BMJ

RESEARCH

Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial

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Cite this as: *BMJ* 2010;340:c147
doi:10.1136/bmj.c147

ABSTRACT

Objectives To compare the efficacy over 12 weeks of two different etanercept regimens in treating the skin manifestations of psoriasis in patients who also have psoriatic arthritis and to evaluate efficacy and safety over an additional 12 weeks of open label etanercept treatment.

Design Randomised double blind multicentre outpatient study.

Setting 98 outpatient facilities in Europe, Latin America, and the Asia Pacific region.

Participants 752 patients with both psoriasis (evaluated by dermatologists) and psoriatic arthritis (evaluated by rheumatologists).

Interventions During the blinded portion of the study, participants were randomised to receive etanercept 50 mg twice weekly (n=379) or 50 mg once weekly (n=373) for 12 weeks by subcutaneous injection. All participants then received open label etanercept 50 mg once weekly for 12 additional weeks, while remaining blinded to the regimen.

Main outcome measures The primary efficacy end point was the proportion of participants achieving "clear" or "almost clear" on the physician's global assessment of psoriasis at week 12. Secondary efficacy analyses included psoriasis area and severity index, American College of Rheumatology responses, psoriatic arthritis response criteria, and improvement in joint and tendon disease manifestations.

Results At week 12, 46% (176/379) of participants receiving etanercept 50 mg twice weekly achieved a physician's global assessment of psoriasis of "clear" or "almost clear" compared with 32% (119/373) in the group treated with 50 mg once weekly (P<0.001). In contrast, an equally high percentage of participants in both groups achieved psoriatic arthritis response criteria (77% (284/371) in the twice weekly/once weekly group versus 76% (282/371) in the once weekly/once weekly group). Participants treated with 50 mg twice weekly/once weekly had greater mean reductions from baseline in the psoriasis area and severity index at week 12 compared with those who received 50 mg once weekly/once weekly (71% *v* 62%, P<0.001), with less difference at week 24 (78% *v* 74%, P<0.110). Joint and tendon disease manifestations improved from baseline in both groups to a similar extent. No new safety signals were seen in either etanercept treatment group, and no significant difference in the safety profiles was observed.

Conclusions In participants with active psoriasis and psoriatic arthritis, initial treatment of the psoriasis with etanercept 50 mg twice weekly may allow for more rapid clearance of skin lesions than with 50 mg once weekly. A regimen of 50 mg once weekly seems to be appropriate for treatment of joint and tendon rheumatic symptoms. The choice of regimen should be determined by the clinical needs of the individual patient.

Trial registration Clinical trials NCT00245960.

INTRODUCTION

The major manifestation of psoriasis is chronic inflammation of the skin characterised by scaling and erythematous plaques that may be painful or severely pruritic.[1] Recommended treatment for the management of psoriasis includes topical treatments, ultraviolet light therapy, oral retinoids, methotrexate, ciclosporin, and biological agents.[1] In many psoriasis patients, an inflammatory arthritis develops, with a distinct clinical picture. Psoriatic arthritis is distinguished by a chronic inflammation of joints and entheses, the point at which the collagen fibres of ligaments or tendons become mineralised and integrated into bone tissue.[2] Enthesitis (the inflammation of entheses) and dactylitis or "sausage digit" (the uniform swelling of an entire digit) are frequent components of the clinical picture of psoriatic arthritis.[2] The cutaneous symptoms of psoriatic arthritis usually appear a decade or more before the joint symptoms, enthesitis, and dactylitis.[3] The disease affects men and women equally and has a worldwide distribution.[3 4] Although incidence of psoriatic arthritis is less than 1% in the general population, the prevalence of psoriatic arthritis in patients with psoriasis is estimated to be as high as 30%.[5-7] The goal of treating the arthritis component of psoriatic arthritis

Table 1 | Assessment tools

Assessment tool	Rating	End point
Physician's global assessment (PGA) of psoriasis	0 (clear, no lesions) to 5 (severe)	PGA of psoriasis of "clear" (0) or "almost clear" (1)
Psoriasis area and severity index (PASI)	0 (no lesions) to 72 (severe lesions on 100% of body)	PASI improvement ≥75% and ≥90% at weeks 12 and 24
Psoriatic arthritis response criteria (PsARC)	Improvement in 2/4 PsARC criteria; no criteria could worsen	Proportion of participants achieving PsARC at weeks 12 and 24
PGA of arthritis	0 (no arthritis activity) to 100 (severe disease)	% improvement from baseline
American College of Rheumatology (ACR) response	% reduction in tender and swollen joint counts plus 3/5 other parameters	ACR ≥20, ACR ≥50, and ACR ≥70
Enthesitis at baseline	No of tendons showing enthesitis (0-4), based on Achilles tendons and plantar fasciae bilaterally	Proportion with improvement in ≥1 tendon/ligament insertion
Dactylitis at baseline	Rate each digit 0 to 3; total score for hands and feet 0 (none) to 60 (severe)	% change from baseline based on 60 point scale

is to reduce inflammation related joint swelling and pain and to inhibit radiological progression, thereby preserving function and improving quality of life. Historically, treatment options for psoriatic arthritis have favoured non-steroidal anti-inflammatory drugs and disease modifying antirheumatic drugs. However, the literature to support the effectiveness of these agents is scant.[8] Biological agents have changed the management of psoriatic arthritis by showing clinical as well as radiographic efficacy.

