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ORIGINAL ARTICLE

Efficacy and safety of etanercept in psoriasis and psoriatic arthritis in the PRESTA study: analysis in patients from Central and Eastern Europe

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ABSTRACT

Background: Data are limited on the effectiveness of anti-TNF and other biologics on psoriatric arthritis (PsA) in Central and Eastern Europe (CEE). The objective of this analysis was to evaluate the efficacy of etanercept (ETN) in PsA patients from CEE.

Methods: In PRESTA, patients were randomized to receive ETN 50 mg BIW or 50 mg QW for 12 weeks (double-blind phase) and ETN 50 mg QW for 12 additional weeks (open label). In this analysis, only patients from Czech Republic, Hungary, Poland and Serbia were included. The primary efficacy variable was the proportion of subjects achieving a physician global assessment (PGA) of psoriasis status: "clear" or "almost clear" at week 12.

Results: In the 307 patients, 54% BIW/QW compared with 40% (QW/QW) ($p = .02$), achieved "clear"/ "almost clear" for PGA of psoriasis at week 12 increasing, to 68% and 60%, respectively ($p = .134$) by week 24. Mean improvement from baseline in PASI were 59% versus 49% ($p = .005$) at week 6 and 87% versus 81% ($p < .05$) at week 24, for the BIW/QW and QW/QW groups, respectively. ETN was well tolerated in both groups over 24 weeks.

Conclusions: Both dose regimens of ETN provided significant improvements in efficacy in PsA treatment and were well tolerated.

Introduction

Psoriatic arthritis (PsA) is a chronic, progressive, inflammatory arthropathy affecting up to 40% of patients with skin or nail psoriasis (1). If not treated adequately, joint disease in PsA can lead to irreversible bone damage resulting in compromised physical function and a reduced quality of life.

The need to treat two diseases simultaneously can make the comanagement of PsA and psoriasis challenging. The presence of elevated tumor necrosis factor (TNF) levels in both psoriatic skin lesions and synovial fluid from joints affected by PsA has led to the use of anti-TNF biologics to treat both skin and joint manifestations (2–5). Although the effectiveness of anti-TNF agents and other biologics is well established through clinical trials in the USA and Western Europe, there are relatively few data related to other parts of the world, such as Central and Eastern Europe (CEE).

In the PRESTA (Psoriasis Randomized Etanercept Study in Subjects with Psoriatic Arthritis) study, two dose regimens of etanercept (ETN) were evaluated (ETN 50 mg twice weekly [BIW] for 12 weeks followed by ETN 50 mg once weekly [QW] or ETN 50 mg QW for 24 weeks) (6). Both dose groups showed significant improvements in skin and joint symptoms and quality of life measures with no new safety signals. PRESTA was a multinational trial that included patients from countries in CEE. The objective of this subset analysis is to evaluate the efficacy of ETN therapy in patients from these countries compared with the overall study population.

Methods

Study group

The details of the PRESTA trial (Clinicaltrials.gov Identifier: NCT00245960) have been previously published (6). PRESTA was a randomized, 24-week, multicenter study enrolling adult (≥ 18 years of age) patients diagnosed with active but stable plaque psoriasis involving at least 10% of body surface area and a physician's global assessment (PGA) of psoriasis of moderate-to-severe at baseline. In addition, all patients had active PsA defined as ≥ 2 swollen joints, ≥ 2 tender joints, joint pain for ≥ 3 months and a negative serum rheumatoid factor within 6 months prior to screening. Patients were randomized to receive ETN 50 mg BIW or 50 mg QW for 12 weeks in a double-blind phase and open-label ETN 50 mg QW for 12 additional weeks. For this *post hoc* analysis, only patients who participated in PRESTA from four CEE countries (Czech Republic, Hungary, Poland and Serbia) were included.

Efficacy and safety assessments

The primary efficacy variable was the proportion of subjects who achieved a PGA of "clear" or "almost clear" at week 12. This assessment was reported on a scale ranging from 0 to 5, with 0 indicating no psoriasis (clear skin), 1 being almost clear and 5 indicating severe disease.

