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 ORIGINAL ARTICLE

Evaluation of Patient-Reported Outcomes With Etanercept in Moderate to Severe Plaque Psoriasis Patients After Therapy With Apremilast

Jerry Bagel MD DO,[a] Bradley S. Stolshek PharmD,[b] Yue Yang PhD,[b] Gregory Kricorian MD DO,[b] and Leon H. Kircik MD[c]

[a]Psoriasis Treatment Center of Central New Jersey, East Windsor, NJ
[b]Amgen Inc., Thousand Oaks, CA
[c]Icahn School of Medicine, Mount Sinai, New York, NY; Indiana Medical Center, Indianapolis, IN; Physicians Skin Care, PLLC; DermResearch, PLLC, Louisville, KY

ABSTRACT

Background: Patients with moderate-to-severe psoriasis can have symptoms resulting in significant impact on patient-reported outcomes (PROs). The effect of etanercept (ETN) in moderate-to-severe psoriasis patients who previously received apremilast (APR) was studied, including impact on PRO endpoints.

Methods: In this multicenter, open-label, single-arm, phase 4 estimation study, patients with moderate-to-severe psoriasis who did not have adequate response to APR in the opinion of the investigator received ETN 50mg subcutaneous (SC) twice weekly for 12 weeks, followed by ETN 50mg SC once weekly for an additional 12 weeks. Analysis was conducted for PROs directly and by the Psoriasis Area and Severity Index (PASI) achievement thresholds.

Results: Of the 80 patients enrolled, the Psoriasis Symptom Inventory (PSI; total and individual items) had substantial improvement at weeks 12 and 24. Improvement in PSI total score (percent; mean [SD]) in patients who achieved PASI 50, -75, and -90 at week 12 was 57% (30), 67% (24), and 83% (18), respectively and at week 24 was 56% (40), 68% (29), and 80% (25). DLQI responders by PASI 50, -75, and 90 achievements were 69%, 68%, and 90%, respectively, at week 12 and 68%, 77%, and 82% at week 24. The percent of patients reported being "very satisfied" or "satisfied" with treatment at week 12 was 79%, 81%, and 100%, respectively, and at week 24 was 77%, 86%, and 88%.

Conclusion: Patient-reported symptoms are important outcomes to consider in psoriasis management. ETN provided benefits in patients who did not have adequate response with APR, with improvements seen in both psoriasis symptoms and patient impact.

Clinical Trial Number: NCT02749370

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INTRODUCTION

Psoriasis is a chronic, inflammatory disease primarily affecting the skin and has been historically known to impact quality of life. Patients with uncontrolled psoriasis can experience substantial clinical symptoms leading to reduced functioning and activity that can be measured by patient-reported outcomes (PROs). Specifically, PROs in psoriasis can assess the symptoms, impact, and satisfaction experienced by a patient. Previous studies have correlated clinical measures, including the Psoriasis Area and Severity Index (PASI) and the static Physician Global Assessment (sPGA), with PROs such as the Dermatology Life Quality Index (DLQI).[1,2,3]

A recently published report described the primary and key secondary outcomes of a phase 4 study assessing the efficacy of etanercept in patients with moderate-to-severe plaque psoriasis who did not achieve or lost adequate clinical response or had intolerability to apremilast, in the opinion of the investigator.[4] In this study, PASI 75 was achieved in 42% and 46% of etanercept patients at weeks 12 and 24, respectively while PASI 90 was achieved in 13% and 22% of patients at weeks 12 and 24, respectively. In addition, the majority of patients reported favorable PROs—66% and 57% were DLQI responders (5-point improvement in DLQI from baseline or score of 0) and 61% and 53% were satisfied/very satisfied with their psoriasis treatment at weeks 12 and 24, respectively. In addition, mean Psoriasis Symptom Inventory (PSI) scores meaningfully improved from 17 at baseline to 9 and 10 at weeks 12 and 24, respectively.

The PSI was developed in accordance with the US Food and Drug Administration guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282) and measures the severity of psoriasis signs and symptoms. Briefly, the PSI is an eight-item questionnaire assessing itch, redness, scaling, burning, stinging, cracking, flaking, and pain.[5,6,7] It has been used in both clinical trials[8,9] and clinical practice.[10,11]

Here we report the full results from the PROs and post-hoc analyses to determine the effect of etanercept treatment on PROs by PASI achievement category (i.e., PASI 50, PASI 75, and PASI 90).