Analyses of skin, joint synovium, and synovial fluid from patients with psoriasis and psoriatic arthritis have indicated that T cells and cytokines, such as tumour necrosis factor alpha, may play an important role in this disease.[4] Etanercept, a fully human tumour necrosis factor soluble receptor fusion protein that antagonises the effects of endogenous tumour necrosis factor, has been approved as a treatment option for patients with rheumatoid arthritis, juvenile idiopathic arthritis, and ankylosing spondylitis, as well as both moderate to severe plaque psoriasis and active psoriatic arthritis.[9 10] Etanercept is approved in the European Union for the treatment of psoriasis with either intermittent (50 mg twice weekly for 12 weeks, followed by 50 mg weekly) or continuous dosing (50 mg once weekly for 24 weeks) and has a favourable safety profile with no observed dose dependent toxic effects.[9] In a double blind phase 3 trial, the exposure adjusted rates of adverse events and infections in patients treated with etanercept were similar to those for placebo in adults with psoriasis (n=618) for 96 weeks.[11] Long term evaluation of the safety of etanercept in patients with psoriasis has found no signs of dose related or cumulative toxicity over time in registry data (up to 156 weeks).[12] Moreover, etanercept treatment in patients with psoriatic arthritis has been found to be within the range of cost effectiveness estimates considered to represent value in the NHS by the National Institute for Health and Clinical Excellence.[13] Patients with this combination of skin disease and arthritis present a management challenge, as they have two serious disease manifestations. However, similarities in their pathological processes present an opportunity to use a single treatment to effectively treat both components.[9]

The aim of the PRESTA (Psoriasis Randomized Etanercept STudy in Subjects with Psoriatic Arthritis) trial was to determine the efficacy of two different etanercept regimens not previously studied in patients with both moderate to severe psoriasis and active psoriatic arthritis. In an effort to optimise patients' care, PRESTA paired dermatologists and rheumatologists in a cooperative strategy to assess the impact of etanercept treatment on both skin and arthritic manifestations.

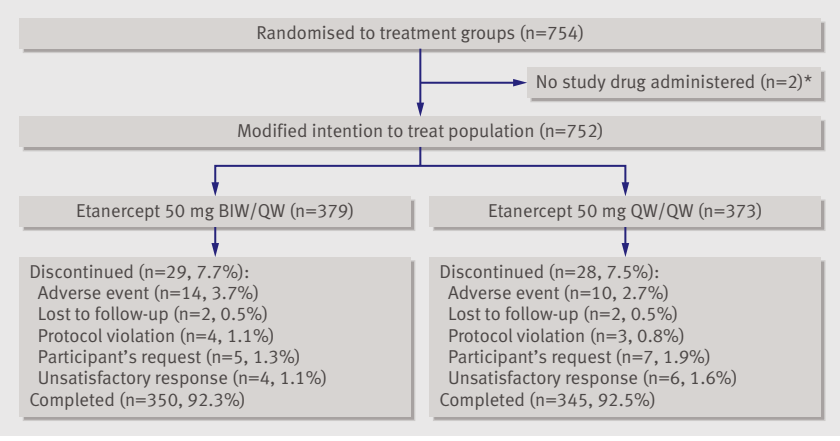

Fig 1 | Flow of participants through study. *Two patients were enrolled and had study drug dispensed but not administered; they were not included in safety or efficacy analyses. BIW=twice weekly; QW=once weekly

METHODS

Study population

Patients were eligible for this study if they were aged at least 18 with active but clinically stable plaque psoriasis involving at least 10% of the total body surface area and a physician's global assessment of psoriasis of moderate to severe at screening and at baseline. Additionally, all participants were required to have active psoriatic arthritis, defined as at least two swollen joints, at least two tender or painful joints, joint pain (including axial) for at least three months before screening, and negative serum rheumatoid factor within six months before screening. In most cases, a rheumatologist did the rheumatic assessments and diagnosed psoriatic arthritis; when this was not possible, joint evaluations were done by trained assessors. Female participants were required to have a negative pregnancy test at baseline, and all participants were required to use a medically acceptable form of contraception throughout the trial.

Patients were excluded if they had other active skin conditions that would interfere with study evaluations; a tender, swollen joint not assessed by a rheumatologist as psoriatic arthritis; severe comorbidities; recent

Table 2 | Demographics and baseline clinical data. Values are numbers (percentages) unless stated otherwise

Characteristics	Etanercept 50 mg BIW/QW (n=379)	Etanercept 50 mg QW/QW (n=373)
Mean (SD) age (years)	46 (11)	47 (11)
Male sex	243 (64)	230 (62)
White ethnicity	333 (88)	335 (90)
Mean (SD) body mass index (kg/m^2)	28 (5)	28 (6)
Mean (SD) duration of psoriasis (years)	19 (12)	19 (11)
Mean (SD) duration of psoriatic arthritis (years)	7 (7)	7 (7)
PGA-psoriasis	3.6 (0.7)	3.6 (0.7)
PASI	20 (11)	19 (10)
Mean (SD) affected body surface (% area)	31 (22)	30 (22)
Mean (SD) No of swollen joints	12 (15)	13 (15)
Mean (SD) No of tender joints	19 (18)	19 (18)
Previous methotrexate use*†	120 (32)	150 (40)
Previous topical steroids‡	218 (58)	183 (49)
Mean (SD) C reactive protein (mg/l)	15.3 (25.5)	16.2 (27.7)

BIW=twice weekly; PASI=psoriasis area and severity index; PGA=physician's global assessment; QW=once weekly.
*Within six months before screening.
†P=0.018, Fisher exact test, two tailed.
‡P=0.0.19, Fisher exact test, two tailed.