Secondary endpoints reported in this subset analysis included the PGA status at week 24; mean percentage improvements from baseline in PGA; psoriasis area and severity index (PASI); PGA for arthritis, painful and swollen joints; enthesitis and dactylitis at weeks 12 and 24; proportion of patients who achieved PASI 50/75/90 response; American College of Rheumatology (ACR) 20/50/70 response and Psoriatic Arthritis Response Criteria (PsARC) response at weeks 12 and 24, as well as the change in C-reactive protein (CRP) levels. Safety assessments included physical examinations, laboratory analyses and reporting of adverse events (AEs) that was collected by telephone up to two weeks after the study.

Statistical analysis

Detailed information on the statistical analyses in the PRESTA study has been described previously (7). Efficacy and safety analyses were conducted on the modified intention to treat (mITT) population, which included all randomized subjects receiving ≥ 1 dose of test drug and who had at least one postbaseline efficacy evaluation. Endpoint measurements that were based on the proportions of subjects were compared using the Mantel–Haenszel χ^2 test. Analysis of covariance (ANCOVA) models using baseline value as covariant were used for continuous and ordinal endpoints. (ANOVA was used when the baseline value was not available.) Mean percent change was calculated from the change mean divided by baseline mean. Efficacy analyses used the last-observation-carried-forward approach for missing data imputation. Statistical testing was done at $\alpha = .05$ level, two-sided testing, without any adjustment for multiple comparisons unless otherwise specified.

Results

Baseline demographics

Of the 752 patients randomized to either the ETN 50 mg BIW/QW or the ETN 50 mg QW/QW arm in the PRESTA study, 307 patients from four CEE countries (Czech Republic, $n = 51$; Hungary, $n = 107$; Poland, $n = 41$; Serbia, $n = 108$) were included in this *post hoc* analysis. Baseline demographic and disease characteristics were balanced between the two treatment groups (Table 1).

Efficacy assessments

Skin

A significantly greater proportion of participants in the BIW/QW group (54%) achieved a status of "clear" or "almost clear" for PGA of psoriasis at week 12 compared with those in the QW/QW group (40%) ($p = .02$) (Figure 1). By week 24, the proportions had increased to 68% versus 60%, respectively ($p = .134$). Mean percentage improvement from baseline in the PGA of psoriasis at week 12 was significantly greater in the BIW/QW group than in the QW/QW group (57% vs. 50%, $p = .014$). At week 24, the mean percentage improvement from baseline in PGA of psoriasis was similar for both groups (64% vs. 62%, $p = .413$) (Table 2).

At week 6, the mean improvement from baseline in PASI was significantly greater in the BIW/QW group than in the QW/QW

Table 1. Baseline demographics and disease characteristics.

Parameters	ETN 50 mg BIW/QW ($n = 153$)	ETN 50 mg QW/QW ($n = 154$)
Age, years	46.8 (11.5)	46.6 (11.1)
Female gender, n (%)	60 (39.2)	67 (43.5)
BMI, kg/m²	27.6 (4.7)	28.1 (5.6)
Duration of PsA, years	7.0 (6.8)	7.0 (6.4)
Duration of psoriasis, years	19.7 (11.8)	18.7 (12.6)
PGA of psoriasis	3.6 (0.7)	3.7 (0.6)
BSA affected by psoriasis, %	31.6 (23.1)	29.9 (22.9)
PASI	20.0 (11.2)	19.0 (9.5)
Swollen joint count	15.7 (18.4)	18.0 (18.6)
Tender joint count	23.3 (21.1)	24.5 (20.3)
Previous topical steroids, n (%)	97 (63.4)	81 (52.6)
CRP, mg/L	14.5 (24.2)	18.3 (33.6)

All values shown are means (SD) unless otherwise stated. BIW: twice weekly; BSA: body surface area; CRP: C-reactive protein; ETN: etanercept; PASI: psoriasis area and severity index; PGA: physician global assessment; PsA: psoriatic arthritis; QW: once weekly.
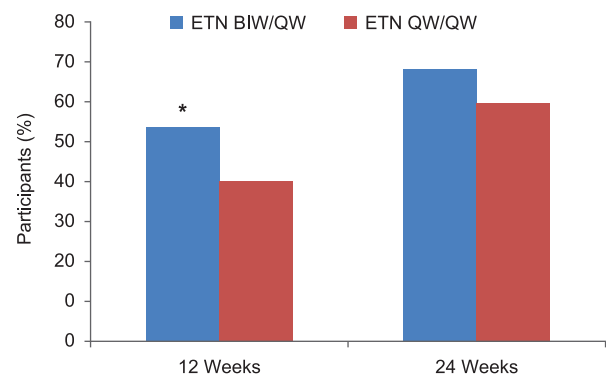

