CLINICAL REPORT

Etanercept Reduces Symptoms and Severity of Psoriasis After Cessation of Cyclosporine Therapy: Results of the SCORE Study

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Cyclosporine is an established therapy for psoriasis that provides rapid relief of symptoms but has long-term toxic side effects. The objective of this study was to demonstrate the efficacy of etanercept as replacement therapy for cyclosporine in patients with moderate-to-severe plaque psoriasis. Patients with plaque psoriasis were given cyclosporine 5 mg/kg/day until achievement of PASI 50 at which point cyclosporine was tapered to 0 over 6 weeks. At week 6, patients were randomised (1:1) to receive etanercept (50 mg/week) or placebo for an additional 24 weeks. Patients in the etanercept group ($n = 58$) experienced a reduction of –1.1 in mean PASI score ($p = 0.233$ vs. cyclosporine) at week 30; patients in the placebo group ($n = 62$) had mean PASI increase of 3.7 ($p < 0.001$ vs. cyclosporine). The incidence of patients reporting any adverse events was not significant between groups (77% etanercept, 74% placebo; $p = 0.675$). Etanercept demonstrated higher efficacy and good tolerability as replacement therapy for cyclosporine in plaque psoriasis. *Key words: psoriasis; tumour necrosis factor; etanercept; cyclosporine.*

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Psoriasis is a chronic, immune-mediated, inflammatory disease that manifests in the skin and/or joints affecting 1–3% of the general population (1, 2). Psoriasis impacts the physical, psychological, and social dimensions of life and may be associated with diabetes, heart disease, and depression (3, 4). Current treatment options consist of topical corticosteroids and other topical agents, phototherapy, conventional systemic therapies, and biologic drugs. As psoriasis requires lifelong treatment, optimal treatment strategies include a rapid relief of symptoms that have long-term sustainability and high tolerability. Combination, rotational, and sequential treatment strategies with traditional, biologic, and topical therapies are used in attempts to achieve these optimal outcomes (4–6).

Historically, cyclosporine was chosen for psoriasis treatment because of its ability to rapidly relieve symptoms of moderate-to-severe cases; however, long-term use became associated with toxic side effects, including renal dysfunction, hypertension, and lymphoproliferative disorders, which led to recommendations that cyclosporine use be limited to 2 years (7, 8). Physicians capitalise on the rapid response seen with cyclosporine treatment by using it as initial therapy until symptoms are relieved; once outcomes are obtained, they transfer patients to alternative therapies to maintain long-term efficacy, thus reducing the risk of toxic side effects of long-term cyclosporine use (7, 8).

Etanercept, a fully human fusion tumour necrosis factor (TNF) soluble receptor, inhibits the TNF-mediated inflammatory response and is indicated for the treatment of chronic plaque and psoriatic arthritis. Preliminary data have shown that etanercept allows for tapering of other psoriasis medications (9–12). In addition, etanercept has been shown to be safe and effective when used in combination with traditional anti-psoriatic therapies (11, 13, 14).

Here, we report the results of the Sustained Cyclosporine Outcome Replacing Etanercept (SCORE) trial.

METHODS

Study population

Individuals were included in this study if they were aged 18–70 years and had stable plaque psoriasis involving ≥10% of body surface area or minimum Psoriasis Area and Severity Index (PASI) score of 10. Women were excluded if they were pregnant or intended to become pregnant during the study or if any patients had skin conditions other than psoriasis (e.g. eczema) that would interfere with evaluations of the effect of study medication on psoriasis. Additional exclusion criteria included treatment with any other systemic anti-psoriatic therapy or disease-modifying antirheumatic drug within 28 days of screening. Systemic therapy such as vitamin A analogues and phototherapy, were excluded within 28 days of screening and; topical therapies, such as steroids, vitamin D analogues, or anthralin were excluded within 14 days of screening. Exceptions included topical steroids no higher than moderate strength for the scalp, axillae, and groin. Prior exposure to any TNF inhibitor or efalizumab was prohibited.