serious infection (within one month); or tuberculosis infection (appropriate screening and treatment of tuberculosis in the setting of anti-tumour necrosis factor treatment was based on guidelines of the local country). Prohibited treatments included all forms of ultraviolet light therapy, psoralen plus ultraviolet A radiation within 28 days before baseline, and ultraviolet B radiation within 14 days before baseline. Therapeutic sunbathing was prohibited from after the baseline visit to week 24 of the study. Participants were not to have received systemic psoriasis treatment, ciclosporin, or disease modifying antirheumatic drugs within 28 days before starting the study drug, with the exceptions of ≤20 mg/week of methotrexate or ≤50 mg/day of acitretin if the patient had been receiving a stable dose of either for at least eight weeks before starting the study drug. Changing the dose of either agent during the study was permitted only if required for the participant's safety. Participants were not to have used topical vitamin A or vitamin D analogue preparations or anthralin within 14 days. Topical corticosteroids of low to moderate strength, and in stable doses and formulations, were permitted only for use on the scalp, axillae, or groin. Use of any tumour necrosis factor inhibitor, including etanercept, at any time before enrolment was not permitted. Participants were not to receive an injectable corticosteroid within 28 days before screening or during the study; however, oral corticosteroids (prednisone ≤10 mg/day or equivalent) for the inflammatory arthritis were permitted as long as the dose did not change within 28 days of baseline. Non-steroidal anti-inflammatory drugs were allowed if the dose remained stable from 14 days before baseline and throughout the study.

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 participant had procedures specific to the protocol carried out until he or she had signed and dated an approved informed consent form.

Study design

Patients who had both moderate to severe plaque psoriasis and psoriatic arthritis were enrolled from 98 international sites into this randomised multicentre study. The study consisted of a 12 week double blind treatment period followed by a 12 week open label treatment period and a two week post-treatment follow-up.

We randomly assigned participants to one of two etanercept treatment regimens. In the double blind period, one group (n=379) received etanercept 50 mg administered subcutaneously twice weekly for 12 weeks and a second group (n=373) received etanercept 50 mg subcutaneously once weekly and matching placebo administered once weekly for 12 weeks. In the subsequent open label period, participants in both groups received etanercept 50 mg once weekly for 12 weeks; patients and investigators remained blinded to their treatment during the first period throughout the study. Participants who did not achieve improvement of at least one unit from baseline on the physician's global assessment of psoriasis by week 12 were deemed treatment failures and were withdrawn from the study, unless the investigator determined that the treatment was providing improvement in joint symptoms.

The primary efficacy end point of the study was the proportion of participants who achieved "clear" or "almost clear" on the physician's global assessment of psoriasis at week 12. This measure was reported on a scale of 0 to 5, with a rating of 0 indicating clear skin, 1 being almost clear, and 5 indicating severe skin symptoms. The physician's global assessment of psoriasis is considered to be similar to the evaluation methods used in clinical practice, with comparable reliability to and lower intra-rater variation than the psoriasis area and severity index.[14-16]

Secondary end points included physician's global assessment of psoriasis at week 24, as well as achievement of 75% and 90% improvement in psoriasis area and severity index, mean improvement in psoriasis

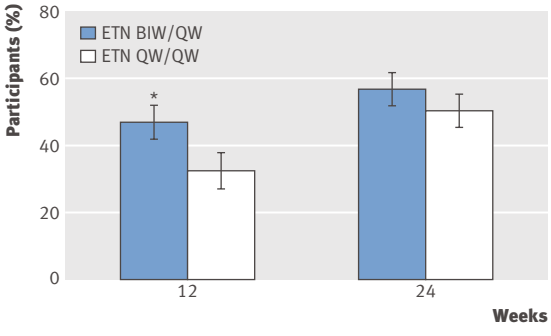

Fig 2 | Physician's global assessment of psoriasis: participants achieving "clear" or "almost clear" responses at 12 weeks (*P<0.001) and 24 weeks. BIW=twice weekly; QW=once weekly

Table 3 | Soft tissue and articular manifestations. Values are numbers (percentages, 95% CI) unless stated otherwise

	Etanercept 50 mg BIW/QW (n=379)	Etanercept 50 mg QW/QW (n=373)
Participants achieving ACR response		
ACR 20 week 12	239/360 (66.4, 61.3 to 71.3)	219/360 (60.8, 55.6 to 65.9)
ACR 20 week 24	249/361 (69.0, 63.9 to 73.7)	258/360 (71.7, 66.7 to 76.3)
ACR 50 week 12	161/360 (44.7, 39.5 to 50.0)	146/360 (40.6, 35.4 to 45.8)
ACR 50 week 24	187/361 (51.8, 46.5 to 57.1)	193/360 (53.6, 48.3 to 58.9)
ACR 70 week 12	73/360 (20.3, 16.2 to 24.8)	79/360 (21.9, 17.8 to 26.6)
ACR 70 week 24	125/361 (34.6, 29.7 to 39.8)	132/360 (36.7, 31.7 to 41.9)
Participants achieving psoriatic arthritis response criteria		
Week 12	284/371 (76.6, 71.9 to 80.8)	282/371 (76.0, 71.3 to 80.3)
Week 24	303/372 (81.5, 77.1 to 85.3)	299/372 (80.4, 76.0 to 84.3)
Enthesitis		
Enthesitis at baseline	153 (40.4)	134 (35.9)
Improved week 12	109/148 (73.7, 65.8 to 80.5)	91/130 (70.0, 61.3 to 77.7)
Improved week 24	114/141 (80.9, 73.4 to 87.0)	100/123 (81.3, 73.3 to 87.8)
Dactylitis		
Dactylitis at baseline	158 (41.7)	160 (42.9)
Mean score at baseline	7.93	8.16
Week 12:		
Mean (SD) score	2.06 (5.51)	2.52 (7.69)
Mean % change from baseline	74.3	78.4
Week 24:		
Mean (SD) score	1.42 (5.12)	1.80 (7.15)
Mean % change from baseline	84.5	84.8

ACR=American College of Rheumatology; BIW=twice weekly; QW=once weekly.

area and severity index,[17 18] psoriatic arthritis response criteria,[19] physician's global assessment of arthritis,[20] and American College of Rheumatology 20%, 50%, and 70% improvement at weeks 12 and 24[21]; reduction in number of enthesitis sites at weeks 12 and 24 compared with baseline; and the mean and percentage improvement from baseline at weeks 12 and 24 in the number of fingers and toes with dactylitis, based on a 60 point scale (table 1). Safety assessments included physical examinations, laboratory analyses, and reporting of adverse events that were collected by telephone up to two weeks after the study.

