficacy by treatment group**
Modified intention-to-treat population. Analysis with the Kaplan-Meier approach for survival estimation. Crosses indicate censoring.

	Open-label period (n=834)	Double-blind period		
		50 mg etanercept plus methotrexate (n=202)	25 mg etanercept plus methotrexate (n=202)	Placebo plus methotrexate (n=200)
Any non-serious treatment-emergent adverse event	513 (62%)	124 (61%)	122 (60%)	105 (53%)
Treatment-emergent serious adverse event	38 (5%)	12 (6%)	7 (3%)	15 (8%)
Treatment-emergent serious infections	14 (2%)	3 (1%)	0	3 (2%)
Herpes zoster*	8 (1%)	4 (2%)	1 (1%)	2 (1%)
Tuberculosis†	1 (<1%)	0	0	0
Malignancy	5 (1%)	2 (1%)	4 (2%)	1 (1%)
Death‡	2 (<1%)	2 (1%)	0	0

Data are n (%). Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities. *Seven of the eight patients with herpes zoster in the open-label period and six of the seven patients in the double-blind period were confirmed as not systemic or disseminating (eg, no more than one dermatome); therefore, they were not judged to be opportunistic infections; one infection occurring in the randomised period (in the placebo group) did not have a documented number of dermatomes and could not be classified as systemic or not. †The case of tuberculosis was not serious and the patient was treated as an outpatient. ‡Two patients died because of pneumonia during the 2009 H1N1 influenza outbreak in the open-label period; two deaths due to pulmonary embolism and septicaemia were reported in the double-blind period, both of which were judged to be unrelated to study treatment.

Table 4: **Safety summary**

with fewer than one in five in the groups who continued taking the drug. The combination of etanercept and methotrexate led to more favourable secondary outcomes at all timepoints in the double-blind period than did methotrexate monotherapy. Time to loss of efficacy was significantly shorter after etanercept withdrawal than when etanercept was continued. More patients in both etanercept groups achieved remission, a normal score on the health assessment questionnaire, and other patient-reported outcomes than did those given placebo.

PRESERVE has addressed various novel aspects of treatment of rheumatoid arthritis because of three crucial design elements: assessment of patients with moderately active rheumatoid arthritis despite methotrexate use; targeting of low disease activity with a conventional dose of etanercept (50 mg) plus methotrexate; and investigation of response maintenance when etanercept is withdrawn but methotrexate is continued compared with continued conventional or reduced (25 mg) doses of etanercept plus methotrexate. These design factors represent three of four elements deemed to be absent from modern rheumatology clinical trials by the ACR Rheumatoid Arthritis Clinical Trial Investigators Ad Hoc Task Force.[15]

In clinical practice, patients with moderate disease activity are seen more frequently than are those with high disease activity and often constitute the most common population of patients with rheumatoid arthritis in daily life.[6,7,16] Therefore, the PRESERVE population represents a sizeable and important subgroup of patients with high needs (panel), especially because they do not have access to biological treatments in some countries.[6] Moreover, the patients studied had disease activity that fell in the whole range of moderate disease activity. Indeed, the range of DAS28 for moderate disease activity (3·2–5·1) is much broader than is that for low disease activity (2·6–3·2) and is similar to the range for high disease activity (>5·1; usual mean value of 6·3[23–25]).

All patients included in the double-blind period had attained low disease activity for a sustained period. The loss of low disease activity in most patients when they stopped taking etanercept indicates that low disease activity—even when sustained—is a labile state that requires maintenance of inhibitors of tumour necrosis factor, at least in patients with established rheumatoid arthritis. Importantly, a reduced etanercept dose was associated with continuation of good responses, which is another novel piece of information. Although this trial was not powered to show differences between the two etanercept regimens, findings with both regimens were similar. The small differences in favour of continuation of 50 mg etanercept might not be clinically meaningful; the overall findings suggest that patients who do well with an inhibitor of tumour necrosis factor could halve their dose without much loss of response and with substantial implications for cost-effectiveness.

Differences between treatments were also recorded for functional and radiographic endpoints. Because impaired physical function has consistently been shown to be related to work disability,[26] the functional effect of withdrawal of etanercept treatment would be associated with decreased working capacity. The proportion of patients in the groups who continued to receive etanercept and achieved radiographic progression rates equal to or less than 2·0 mTSS units per year was significantly higher than in the group given placebo. Mean changes in mTSS were better with 50 mg etanercept than with placebo, but no difference was recorded between 50 mg and 25 mg doses. The significant increase in joint damage when etanercept was withdrawn has to be considered in the context of the mitigating effect of the initial combination of etanercept treatment and its substantial benefits.[14,27] In view of the damage at baseline (mTSS of about 40 units), continued moderate disease activity when methotrexate is taken alone could lead to further changes in damage in subsequent years, as has also been reported in other studies.[28]

Aside from the novel findings from the double-blind period, the proportions of patients who achieved low disease activity and remission for a patient population who had had rheumatoid arthritis for a mean of roughly 7 years were high compared with previous randomised controlled trials.[14,29,30] However, the proportion of patients who achieved DAS28 remission in a 2008 clinical trial of etanercept[27] was also about 50%. The high frequency of low disease activity and remission in the population of patients studied in PRESERVE could be primarily due to the inclusion of patients with only moderate disease activity who might be more prone to shift to a lower disease activity category than would those with high

disease activity with an inhibitor of tumour necrosis factor. Furthermore, the open-label period was designed to last about 9 months, which would allow many patients to attain a favourable state. These findings provide evidence for the substantial benefit that can be achieved by patients who have active disease that is judged to be only moderate but is nonetheless disabling and destructive,[4] often is not well controlled with conventional treatment,[31] and could deteriorate if treatment remains unchanged.[32] Nevertheless, this finding is an ancillary and unexpected result of our study.