Figure 1. PGA psoriasis: participants achieving "clear" or "almost clear" responses at 12 weeks (*$p = .02$) and 24 weeks. LOCF data. BIW: twice weekly; ETN: etanercept; LOCF: last observation carried forward; PGA: physician's global assessment; QW: once weekly.

Table 2. Skin manifestations.

Parameter	ETN 50 mg BIW/QW ($n = 153$)	ETN 50 mg QW/QW ($n = 154$)	p value
PGA psoriasis, Mean score (% change from baseline)			
Baseline	3.63	3.69	.364
Week 12	1.57 (56.7)	1.85 (49.9)	.014
Week 24	1.30 (64.2)	1.43 (61.5)	.413
PASI, Mean score (% change from baseline)			
Baseline	19.99	19.01	.413
Week 12	4.34 (78.2)	6.11 (67.9)	<.001
Week 24	2.85 (85.7)	3.74 (80.3)	.036
Patients achieving PASI response			
PASI 50			
Week 12	132/151 (87.4)	125/153 (81.7)	.169
Week 24	141/151 (93.4)	138/153 (90.2)	.314
PASI 75			
Week 12	98/151 (64.9)	70/153 (45.8)	<.001
Week 24	122/151 (80.8)	110/153 (71.9)	.068
PASI 90			
Week 12	48/151 (31.8)	31/153 (20.3)	.022
Week 24	90/151 (59.6)	67/153 (43.8)	.006

LOCF data. BIW: twice weekly; ETN: etanercept; PASI: psoriasis area and severity index; PGA: physician global assessment; QW: once weekly.

group (59% vs. 49%, $p = .005$); this difference between the two groups was maintained throughout the study up to week 24 (87% vs. 81%, $p < .05$) (Figure 2). At weeks 12 and 24, significantly greater proportions of participants in the ETN 50 mg BIW/QW group than in the ETN 50 mg QW/QW group achieved at least 90% improvement in PASI; the BIW/QW regimen was also significantly more effective in helping patients attain a 75%
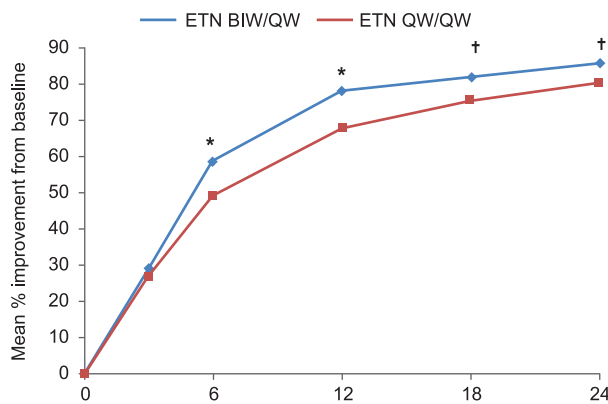
Figure 2. PASI: mean percentage improvement from baseline. LOCF data. *$p < .01$; †$p < .05$. BIW: twice weekly; ETN: etanercept; LOCF: last observation carried forward; PASI: psoriasis area and severity index; PGA: physician's global assessment; QW: once weekly.

improvement in PASI at week 12. There was no significant difference between the regimens in terms of PASI 50 response. The within-group changes from baseline in PGA of psoriasis and PASI were statistically significant at all study visits in both ETN groups ($p < .001$ for each).

Joint and tendon rheumatic manifestations
ACR 20 response at week 12 was significantly greater in the BIW/QW group (71.7%) than in the QW/QW group (59.9%) ($p = .03$), but similar between groups at week 24 (77.6% vs. 75.7%) (Table 3). The proportions of participants who achieved ACR50 and ACR70 responses were similar in the two groups at weeks 12 and 24 (Table 3).