Statistical analysis

The sample size was based on response rates in earlier double blind, placebo controlled trials in patients with psoriasis. The planned enrolment of at least 400 participants per treatment group and conservative assumptions of 12% difference and 39% response rate in the 50 mg once weekly group would provide more than 90% power to demonstrate the primary comparison. We did statistical testing at α=0.05, two tailed testing, without any adjustment for multiple comparisons. We summarised descriptive statistics for continuous demographic and baseline variables. For continuous demographic characteristics of participants and baseline disease characteristics, we did between group testing with a one way analysis of variance. We used the Mantel-Haenszel χ^2 test to compare end points that measured the proportions of participants. We analysed continuous and ordinal end points by using analysis of covariance stratified by geographical region and using baseline as covariate or analysis of variance if the baseline value was not available.

The modified intention to treat population included all randomised participants who took at least one dose of the test drug and had at least one post-baseline efficacy evaluation. We did efficacy and safety analyses on the modified intention to treat population. Two additional patients were enrolled and had study drug dispensed, but the drug was not administered, and they were not included in the safety or efficacy analyses. Efficacy analyses used the last observation carried forward method for imputation of missing data. We used the data analysis software UNIX SAS version 9.1.3 for statistical analyses.

RESULTS

Participants' characteristics

We randomised 754 participants; 752 participants (379 in the etanercept 50 mg twice weekly/once weekly group and 373 in the etanercept 50 mg once weekly/once weekly group) comprised the modified intention to treat population and 92% (695) completed the study (fig 1). Baseline demographic and disease characteristics were balanced between treatment groups (table 2). Participants had a mean age of 46.5 years. Most participants were men (473/752; 63%), and most were white (668/752; 89%). The mean duration of psoriasis was 18.9 years, and the mean duration of psoriatic arthritis was 7.0 years. In general, the extent and severity of arthritic and psoriatic symptoms were similar across treatment groups. Rheumatologists diagnosed the psoriatic arthritis and did the rheumatic assessments 92% of the time; when this was not possible, joint evaluations were done by trained assessors (6%) or by dermatologists (2%). The mean doses of etanercept over 24 weeks were 74.6 (SD 11.4) mg in the twice weekly/once weekly group and 50.0 (4.7) mg in the once weekly/once weekly group. Mean concentrations of C reactive protein were high at baseline in both groups (15.3 (SD 25.5) mg/l in the twice weekly/once weekly group and 16.2 (27.7) mg/l in the once weekly/once weekly group). No statistically significant differences existed

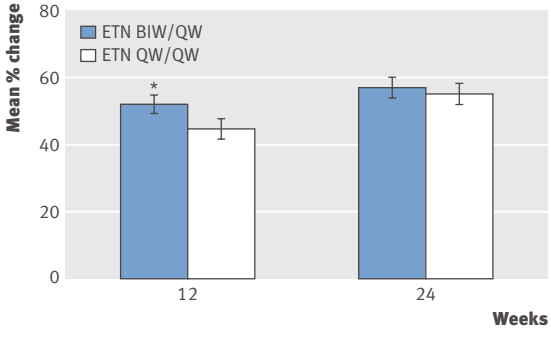

Fig 3 | Physician's global assessment of psoriasis: mean percentage improvement from baseline at 12 weeks (*P<0.001) and 24 weeks. BIW=twice weekly; QW=once weekly

Table 4 | Disease characteristics in participants with and without enthesitis at baseline. Values are mean (SD) score; percentage improvement