METHODS

Study Design

This was a multicenter, open-label, single-arm, phase 4 estimation study in patients with moderate-to-severe plaque psoriasis who did not have adequate response to apremilast. The study design has been described previously.[4] Briefly, patients received etanercept 50 mg subcutaneously (SC) twice weekly for 12 weeks, followed by etanercept 50 mg SC once weekly for an additional 12 weeks. A copy of the protocol proposed informed consent form, other written patient information, and any proposed advertising material were submitted to the Institutional Review Board/Independent Ethics Committee at each center for written approval; all patients provided informed consent before the study.

Study Population

Patients were enrolled in the study if they were at least 18 years of age; had moderate to severe plaque psoriasis (with involved body surface area [BSA] ≥10%, PASI ≥10, and static Physician Global Assessment (sPGA) ≥3 at screening and baseline); and had failed therapy with apremilast for moderate to severe plaque psoriasis, defined as, in the opinion of the investigator, either (1) failure to achieve adequate clinical response, (2) loss of adequate clinical response, or (3) intolerability to apremilast. At least 10 and no more than 20 patients could be enrolled for intolerability. In addition, patients were either currently receiving apremilast or had discontinued apremilast within 3 months before screening and had received at least 4 weeks of apremilast therapy (in patients who qualified by efficacy failure). Patients also were negative for hepatitis B and C, had no known history of tuberculosis, had a negative test for tuberculosis at screening, and had a negative serum pregnancy test ≤4 weeks before etanercept treatment.

Exclusion criteria have been described previously.[4] Briefly, patients were excluded from this study if they had active skin conditions at screening that interfered with evaluations of the treatment effect on psoriasis; active malignancy within 5 years of the first dose of etanercept; history of alcoholic hepatitis, nonalcoholic steatohepatitis, hepatitis B, hepatitis C, or immunodeficiency syndromes; active infection for which anti-infectives were indicated within 4 weeks before the first dose of etanercept; or serious infection requiring hospitalization or intravenous anti-infectives within 8 weeks before screening. Patients were excluded for the following medications: (1) UVB light, topical cyclosporine, a vitamin A or D analog, calcineurin inhibitor, or topical steroids within 2 weeks before the first dose of etanercept; (2) UVA light, oral retinoids, intravenous or oral calcineurin inhibitors, anthralin, systemic psoriasis therapy, cyclophosphamide, sulfasalazine, or methotrexate within 4 weeks before the first dose of etanercept; (3) a biologic agent for psoriasis with either no satisfactory response or a clinically significant adverse event; (4) an interleukin-12/23 inhibitor within 6 months or other biologic therapies for psoriasis within 3 months before the first dose of etanercept; or (5) a biologic agent for psoriasis after discontinuing apremilast.

Outcome Measures

The PROs that were utilized in this analysis included the PSI (total and individual items) at baseline and weeks 12 and 24, as well as over time (at baseline and weeks 1, 2, 3, 4, 8, 12, 16, 20, and 24), the DLQI responder analysis at weeks 12 and 24 and the 'patient assessment of treatment satisfaction' at baseline and weeks 12 and 24.

The PSI is an 8-item questionnaire assessing itch, redness, scaling, burning, stinging, cracking, flaking, and pain. Each item ranges from 0 (not at all severe) to 4 (very severe), for a total score ranging from 0 to 32 (higher scores indicate more severe disease). The PSI has a 7-day recall. The DLQI is a skin-specific, 10-item questionnaire used to evaluate health-related quality of life (HRQoL). Each question ranges in score from 0 to 3, for a total score ranging from 0 (no impact of skin disease on quality of life) to 30 (maximum impact on quality of life). DLQI responders experienced a 5-point improvement or reported a score of 0. The patient assessment of treatment satisfaction is a single item 5-point scale that ranges from "very dissatisfied" to "very satisfied" to indicate a patient's level of satisfaction with control of psoriasis from therapy. Patient satisfaction was based on the percent of patients indicating they were "satisfied" or "very satisfied."

PROs were evaluated based on mean percent improvement in PSI total and item scores, percent of patients who were DLQI responders, and percent of patients who reported being "very satisfied" or "satisfied" with their psoriasis treatment at weeks 12 and 24. Post-hoc analyses evaluated PRO responses according to PASI achievement categories—PASI 50, PASI 75, and PASI 90—at each respective week—12 and 24. Percent of greatest change observed from baseline (i.e., normalized to highest mean percent of improvement) in PASI and PSI was also assessed.

Statistical Analyses

All efficacy and PRO endpoints were analyzed in patients who received at least one dose of etanercept during the study. Missing values were imputed using last observation carried forward method (LOCF). Summary statistics and 95% confidence intervals (CIs) were generated.