No unexpected safety or tolerability findings were reported during this study. Overall, less than 6% of patients had serious adverse events and less than 3% were withdrawn because of adverse events. In the double-blind period, the number, type, and severity of safety events were similar across treatment groups, suggesting that potential differences in safety might not be a concern for clinicians when considering continuation of conventional or reduced doses of etanercept.

One limitation of this study was that it did not have sufficient power to detect differences between the two etanercept groups. For most endpoints, findings for the two groups were similar, with the 50 mg etanercept dose having slightly better results than did the 25 mg dose. The open-label design of the initial 36-week period might also be considered a limitation. At week 40 (first post-randomisation visit), a reduction in DAS28 response was recorded in all groups. Possible explanations for these findings are an artificially increased response at week 36 because patients had to have achieved DAS28 low disease activity to be eligible for the double-blind period and the conversion from an open-label to a blinded, randomised study. Importantly, the patients with moderate disease activity despite previous methotrexate treatment who participated might have been more likely to achieve low disease activity or DAS28 remission than were patients who initially had high disease activity. The characteristics of the population—ie, moderate disease activity despite methotrexate and generally longstanding disease—distinguish this study from most previous clinical trials of biologics that have assessed patients with early moderate-to-severe rheumatoid arthritis who had not previously received methotrexate.

Importantly, results in the PRESERVE population might not be generalisable to patients with early or severe disease. In early disease, withdrawal of inhibitors of tumour necrosis factors seems to be better tolerated than in later stages.[33] Additionally, the findings might not be applicable to all countries. In the Quantitative Standard Monitoring of Patients with Rheumatoid Arthritis (QUEST-RA) cohort,[34] patients' disease activity was more closely correlated with their countries' gross domestic product than with their use of disease-modifying antirheumatic drugs. Regional subanalyses of PRESERVE are planned, but definitive results are not yet available. Furthermore, the open-label period in PRESERVE was limited to 36 weeks, so its findings cannot be extrapolated to patients in the clinical setting who reach low disease activity or remission in shorter or longer times than what was dictated by the protocol. Moreover, patients were followed up for only 52 weeks in the double-blind period and the reported outcomes must be viewed in this temporal context. We did not study whether etanercept doses lower than 25 mg every week would be sufficient to sustain efficacy, although it is unlikely in view of the slight difference between the conventional and reduced doses. Lastly, no attempt was made to recapture low disease activity by reintroducing etanercept at either dose in patients who had deteriorated after etanercept withdrawal.

Panel: Research in context

Systematic review

The European League Against Rheumatism published recommendations for treatment of rheumatoid arthritis in 2010[17] that were based on five systematic literature reviews (therefore, no systematic review was done for this study). Two of these literature reviews are relevant to this investigation: the review of biologic agents and the review of treatment strategies.[18,19] The recommendations have further been supported by the treat-to-target recommendations[5] and another systematic literature review.[20] This review[20] and the second item of the 2010 recommendations[17] stated that treatment should be adjusted as long as the target of remission or low disease activity has not been reached. The 2012 update of the American College of Rheumatology's recommendations for the treatment of rheumatoid arthritis[21] proposed that either remission or low disease activity should be targeted.

Item 12 of the 2010 European recommendations[17] dealt with the tapering of biological disease-modifying antirheumatic drugs and stated that it is unclear how treatment should be continued or discontinued in patients who have achieved remission. However, the suggestion was made that biologic agents could be tapered by expanding the interval between doses or by reducing the dose, whereas synthetic disease-modifying antirheumatic drugs should be continued. In a systematic review of tapering of disease-modifying antirheumatic drugs,[22] O'Mahony and colleagues declared that insufficient primary research had been done into tapering of biologic agents to allow them to do a systematic literature review.

Interpretation

In the open-label period of this trial, most patients with rheumatoid arthritis who reached moderate disease activity while treated with methotrexate achieved low disease activity or remission with conventional doses of etanercept, thus attaining the recommended treatment targets.[17,21] In the double-blind period, withdrawal of etanercept worsened symptoms despite methotrexate continuation. However, a reduction to 25 mg etanercept every week maintained low disease activity in most patients. This study provides crucial information about treatment of a generally understudied population of patients with moderately active rheumatoid arthritis.

Contributors

All authors were involved in the study design and conduct, data analyses, data interpretation, and writing and revision of the report. RP and AS managed and verified all data analyses.

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Conflicts of interest

JSS has received honoraria for consultations or speaking engagements, or grant support, or both, from Abbott, Amgen, AstraZeneca, Bristol-Myers Squibb, Celgene, GlaxoSmithKline, MSD, Novo Nordisk, Pfizer, Roche, Sandoz, Sanofi, and UCB. PN has received grant support and honoraria for consultations from Pfizer. FI-P has received grant support and honoraria for consultations or speaking engagements from Bristol-Myers Squibb, Janssen, Pfizer, and Roche. PM has received grant support from Abbott, Bristol-Myers Squibb, Celltrion, Centocor, GlaxoSmithKline, Human Genome Sciences, Merck, Neovacs, and Pfizer. KP has received honoraria for lectures from Abbott, Fidia, MSD, Pfizer, Roche, and UCB. RP, CH, ASK, and BV are employees of Pfizer and own Pfizer stock. AS is an employee of Inventive Health, who are paid contractors for Pfizer, providing statistical support for the PRESERVE study and the development of this report. The other authors declare that they have no conflicts of interest.

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