The proportion of participants who achieved PsARC was similar in the two groups at week 12 and remained stable at week 24 (Table 3). The mean percentage improvement from baseline in PGA of arthritis was similar in both groups at weeks 12 and 24. There was no significant differences between the two ETN groups regarding the improvement from baseline in the swollen and painful joint counts, the percentage of subjects with enthesitis and the number of fingers/toes with dactylitis from the baseline and weeks 12 and 24 (Table 3). The within-group changes from baseline in PGA of arthritis and swollen and painful joint scores were statistically significant at weeks 12 and 24 in both ETN groups ($p < .001$ for all).

CRP
Decreases from baseline in mean CRP levels were similar between the two treatment regimens and significant within each group. Concentrations decreased from 14.5 (SD 24.2) mg/L at baseline to 5.0 (4.7) mg/L by week 24 in the 50 mg BIW/QW group ($p < .001$) and from 18.3 (33.6) mg/L to 5.4 (4.5) mg/L ($p < .001$) in the QW/QW group.

Safety assessments
ETN was well tolerated in both treatment groups over 24 weeks. Lower AE rates were observed in both treatment groups compared to the overall PRESTA population; AEs were experienced in a higher proportion of patients in the BIW/QW group (36.6%) than the QW/QW group (24.7%) ($p = .026$); corresponding values in the total cohort were 56.2% in the BIW/QW group and 50.9% in the QW/QW group. The most commonly reported treatment-emergent adverse events ($\geq$5% in either treatment group) were upper respiratory tract infection, injection site reaction and pharyngitis; none of these was significantly different between treatment groups.

Table 3. Joint and tendon rheumatic manifestations.

Parameter	ETN 50 mg BIW/QW ($n = 153$)	ETN 50 mg QW/QW ($n = 154$)	p value
Patients achieving ACR response, n (%)			
ACR 20			
Week 12	109/152 (71.7)	91/152 (59.9)	.030
Week 24	118/152 (77.6)	115/152 (75.7)	.685
ACR 50			
Week 12	71/152 (46.7)	56/152 (36.8)	.082
Week 24	90/152 (59.2)	91/152 (59.9)	.907
ACR 70			
Week 12	33/152 (21.7)	29/152 (19.1)	.570
Week 24	60/152 (39.5)	58/152 (38.2)	.814
Patients achieving PsARC, n (%)			
Week 12	126/153 (82.4)	117/154 (76.0)	.170
Week 24	131/153 (85.6)	128/154 (83.1)	.546
PGA arthritis, Mean score (% change from baseline)			
Baseline	53.82	55.80	.396
Week 12	19.55 (63.6)	21.65 (61.2)	.489
Week 24	13.69 (74.6)	14.23 (74.6)	.962
Painful joints, Mean score (% change from baseline)			
Baseline	23.25	24.50	.600
Week 12	9.63 (58.8)	11.50 (53.3)	.350
Week 24	6.59 (71.8)	7.10 (71.2)	.946
Swollen joints, Mean score (% change from baseline)			
Baseline	15.69	18.01	.275
Week 12	5.81 (63.2)	7.50 (58.6)	.607
Week 24	3.98 (74.8)	3.82 (78.9)	.412
Patients reporting enthesitis, n (%)			
Baseline	74/153 (48.4)	69/154 (44.8)	.532
Week 12	25/151 (16.6)	32/150 (21.3)	.291
Week 24	16/146 (11.0)	15/148 (10.1)	.818
Patients with dactylitis >0 (total number of fingers and toes)			
	$N = 61$	$N = 74$	
Baseline	4.7 (5.6)	4.7 (5.6)	–
Week 12	1.8 (4.2)	2.1 (4.8)	–
Week 24	1.5 (4.5)	1.5 (4.7)	–

LOCF data. ACR: American College of Rheumatology; BIW: twice weekly; ETN: etanercept; PGA: physician global assessment; PsARC: Psoriatic Arthritis Response Criteria; QW: once weekly.

A total of 13 (8%) patients in the BIW/QW group and five (3%) in the QW/QW group reported serious adverse events, including serious infections. Two (0.7%) serious infections were reported, both (1.3%) in the QW/QW group. One malignancy, a breast carcinoma in the BIW/QW group, was reported. No cases of tuberculosis, other opportunistic infections, or demyelinating disorders were reported and no participant died during the study.