	Etanercept 50 mg BIW/QW		Etanercept 50 mg QW/QW	
	Enthesitis at baseline	No enthesitis at baseline	Enthesitis at baseline	No enthesitis at baseline
Physician's global assessment of psoriasis				
Baseline	3.75** (0.69)	3.49 (0.63)	3.72* (0.68)	3.56 (0.64)
Week 12	1.70 (0.92); 54.7	1.69 (0.96); 51.4	1.94 (0.92); 47.7	1.99 (0.93); 44.2
Week 24	1.48 (0.97); 60.4	1.45 (0.97); 58.5	1.43* (1.12); 61.6	1.59 (0.90); 55.2
Psoriasis area and severity index				
Baseline	21.63** (12.06)	18.56 (9.53)	19.97 (10.61)	18.47 (9.25)
Week 12	5.26 (5.60); 75.6	5.57 (5.74); 70.0	6.98 (6.44); 65.4	6.89 (5.83); 62.4
Week 24	3.40 (4.15); 84.0	3.88 (5.09); 79.2	4.38 (6.49); 78.1	4.38 (4.80); 76.1
Physician's global assessment of arthritis				
Baseline	57.56** (20.19)	45.85 (19.89)	55.13** (20.86)	46.95 (20.31)
Week 12	23.03* (21.09); 59.7	15.20 (16.87); 66.8	22.89 (21.15); 58.6	16.83 (15.82); 64.3
Week 24	14.80 (19.16); 73.8	10.48 (12.79); 77.0	15.58* (17.72); 71.7	10.43 (13.24); 78.0
Painful joints				
Baseline	28.34** (21.05)	12.75 (11.54)	28.43** (21.40)	14.03 (12.33)
Week 12	13.23 (18.48); 53.2	5.06 (7.23); 60.7	13.70* (18.03); 51.9	5.29 (7.42); 62.5
Week 24	9.12 (16.24); 67.5	3.79 (6.77); 70.7	8.71 (15.20); 69.2	3.53 (6.82); 74.7
Swollen joints				
Baseline	18.17** (19.92)	7.73 (7.55)	19.48** (20.35)	9.03 (8.97)
Week 12	7.28 (14.70); 60.5	2.12 (3.55); 72.7	7.85 (14.79); 59.7	2.58 (3.93); 71.5
Week 24	4.77 (12.69); 73.6	1.35 (3.25); 83.9	4.42 (10.49); 77.8	1.68 (3.36); 81.1
C reactive protein				
Baseline	16.17 (26.16)	14.88 (24.97)	17.34 (22.79)	15.52 (29.76)
Week 12	5.29 (7.12); 66.5	4.66 (2.70); 68.0	5.98 (7.43); 66.0	5.88 (8.55); 62.9
Week 24	5.13 (4.77); 60.6	5.76 (11.62); 59.4	5.76 (4.67); 66.6	5.60 (5.04); 61.1

*P<0.05, enthesitis versus no enthesitis within treatment arm.
**P<0.01, enthesitis versus no enthesitis within treatment arm.

between groups in the proportions of participants receiving concomitant treatment for psoriasis.

Efficacy

Skin

A significantly greater proportion of participants in the twice weekly/once weekly group (46%; 176/379) achieved a status of "clear" or "almost clear" for physician's global assessment of psoriasis at week 12 compared with those in the once weekly/once weekly group (32%; 119/373) (P<0.001) (fig 2). By week 24, the proportions were similar (56% (214/379) *v* 50% (187/373), P=0.104). The mean percentage improvement from baseline in the physician's global assessment of psoriasis at week 12 was significantly greater in the twice weekly/once weekly group than in the once weekly/once weekly group (52% *v* 45%, P<0.001). At week 24, the mean percentage improvement from baseline in physician's global assessment of psoriasis was similar for both groups (57% *v* 55%, P=0.420) (fig 3).

At week 12, the mean improvement from baseline in the psoriasis area and severity index was significantly greater in the twice weekly/once weekly group than in the once weekly/once weekly group (71% *v* 62%, P<0.001) (fig 4); however, at week 24, the change from baseline was similar in the two groups (78% *v* 74%, P=0.110). A significantly greater proportion of participants in the etanercept 50 mg twice weekly/once weekly group than in the 50 mg once weekly/once weekly group achieved at least 75% improvement in the psoriasis area and severity index (55% (207/377) *v* 36% (135/371) at week 12, P<0.001; 70% (265/377) *v* 62% (231/371) at week 24, P<0.026). The within group changes from baseline in physician's global assessment of psoriasis and psoriasis area and severity index were statistically significant at all study visits in both etanercept groups (P<0.001 for each).

Joint and tendon rheumatic manifestations

The proportions of participants who achieved American College of Rheumatology (ACR) 20, 50, and 70 responses were similar in the two groups at weeks 12 and 24. At week 24, 69% of the twice weekly/once weekly group and 72% of the once weekly/once weekly group had ACR 20 responses (P=0.379), 52% and 54% achieved ACR 50 responses (P=0.594), and 35% and 37% achieved ACR 70 responses (P=0.530) (table 3[3], fig 5). Six participants who failed to meet the inclusion criteria for active psoriatic arthritis of at least two painful and two swollen joints at baseline were excluded from this analysis. The proportions of participants who achieved psoriatic arthritis response criteria were similar in the two groups at week 12 and remained stable at week 24. At week 12, 77% in the twice weekly/once weekly group and 76% in the once weekly/once weekly group achieved psoriatic arthritis response criteria, as did 82% and 80% at week 24 (table 3). The percentage improvements from baseline in physician's global assessment of arthritis were similar in the two groups at weeks 12 and 24. At week 12, the percentage reduction in physician's global assessment of arthritis was 60% for the twice weekly/once weekly group and 62% for the once weekly/once weekly group (P=0.823); at week 24, the corresponding reductions were 73% and 74% (P=0.760).

At baseline, enthesitis was present in 287 participants and dactylitis was present in 318 participants (table 3). Participants with enthesitis at baseline had more extensive skin and joint involvement and higher C reactive protein concentrations than did those who did not present with enthesitis at baseline (table 4). The

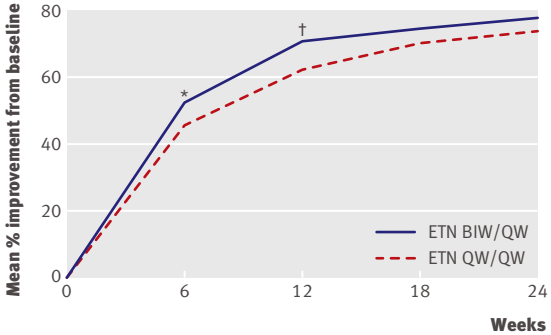

Fig 4 | Psoriasis area and severity index: mean percentage improvement from baseline. *P=0.003 at 6 weeks. †P<0.001 at 12 weeks. BIW=twice weekly; QW=once weekly

Table 5 | Safety summary. Values are numbers (percentages) unless stated otherwise