RESULTS

Patient Characteristics

A total of 80 patients (all received ETN) enrolled in this study; 60 due to apremilast efficacy failure (primary [n = 45] or secondary [n = 15]) and 20 because of apremilast intolerability (Table 1). Sixty-six patients (82.5%) completed the study, with 14 patients (17.5%) discontinuing. Overall, 41% of patients were female and 75% Caucasian; mean (SD) age was 50 (15) years and BMI was 30 (6). Mean (min – max) duration of psoriasis was 16 (1 – 62) years.

Efficacy

At week 12, 54 (70.1%), 32 (41.6%), and 10 (13.0%) of patients achieved PASI 50, PASI 75, and PASI 90, respectively. By week 24, 48 (62.3%), 35 (45.5%), and 17 (22.1%) of patients achieved PASI 50, PASI 75, and PASI 90, respectively.

DLQI and Satisfaction Scores

Among patients who achieved PASI 50, PASI 75, and PASI 90, 69.2%, 67.7%, and 90.0%, respectively, were DLQI responders at week 12 and 68.1%, 77.1%, and 82.4%, respectively, were DLQI responders at week 24 (Table 2). Among patients who achieved PASI 50, PASI 75, and PASI 90, 78.9%, 80.7%, and 100.0%, respectively, at week 12 and 77%, 86%, and 88%, respectively, at week 24 reported being "very satisfied" or "satisfied" with treatment (Table 2).

PSI Scores

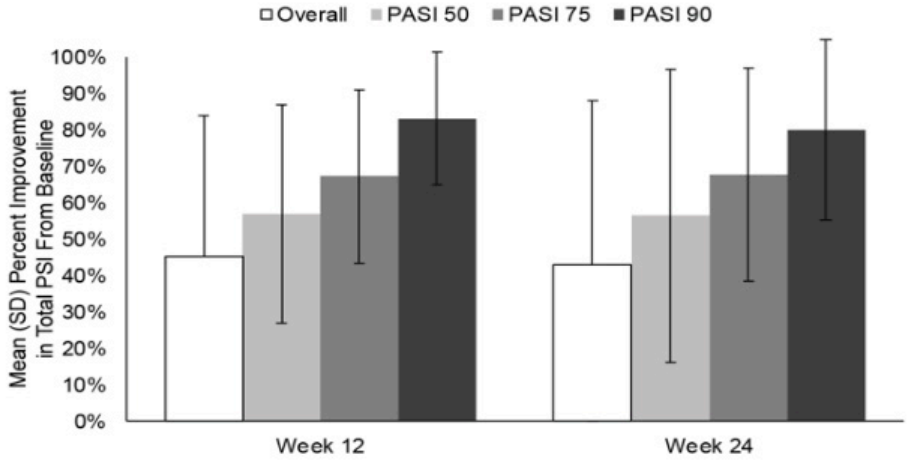
Among patients who achieved PASI 50, PASI 75, and PASI 90 at week 12, baseline PSI total scores mean (SD) percent were 15.8% (6.3), 15.3% (6.8), and 14.8% (6.3), respectively. PSI total score mean (SD) percent improvement at week 12 was 45.1% (39.0), 57.0% (30.1), 67.2% (23.7), and 83.1% (18.3) in the overall study population and patients who achieved PASI 50, 75, and 90, respectively (Figure 1). At week 24, percent improvement was

TABLE 1.

Mean Volume Injected per Treatment Area at Visit 1 (Day 0)	
Characteristic	**Etanercept 50 mg twice weekly / 50 mg once weekly N = 80**
Sex (female), n (%)	33 (41.3)
Race (white), n (%)	60 (75.0)
Age (years), mean (SD)	50.4 (14.8)
BMI (kg/m2), mean (SD)	30.4 (6.3)
PASI, mean (SD)	16.4 (13.8)
BSA, mean (SD)	16.4 (10.5)
sPGA, n (%)	
0	0 (0.0)
1	0 (0.0)
2	0 (0.0)
3	51 (63.8)
4	28 (35.0)
5	1 (1.3)
DLQI, mean (SD)	12.5 (7.4)
PSI, mean (SD)	16.6 (6.6)
Patient assessment of treatment satisfaction	
Very dissatisfied	33 (41.3)
Dissatisfied	13 (16.3)
Neither satisfied nor dissatisfied	30 (37.5)
Satisfied	4 (5.0)
Very satisfied	0 (0.0)
History of psoriatic arthritis (yes), n (%)	27 (33.8)
Duration of psoriasis (years), mean (SD)	16.4 (14.4)

BMI Body mass index; BSA Body surface area; DLQI Dermatology Life Quality Index; PASI Psoriasis Area Severity Index; PSI Psoriasis Symptom Inventory; SD Standard deviation; sPGA static Physician Global Assessment

FIGURE 1. Mean percent improvement in PSI total scores from baseline in overall study population and by PASI achievement through weeks 12 and 24.