Discussion
The effectiveness of ETN in the treatment of PsA, including the inhibition of radiographic disease progression, has been previously reported in a number of randomized clinical trials and observational studies. In this subset analysis of the PRESTA trial, we evaluated the efficacy and safety of two different ETN (4,8,9) regimens in subjects from CEE with both moderate-to-severe psoriasis and active PsA. Overall, baseline demographics and disease characteristics were similar in the CEE population and the total PRESTA cohort, although the swollen and tender joint counts appeared to be higher in CEE subjects. While both ETN 50 mg BIW/QW and 50 mg QW/QW regimens significantly improved skin manifestations of psoriasis, the twice-weekly regimen had a significantly greater effect on the physician global assessment of psoriasis (at week 12) and PASI75 and PASI90 responses than the once-weekly treatment. Improvement from baseline in PASI was significantly greater in the BIW/QW group than in the QW/QW group after six weeks of treatment and this difference between regimens was maintained up to week 24. These findings are similar to those

reported for the overall PRESTA study although a significant difference between the two regimens was observed up to week 12 in the total population.

Both ETN regimens achieved improvements from baseline in various joint components. However, apart from ACR 20 response at week 12, there were no significant differences between treatment groups in effects on joint manifestations: ACR50 and ACR70 responses were similar in the BIW/QW and QW/QW groups, as were swollen and painful joint scores and levels of enthesitis and dactylitis. Improvement observed in PsARC was also similar with both regimens.

These findings are similar to those of the overall PRESTA study. In 754 patients randomized at 98 sites worldwide, ETN 50 mg administered twice weekly provided greater improvement in skin outcomes than once-weekly administration but similar effects on joint outcomes. Further analyses have shown that the beneficial effects of ETN on skin and joint manifestations have enhanced the quality of life of patients with PsA. Both ETN 50 mg BIW/QW and 50 mg QW/QW have been shown to provide sustained improvements in skin-related, patient-reported health outcomes within three weeks of commencing therapy (10). ETN treatment also resulted in reductions in the time taken off sick and job responsibility changes due to disease (11).

Overall, both ETN regimens were safe and well tolerated. Reported adverse event rates in patients from CEE were lower than those reported in the total PRESTA population (6). The explanation for this difference is not readily apparent. Unlike in the overall study, the proportion of patients experiencing adverse events was significantly higher in the BIW/QW group than the QW/QW group.

Evidence suggests that RA patients are generally in poorer health in CEE countries than in Western European countries, and one possible cause is the slower and more restricted utility of biological treatments. Data indicate that uptake of biologics for the treatment of RA is markedly lower in CEE countries (1–5% of patients) than in Western Europe (11–12%) (12), and it is reasonable to suppose that a similar if not greater disparity exists for the management of PsA. Concerns have also been raised about the substantial variability across CEE countries in access to biologic therapy for the treatment of inflammatory bowel disease (13). The limited use of biologics in CEE has been attributed not only to varying economic conditions across geographical locations but also to other determining factors, such as restrictive national clinical guidelines, administrative obstacles and availability of care (12).

Overall, there continues to be a shortage of data on the utility of TNFα inhibitors for the management of inflammatory rheumatic diseases in CEE populations. While some progress has been made in certain countries, the paucity of published data is still concerning. With the lack of clinical analyses and health economic evaluations the management of PsA remains a major issue (14). In view of the large gaps in basic information, there is an urgent need to perform more studies focusing specifically on CEE populations or post hoc analyses of larger multinational trials such as reported here.

In conclusion, the study in PsA patients from CEE demonstrated that both ETN dose regimens provided significant improvements in treatment efficacy without new safety signals. Clinical improvement in skin manifestations occurred earlier and was greater in those patients receiving ETN 50 mg BIW/QW compared with patients receiving 50 mg QW/QW. Both treatments were well tolerated. These data suggest that ETN is effective for the treatment of PsA in populations from regions where prior data are limited and will improve the quality of treatment of these patients. We hope that our findings help to address the dearth of information on the efficacy and safety of TNFα inhibitors in the management of PsA in CEE and ensure that treatment recommendations for the use of biologic drugs in PsA in CEE are allowed to be based on evidence-based decision making, rather than limited by financial constraints.

Disclosure statement

Funding

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