Study design

Patients across 22 sites in Germany, Greece, Italy, Malta, and Spain were enrolled in this randomised double-blind study that

was conducted from October 2007 to November 2009. This study consisted of a 6-week, open-label, lead-in period, followed by a 24-week double-blind treatment period and a 2-week follow-up phase (32 weeks total). Study 0881A6-410; NCT00581555.

Patients who met the inclusion criteria were treated with open-label cyclosporine (5 mg/kg/day) until they achieved PASI 50 or until week 6, whichever occurred first. At the time PASI 50 was achieved, cyclosporine was reduced by 1 mg/kg every 2 weeks to a final dose of 2 mg/kg/day for 2 weeks and then terminated (6 weeks total) in line with the international consensus statement for the use of cyclosporine in the management of psoriasis (7). Patients who did not achieve PASI 50 by week 6 were discontinued from the study. At week 6, PASI 50 responders were blinded and randomised 1:1 to etanercept (50 mg/week) or placebo for 24 weeks (Fig. S1[1]). Patients received blinded etanercept/placebo treatment without cyclosporine for 18 weeks. End of treatment was defined as the last dose of study drug after 24 weeks of etanercept treatment (week 30), and end of study was defined as the last visit at week 32.

The landmark assessment of efficacy occurred after 24 weeks of etanercept treatment (week 30). The primary efficacy endpoint of this study was the mean change in PASI score from randomisation (week 6) to week 30 after 24 weeks of etanercept/placebo treatment. Secondary efficacy endpoints included the PASI area under the curve (AUC), change in physician global assessment (PGA), percent improvement of PASI score, and change in Dermatology Life Quality Index (DLQI) from randomisation (week 6) to end of treatment (week 30). The percentage of disease relapse or loss of PASI 50, achievement of PASI 75, and time to relapse during the 24 weeks of treatment was also assessed.

Patients were monitored throughout the study by physical examinations and laboratory measurements for adverse events (AEs). Specific safety assessments included monitoring of treatment-emergent AEs and rebound effects (worsening of psoriasis to 125% of baseline PASI or the appearance of psoriasis variants, such as erythrodermic or pustular psoriasis, within 12 weeks of discontinuation of therapy).

This study was conducted in compliance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guidelines, and all applicable local/country specific regulations. Prior to the start of the study, independent ethics committees or institutional review boards in each country reviewed and approved this study, and written and informed consent were received from all patients.

Statistical analyses

Efficacy analyses were performed on the intent-to-treat (ITT) population defined as all randomised patients. Continuous baseline demographic and clinical characteristic variables were summarised by treatment arm using descriptive statistics. Between-group comparisons for continuous variables were assessed using unpaired *t*-test or Mann-Whitney *U*-test. Between-group comparisons for categorical variables were assessed using Pearson's chi-square or Fisher exact test.

Analyses of the primary and secondary endpoints utilised a linear mixed model using an autoregressive correlation with treatment group, visit, and interaction treatment by visit as fixed factors, patients as a random factor, and baseline as a covariate. Comparison of the 2 treatment arms at each visit was reported using the appropriate contrasts. The proportion of patients achieving PASI 75 and the proportion of patients who had PGA of clear/almost clear were analysed using a logistic model with

treatment group, visit, and interaction treatment by visit as fixed factors, with missing responses replaced by the last observed response (last observation carried forward). The time to first relapse was estimated using Kaplan-Meier method; comparisons between treatment arms were tested with a log-rank test. All statistical tests were two-sided at a significance level of 0.05.

The safety data were based on a safety population defined as all patients who received at least 1 dose of study medication. AEs were classified by investigators according to the Medical Dictionary for Regulatory Activities, and listings and summary tabulations were generated. TEAEs were defined as events reported during the treatment-emergent period (between screening and 14 days after the last treatment was administered) that were not present prior to treatment or as an event that was present before treatment but became more severe during the treatment-emergent period.