	50 mg BIW/QW (n=379)	50 mg QW/QW (n=373)	Total (n=752)	Overall P value*
Any adverse event	213 (56.2)	190 (50.9)	403 (53.6)	0.165
Serious adverse events	15 (4.0)	11 (2.9)	26 (3.5)	0.550
Death	0	0	0	—
Malignancy	3 (0.8)†	1 (0.3)‡	4 (0.5)	—
Serious infections	2 (0.5)§	3 (0.8)¶	5 (0.7)	0.684

BIW=twice weekly; QW=once weekly.
*Fisher exact test, two tailed.
†2 skin carcinomas (1 basal cell, 1 squamous cell), 1 breast carcinoma.
‡1 skin carcinoma (basal cell).
§1 fever, 1 infection.
¶1 abscess, 2 infections.

number of sites of enthesitis, determined by manual pressure on the tendon insertion, decreased from baseline in both treatment groups (table 3). Similarly, among participants with dactylitis at baseline, comparable decreases occurred in the mean number of toes and fingers with objective dactylitis in the two etanercept groups at weeks 12 and 24 (table 3).

Concomitant treatment

Only 25% of participants in this trial received concomitant methotrexate treatment; the mean dosage was 12.7 (SD 4.3) mg/week. In this subset of participants, some benefit of combination therapy was apparent at week 12 for skin but not joint symptoms and only in those who received etanercept 50 mg twice weekly during this period.

C reactive protein

Mean concentrations of C reactive protein were significantly decreased from baseline to a similar extent in both groups. Concentrations decreased from 15.3 (SD 25.5) mg/l at baseline to 5.5 (9.5) mg/l by week 24 in the 50 mg twice weekly/once weekly group and from 16.2 (27.7) mg/l to 5.7 (4.9) mg/l in the once weekly/once weekly group. Interestingly, participants who presented with enthesitis at baseline had higher C reactive protein concentrations than did those who did not have enthesitis at baseline. Baseline C reactive protein concentrations were 16.2 (26.2) mg/l in the 50 mg twice weekly/once weekly group and 17.3 (22.8) mg/l in the once weekly/once weekly group among participants with enthesitis at baseline. In participants who did not present with enthesitis, the baseline C reactive protein concentrations were 14.9 (25.0) mg/l and 15.5 (29.78) mg/l in the two groups (table 4).

Safety

Etanercept was well tolerated in both treatment groups over 24 weeks; we found no significant differences between the groups in the incidence of adverse events. The most commonly reported treatment emergent adverse events were upper respiratory tract infection, injection site reaction, pharyngitis, and headache. A total of 15 (4%) participants in the twice weekly/once weekly group and 11 (3%) in the once weekly/once weekly group reported serious adverse events, including serious infections. Five (0.7%) serious infections were reported, two (0.5%) in the twice weekly/once weekly group and three (0.8%) in the once weekly/once weekly group (table 5). No cases of tuberculosis, other opportunistic infections, or demyelinating disorders were reported. Four malignancies were reported: two skin carcinomas and one breast carcinoma in the twice weekly/once weekly group and one skin carcinoma in the once weekly/once weekly group. No participant died during the study.

DISCUSSION

In participants with active psoriasis and psoriatic arthritis, we found that initial treatment of the psoriasis with etanercept 50 mg twice weekly may allow for more rapid clearance of skin lesions than a 50 mg weekly regimen. The recommended dose regimens of etanercept for psoriasis and psoriatic arthritis are different.[9] In the European Union, the summary of product characteristics recommends that psoriasis can be treated with either 50 mg weekly or 50 mg twice weekly for 12 weeks followed by 50 mg weekly, whereas the recommended etanercept dose for psoriatic arthritis is 50 mg weekly. The greater effect of the twice weekly/once weekly regimen on skin manifestations at 12 weeks seen in this study was similar to what has been found in the treatment of psoriasis in the absence of arthritis.[22] The results also suggest that the skin manifestations may benefit from 50 mg twice weekly initially and that more than 12 weeks of treatment may be needed to achieve a maximal response—in this case 24 weeks.

The effect on skin was greater than that seen in the first study of etanercept in patients with both psoriasis and psoriatic arthritis and may reflect the lower baseline severity of psoriasis in that trial.[10] In that study, the analysis of skin improvement was done only for patients with 3% or more body surface area involvement compared with the far more severe involvement seen in the PRESTA trial, in which the mean body surface area involved was more than 30%. Demonstrating a 75% improvement in the psoriasis area and severity index may be more difficult in patients with less severe

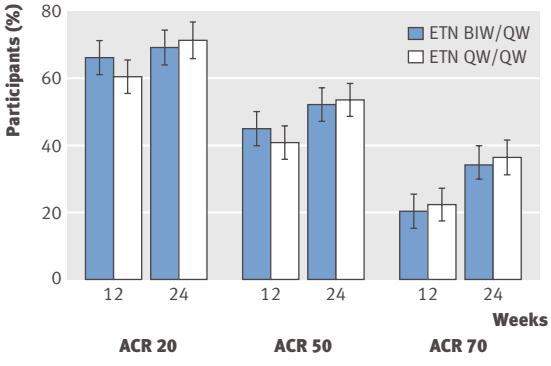

Fig 5 | Percentage of participants who achieved American College of Rheumatology 20/50/70 responses at weeks 12 and 24. ACR= American College of Rheumatology; BIW=twice weekly; QW=once weekly

WHAT IS ALREADY KNOWN ON THIS TOPIC

Dermatologists and other practitioners treating patients with plaque psoriasis are in an ideal position to screen for psoriatic arthritis and provide therapeutic management or referral