RESULTS

Patient disposition and baseline characteristics

Of the 153 patients enrolled at baseline, 120 (78.4%) responded to cyclosporine therapy (PASI 50) and were randomised at week 6 to receive study medication. A total of 31 (20.3%) patients were not randomised due to lack of achievement of PASI 50 within 6 weeks, and 2 (1.3%) patients withdrew due to AEs prior to week 6 (Fig. 1). Of those randomised at week 6, 48.3% (58/120) were treated with etanercept and 51.7% (62/120) received placebo. The majority of withdrawals (*n* = 63) were due to subject request or withdrawal of consent (9 etanercept; 18 placebo), lack of efficacy (2 etanercept; 10 placebo), AEs (3 etanercept; 4 placebo), and other reasons (6 etanercept; 11 placebo).

Patient demographics and baseline characteristics were comparable across treatment groups with no significant differences between groups (Table I). The majority of patients were men (etanercept 65.5%; placebo 72.6%). The mean age was 41.8 (range 36–48) years in the etanercept group and 41.5 (range 31–58) years in the placebo group. Mean and standard error (SE) PASI baseline score was 20.2 (1.8) and 19.4 (1.5) in the etanercept and placebo groups, respectively. Patients had mean DLQI (SE) total score of 11.2 (1.0) and 11.3 (0.8), respectively, suggesting reduced quality of life (QoL) at baseline due to skin disease (15, 16).

Efficacy

After tapering of cyclosporine at week 12 (6 weeks of randomised concomitant treatment), mean change from baseline in PASI was –4.3 [95% confidence interval (CI): –5.9; –2.8; *p* < 0.001 vs. randomisation] in the etanercept group and –3.2 (95% CI: –4.8; –1.6; *p* < 0.001 vs. randomisation) in the placebo group, with no significant difference between the groups. At week 30, after treatment with cyclosporine followed by 24 weeks of etanercept, patients had a non-significant reduction of mean change in PASI score to –1.1 (95% CI: –2.8, 0.7; *p* = 0.233 vs.
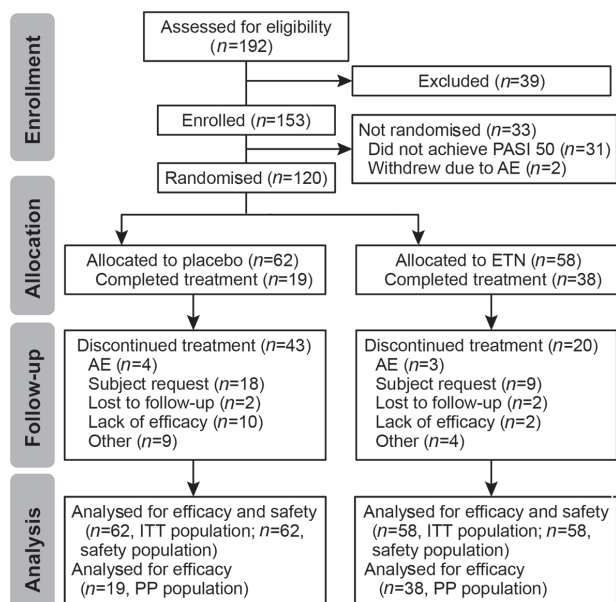
Fig. 1. Patient disposition. AE: adverse event; ETN: etanercept; ITT: intent to treat; PASI: Psoriasis Area and Severity Index; PP: per protocol.

randomisation). Treatment with cyclosporine followed by 24 weeks of placebo resulted in a significant increase in mean PASI score to 3.7 (95% CI: 1.9, 5.5; $p<0.001$ vs. randomisation). The difference in mean change between treatment arms was –4.8, which was statistically significant (95% CI: –7.3, –2.3; $p<0.001$).