Etanercept is approved for treatment of moderate to severe plaque psoriasis and active psoriatic arthritis on the basis of its efficacy in treating both skin and joint symptoms

WHAT THIS STUDY ADDS

For patients with plaque psoriasis and psoriatic arthritis, etanercept 50 mg twice weekly was superior to 50 mg once weekly for skin manifestations at week 12 but similar for joint manifestations

Both regimens achieved significant improvement from baseline in skin, joint, and entheseal disease components at week 24 without notable differences in safety

Either etanercept dose regimen can be used in the treatment of psoriasis with or without the presence of psoriatic arthritis, allowing for individualised care

psoriasis.[18] Recent studies using similar dosing regimens in psoriasis alone support a greater and faster response with the use of etanercept 50 mg twice weekly during the first 12 weeks.[22-24] The results of the PRESTA trial suggest that 50 mg twice weekly followed by 50 mg weekly is an appropriate dose regimen for treating skin symptoms in these patients, whether or not they have concomitant psoriatic arthritis. The 50 mg twice weekly/once weekly regimen allowed for a faster cutaneous response and may be preferable in patients with more severe skin disease. On the other hand, at no time point was the twice weekly/once weekly regimen more advantageous in treating joint or tendon symptoms than the 50 mg once weekly dose regimen that is approved for psoriatic arthritis. The challenge of treating patients with both active psoriasis and active psoriatic arthritis is to optimise the treatment of both disease manifestations to give the best overall outcome.

The noteworthy improvements in psoriatic arthritis response criteria and the high percentage of participants who achieved American College of Rheumatology 20/50/70 responses were similar to the results of the original registration study using a 25 mg twice weekly regimen, suggesting that a 50 mg once weekly dose is comparable in efficacy to 25 mg twice weekly.[10] Dissociation clearly existed with regard to the optimal dosages for the skin lesions at week 12. However, when the dosage was decreased in the second 12 weeks of the trial, both skin and joint symptoms continued to improve, and the 50 mg once weekly/once weekly group achieved responses similar to those of the 50 mg twice weekly/once weekly group at week 24.

Enthesitis and dactylitis, which are clinically important components of psoriatic arthritis, improved equally well on both etanercept regimens. This study confirms previous data suggesting that patients with enthesitis have more severe disease than do those without these extra-articular problems.[25] The response to etanercept in this study is consistent with the results of a previous study that evaluated the effect of infliximab on enthesitis and dactylitis in patients with psoriatic arthritis.[26] This is the first definitive demonstration that etanercept significantly improves both of these important extra-articular disease manifestations of psoriatic arthritis, even at the lower doses commonly used to treat arthritis alone, compared with the infliximab studies in psoriatic arthritis which used the higher 5 mg/kg dosage.[26]

Under the conditions of this study, the higher dose of etanercept improved skin manifestations more rapidly than did the lower dose but did not seem to provide an additional advantage in treating joint or entheseal symptoms. The explanation for this differential effect on skin and joints is unclear. The ideal dosing for psoriatic arthritis is apparently more similar to the regimen used in rheumatoid arthritis than to that used in psoriasis. These two different organ systems may have dissimilar autoimmune inflammatory environments, allowing for differences in local concentrations of tumour necrosis factor or in disease burdens or a subtle difference in tissue penetration of drug, although little information is available to support any particular mechanism.

Although trials of anti-tumour necrosis factor agents have been done in psoriatic arthritis,[5 10 27] PRESTA is unique in its collaboration between dermatologists and rheumatologists for the evaluation of both skin and joint symptoms in this complex population. The advantage of the cooperative strategy between specialists in this trial can be supported by the consistent measurement of outcomes for both psoriasis and psoriatic arthritis compared with previous disease specific trials.

Conclusion

The results of this study indicate that, although significant differences in skin responses were seen at week 12 between the 50 mg twice weekly/once weekly and 50 mg once weekly/once weekly dosages, 50 mg weekly is a sufficient dose for treatment of joint symptoms alone. Both regimens achieved significant improvement from baseline in skin, joint, and entheseal disease components at week 24. Furthermore, these improvements were achieved without any notable differences in safety.

We thank Xuesong Zhang for assistance with statistical content, Robyn Boyle and Precise Publications for manuscript preparation, and Joanne Foehl for assistance with preparation and review of the manuscript. We also to thank the other investigators and their staff who participated in the PRESTA (study 401) study, including: A Gonda and S Szanto, Hungary; S Karpati and E Koo, Hungary; N Aste and A Mathieu, Italy; P Calzavara-Pinton and F Franceschini, Italy; G Trevisan and P Morassi, Italy; G Altomare and F Capsoni, Italy; G Girolomoni and L M Bambara, Italy; M Goitre and R Carignola, Italy; S Calvieri and G Valesini, Italy; P Lisi and R Gerli, Italy; A Katsambas and D Goules, Greece; O Mourelou and I Chatzigiannis, Greece; N Atakan and A I Ertenli, Turkey; S Philipp, Germany; J Prinz and S Schewe, Germany; K Reich and A S Everding, Germany; T Bieber and M Seidel, Germany; M Sebastian and C Holzheimer-Stock, Germany; J Norgauer and T Eidner, Germany; K G Meyer and U Reuter, Germany; G Schuler, M Sticherling (current principal investigator) and M Ronnenberg, Germany; M Schön and C Kneitz, Germany; R Kaufmann and F Behrens, Germany; J Elsner and V Waltz, Germany; T Rosenbach and W Hungerbach, Germany; C L M. Van Hees and C Bijkerk, Netherlands; P C M van de Kerkhof and M Creemers, Netherlands; P M Steijlen and R Landewe, Netherlands; E P Prens and M V van Krugten, Netherlands; M de la Brassinne and M Malaise, Belgium; J Deweert and F van de Bosch, Belgium; W Placek and N Szalwinska-Dolata, Poland; A Langner and E Wiesik-Szewczyk, Poland; M Bagot and P Claudepierre, France; J M Bonnet Blanc and P Bertin,