Mean PASI AUC represents the mean psoriasis activity of all patients at any given time point, indicated as the smaller the AUC, the less severe the psoriasis and subsequently the more effective the treatment. Therefore, a greater (negative) mean change between time points represents a larger improvement in psoriasis activity. At week 30 after 24 weeks of etanercept treatment, the mean (SE) AUC increased to 27.7 (5.5), whereas treatment with placebo resulted in an increase to 83.5 (5.3), indicating that etanercept exhibited a sustained therapy response after initial cyclosporine treatment. The significant difference in mean change between arms was –55.8 (95% CI: –70.8, –40.8; $p<0.001$), indicating the superiority of etanercept treatment vs. placebo. These results indicate that etanercept therapy maintained the clinical response achieved by initial cyclosporine use.

Etanercept was significantly superior in the treatment of psoriasis as measured by the percent increase in PASI scores from baseline to week 30 compared with placebo (5.3% etanercept vs.123.5% placebo; $p<0.001$; Table I). At week 6 (randomisation) and week 12 (cessation of cyclosporine), PASI 75 was 29.3% and 89.7% in the etanercept group and 38.7% and 75.8% in the placebo group, respectively, which were not significant between groups at either time point. At week 30, PASI 75 was achieved in 60.3% and 32.3% of patients in the etanercept and placebo groups, respectively ($p=0.002$; Table I). In the etanercept group, 11/17 patients (64.7%) who had PASI 75 at randomisation maintained PASI 75 at week 30 compared with 12/24 (50.0%) patients in the placebo group ($p=0.352$).

The mean (SE) PGA was 2.9 (0.1) and 3.2 (0.1) at week 30 for the etanercept and placebo groups, respectively, for a mean (SE) increase of 0.5 (0.2) and 0.9 (0.2). Differences in mean change were not statistically significant (95% CI: –1.0, 0.2; $p=0.176$; Table I). The proportion of patients who had a PGA of clear/almost clear at week 30 was 13.8% in the etanercept group and 4.8% in the placebo group ($p=0.103$).

At baseline, patients in both the etanercept and placebo groups had a severely affected QoL due to their psoriasis. At week 12, mean (SE) DLQI was similar in the etanercept group compared with placebo [1.0 (0.7) vs. 2.0 (0.7); $p=0.511$], indicating a small effect on QoL in both groups. Mean (SE) DLQI scores at week 30 in the etanercept and placebo arms were 4.5 (0.7) and 7.3 (0.7) for a significant difference of –2.8 (95% CI: –4.7, –0.9; $p=0.004$). The difference in mean change of DLQI scores was –2.8 but did not reach statistical significance (95% CI: –5.8, 0.2; $p=0.069$; Table I).

The proportion of patients who met the criteria for relapse (loss of 50% improvement in PASI score) was significantly lower for patients who transitioned from cyclosporine to etanercept (25 patients; 43%) compared with those who transitioned to placebo (44 patients; 71%; $p=0.002$). Time to relapse was faster for patients treated with placebo compared with those treated with etanercept ($p<0.001$; Fig. 2). All efficacy analyses were also conducted in the per-protocol (PP) population, which included all patients who completed

Table I. *Efficacy parameters by treatment group; last observation carried forward (intent-to-treat and safety population;* n = *120)*

Efficacy parameters	Etanercept ($n=58$)				Placebo ($n=62$)			
	Baseline	Week 6[a]	Week 12[b]	Week 30	Baseline	Week 6[a]	Week 12[b]	Week 30
PASI score, mean (SE)	20.2 (1.8)	3.4 (1.5)	1.8 (0.6)	5.0 (0.6)	19.4 (1.5)	5.2 (1.0)	2.4 (0.6)	9.3 (0.6)
PASI 75, %		29.3	89.7	60.3[c]		38.7	75.8	32.3
PASI area under the curve, mean (SE)			4.4 (5.4)	27.7 (5.5)			6.7 (5.3)	83.5 (5.3)
% increase in PASI, mean (SE)		–14.0 (46.3)	–65.6 (20.1)	12.4 (20.7)		–15.0 (31.2)	–57.4 (20.0)	127.5 (20.3)
Physician global assessment, mean (SE)	4.3 (0.2)	2.2 (0.4)	1.7 (0.1)	2.9 (0.1)	4.1 (0.1)	2.5 (0.2)	1.9 (0.1)	3.2 (0.1)
DLQI total score, mean (SE)	11.2 (1.0)	1.9 (1.9)	1.0 (0.7)	4.5 (0.7)	11.3 (0.8)	1.5 (1.2)	2.0 (0.7)	7.3 (0.7)