France; L Dubertret and F Lioté, France; G Guillet and I Azais, France; P Joly and O Vittecoq, France; G Lorette and D Mulleman, France; L Misery and A Saraux, France; J F Nicolas and J P Larbre, France; A Taieb and C Gracia, France; P Celerier and E Dernis, France; M Vuillamie and G Guaydier-Souquieres, France; R Gniadecki and K Asmussen, Denmark; G Jemec and M Sonne, Denmark; L Skov and H Slott Jensen, Germany; K E Andersen and L Ejstrup, Denmark; G Larsen and D Vendelbo, Denmark; L Paimela and M Soini, Finland; S Saari and A Similä, Finland; U Lindqvist, Sweden; G M Alenius, Sweden; S Transö, Sweden; P Foley and L Clemens, Australia; J Sullivan and P McNeil, Australia; T F Tsai and S C Hsieh, Taiwan; J C Ho and Y C Chen, Taiwan; J M Vozmediano and J Bernal, Spain; L Puig and C Diaz, Spain; M Garate and E Brito, Spain; L Borrego and A Rosas, Spain; R Vallverdu and J Maymo, Spain; J Zubizarreta Sr and J Belzunegui, Spain; M Gallego and M Crespo, Spain; M Selores, M Brandão, A Marinho and C Vasconcelos, Portugal; A Figueiredo and M J Salvador, Portugal; K Rappersberger and J Hitzelhammer, Austria; H Kerl, B Yazdani, and T Mueller, Austria; J I Youn and Y W Song, Korea; J H Choi and B Yoo, Korea; R M Trueb and D Kyburz, Switzerland; A K L So, Switzerland; E Hamada and S Al-Saleh, Saudi Arabia; A Alajlan and A R Al-Arfaj, Saudi Arabia; R Galimberti, L Cattogio, and J de la Rosa, Argentina; E Chouela, L Messina, and N Villa, Argentina; C Ramos-Remus and F J Aceves Avila, Mexico; J Barker, UK; M Rustin and H L Beynon, UK; J Berth-Jones and R Neame, UK; C Griffiths and R Benitha, UK; A Layton and B Neville, UK; T Tuomiranta and O M Kekki, Finland; A Finlay and S Smale, UK; A Ormerod and N Basu, UK; B Didona and C R Girardelli, Italy; M Majdan, M Piotrowski, B Kolarz, Z Kielbik, M Dryslewska, and J Arsznal, Poland; W Tlustochowicz, M Sulek, M Tlustochowicz, J Rojek, K Ludwiniak, and Z Samochodzki, Poland; L Kemény and G Sonkodi, Hungary; E Szepes and G Horvath, Hungary; N Bakos and T Arok, Hungary; Z Karolyi and K Fazekas, Hungary; N Damjanov, Serbia; A Dimic, Serbia; K Cobeljic, Serbia; B Bobic, Serbia; M Simon and R Haux, Germany; E Dokoupilova, Czech Republic; J Stolfa and L Šedova, Czech Republic; P Vitek, Czech Republic; H N Cabrera and H Leczycki, Argentina; C F Gatti and A Capuccio, Argentina; F Stengel and C Perandones, Argentina; R Burgos Vargas and G Huerta Sil, Mexico; R Alten and E Toppe, Germany; J Wollenhaupt and P Buck, Germany; R T Lehmann and T Hoffmann, Germany; M Fimiani and M Galeazzi, Italy; S Di Nuzzo and D Santilli, Italy; V Descamps and P Dieudé, France; H Castellanos and J F Restrepo, Colombia; E Melendez and E Forero, Colombia; M Richter, Germany.

Contributors: WS, J-PO, BK, and OB recruited and enrolled participants, collected data, and drafted the report. DR and JE designed the trial, wrote protocols for the participating institutions, interpreted the data, and drafted the report. RDP designed the trial, analysed the data, and drafted the report. CM interpreted the data, served as medical monitor during the trial, and drafted the report. All authors edited the final version of the manuscript. WS is the guarantor.

Funding: Wyeth Research, which was acquired by Pfizer in October 2009, sponsored this clinical trial and was responsible for the collection and analysis of data. The authors and the sponsor were involved in the study design, interpretation of data, manuscript preparation, and decision to publish. All statistical analyses were done by the Global Biostatistics and Programming Department of Wyeth Research.

Competing interests: WS has received fees for speaking/consulting from Abbott, Schering-Plough, Wyeth, and Janssen-Cilag. J-PO has received fees for speaking/conferences/consulting from Schering-Plough, Abbott, Merck-Serono, Centocor, Wyeth, Janssen-Cilag, MedPharma, Laboratorios Pierre-Fabre, Galderma Laboratories, and Leo Pharma. BK has served on advisory boards for Schering-Plough and Roche; has received funds for research/travel/conferences from Wyeth, Centocor, Abbott, Schering-Plough, Roche, and Bristol-Myers Squibb; and has served on a speaker panel for Bristol-Myers Squibb. OB has received fees from Wyeth, Schering-Plough, Abbott, Roche, Chugai, and Bristol-Myers Squibb. DR, RDP, JE, CM, and BF are all employees of Pfizer.

Ethical approval: 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 participants signed and dated an approved informed consent form.

Data sharing: None.

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Accepted: 16 Nov 2009