[a]Randomisation, [b]Cyclosporine cessation. [c]$p<0.01$ versus placebo at the same time point.
DLQI: dermatology life quality index; PASI: psoriasis area and severity index; SE: standard error.

study treatment and did not deviate from study protocol during the double-blind phase of the study. Results of the PP population analysis were consistent with those of the ITT population.

Safety

Etanercept was well tolerated with the overall incidence of patients reporting at least 1 AE not significant compared with placebo [43/58 (74.1%) etanercept; 48/62 (77.4%) placebo; $p = 0.675$]. Treatment-emergent AEs were lower in the etanercept (25.9%) arm compared with placebo (35.3%); the most commonly reported (in ≥ 10% of system organ class) were infections, nervous system disorders, and vascular disorders in 5.2%, 13.8%, and 5.2% of the etanercept group and 17.7%, 14.5%, and 11.3% in the placebo group, respectively. Skin disorders were more frequent in those treated with etanercept (17.2%) compared with placebo (9.7%).

Overall, 7 patients (5.8%) discontinued from the blinded portion of the study after randomisation due to AEs [3 (5.2%) etanercept 4 (6.5%) placebo]; 2 patients withdrew due to AEs prior to randomisation during which they received open-label cyclosporine. AEs cited for discontinuation in the etanercept arm were aggravated psoriasis, increased blood creatinine, and inborn error of bilirubin metabolism nitric oxide synthase. Exacerbation of psoriasis, increased blood creatinine, severe hypertension, and chronic prostatitis were AEs cited for discontinuation in the placebo arm. Serious AEs were reported by 2 patients in the etanercept arm (3.4%; tonsillitis and bronchial carcinoma) and by 1 patient in the placebo arm (1.6%; benign prostatic hyperplasia). No serious AEs were deemed to be related to the study drugs and no deaths occurred during this study.

DISCUSSION

The objective of this trial was to demonstrate that in patients with moderate to severe plaque psoriasis eligible for systemic therapy, etanercept, first in combination, then in monotherapy, was able to allow successful tapering of cyclosporine until cessation with sustained efficacy and safety.

The findings from this study demonstrated etanercept as an effective and safe alternative for the treatment of moderate-to-severe psoriasis in patients who had an adequate response to cyclosporine monotherapy.

Traditional systemic anti-psoriatic drugs like cyclosporine have a desirable fast onset with high efficacy. Unfortunately, they are associated with organ toxicities (e.g. nephrotoxicity) that limit dosage and duration (7, 8). There is a risk of exacerbation of psoriasis when breaking therapy to begin a new treatment regimen, and therefore continuous therapy with overlapping treatment is the ideal transition regimen (7). Organ toxicities of TNF antagonists usually are not significant, and combination use with traditional anti-psoriatic systemic therapies does not cause a limiting increase of such toxicities. Potential side effects that cause most concern with combination therapy are infections and carcinogenesis; however, for the short duration of combined treatment needed to bridge a gap to a new therapy, carcinogenesis is very unlikely.

Previous case reports, case series, and open-label trials in patients with psoriasis and/or psoriatic arthritis have evaluated the combined use of etanercept and traditional anti-psoriatic therapies (cyclosporine, methotrexate, and acitretin) with good treatment response and comparable rates of AEs (9, 13, 14, 17, 18). These previous reports further confirm the findings of this clinical trial that the use of etanercept is a safe and effective alternative for uninterrupted transitioning from a traditional therapy while maintaining treatment response.

A limitation to this study is the modest number of patients who were enrolled in the trial and the substantial number of patients who discontinued, especially among those enrolled in the placebo arm. After randomisation, 52.5% (63/120) discontinued prior to the end of the study with 34.5% (20/58) and 69.4% (43/62) in the etanercept and placebo arms, respectively. The majority of discontinuations in the etanercept group were due to subject request or withdrawal of consent and other followed by AEs and lack of efficacy, similar to
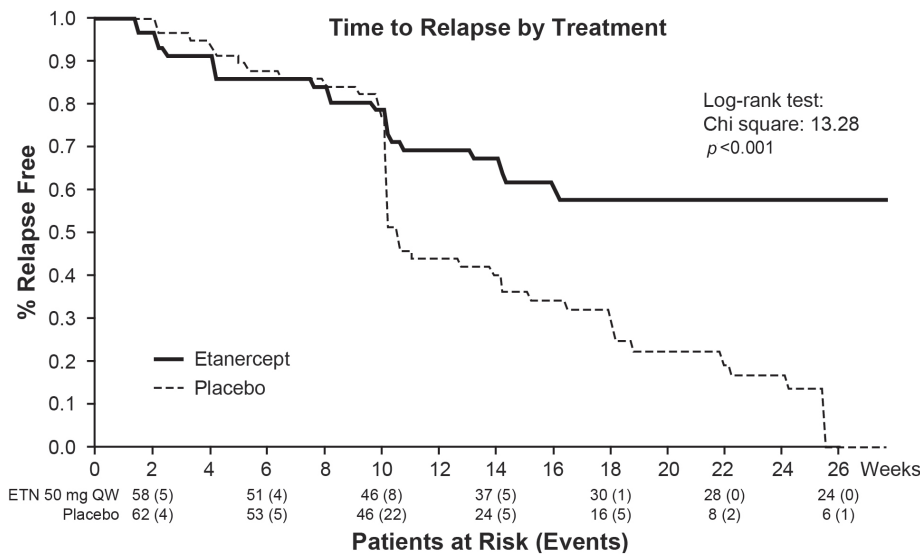

Fig. 2. Time to relapse (loss of 50% improvement in PASI). PASI: Psoriasis Area and Severity Index.

other anti-TNF clinical trials for the treatment of psoriasis. The majority of discontinuations in the placebo group were due to subject request or withdrawal of consent, other, and lack of efficacy, followed by AEs. These discontinuations should be compared with the occurrence of relapses in the placebo arm after the completion of the cyclosporine tapering phase and mirror the efficacy results obtained with other etanercept/placebo trials in psoriasis. Results in this trial were obtained over a treatment period of 24 weeks, which is in line with the labelling instructions for use of etanercept in psoriasis, whereas time to full benefit may vary between patients (19). This study was designed for a course of cyclosporine of at least 12 weeks in both the etanercept and placebo arms for ethical reasons and in accordance with the consensus statement for cyclosporine use in psoriasis (7). Although combination use of etanercept and cyclosporine was short in this clinical trial (6 weeks), the duration was sufficient enough for etanercept therapy to take effect prior to cyclosporine cessation and protect against a psoriasis rebound while transitioning. In individual cases, a prolonged duration of combination etanercept and cyclosporine therapy may be advantageous in avoiding a rebound of disease as Yamauchi & Lowe (17) previously observed.

This study explores for the first time in a clinical trial setting the possibility to induce a clinical and meaningful response with cyclosporine maintained through replacement with etanercept in responder subjects. To avoid the disadvantages of long-term cyclosporine therapy, initial treatment with cyclosporine overlapped with etanercept therapy may be an effective alternative in daily practice, especially for refractory types of psoriasis. This study documented statistically significant differences between etanercept and placebo in the maintenance of a clinical response previously achieved with cyclosporine. Based on these results, patients with moderate-to-severe plaque psoriasis can be treated effectively and safely with etanercept as replacement therapy for cyclosporine, thus reducing the risk of threatening adverse effects linked to cyclosporine use.

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