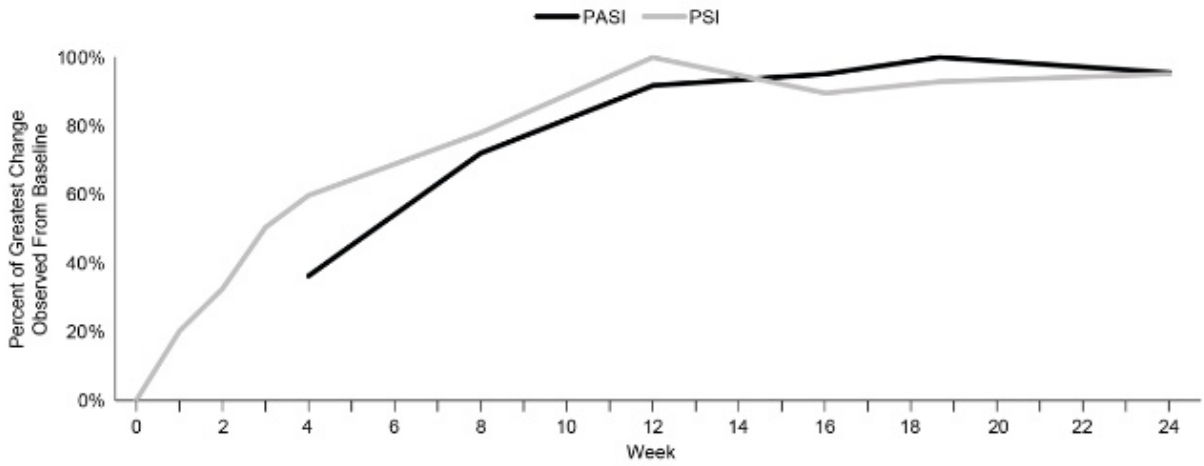


PASI: Psoriasis Area and Severity Index; SD: Standard deviation

42.9% (45.3), 56.4% (40.1), 67.7% (29.3), and 80.1% (24.7) in the overall study population and patients who achieved PASI 50, 75, and 90, respectively (Figure 1). Among the overall study population, the percent of greatest change observed from baseline in PASI and PSI followed similar patterns (Figure 2); however, the PSI appeared to improve more rapidly than PASI clinical outcome score during etanercept treatment.

For individual PSI item scores, mean (SD) percent improvement across each of the 8 items was similar to PSI total score at the different levels of PASI achievement. Among patients who achieved PASI 50, PASI 75, and PASI 90, itch improved by 57.9% (39.9), 72.0% (28.2), and 89.8 (15.5) at week 12 and 50.2% (46.0), 59.8% (38.3), and 74.0% (26.3) at week 24, respectively. Redness improved by 55.5% (32.6), 61.3% (31.6), and 82.4% (18.4) at week

FIGURE 2. Percent of greatest change observed from baseline in PASI and PSI over time.



PASI: Psoriasis Area and Severity Index; PSI: Psoriasis Symptom Inventory

TABLE 2.

DLQI Responders and Patient Satisfaction by PASI Achievement						
	Week 12			Week 24		
PRO, %*	PASI 50	PASI 75	PASI 90	PASI 50	PASI 75	PASI 90
DLQI Responder	69.2	67.7	90.0	68.1	77.1	82.4
Patient Satisfaction†	78.9	80.7	100.0	76.6	85.7	88.2
Very Satisfied	40.4	61.3	80.0	46.8	57.1	58.8
Satisfied	38.5	19.4	20.0	29.8	28.6	29.4

TABLE 3.

Improvement in PSI Total Score by PSI Item						
	Percent Improvement in PSI Total Score; % (SD)					
	Week 12			Week 24		
PSI Item	PASI 50	PASI 75	PASI 90	PASI 50	PASI 75	PASI 90
Itch	57.9 (39.9)	72.0 (28.2)	89.8 (15.5)	50.2 (46.0)	59.8 (38.3)	74.0 (26.3)
Redness	55.5 (32.6)	61.3 (31.6)	82.4 (18.4)	56.8 (36.2)	62.9 (37.8)	73.5 (35.3)
Scaling	54.6 (31.5)	59.9 (30.8)	86.7 (18.5)	61.8 (37.0)	68.1 (33.7)	79.4 (27.5)
Burning	47.0 (49.0)	52.8 (45.5)	50.0 (47.1)	44.8 (51.6)	50.8 (54.1)	50.0 (51.6)
Stinging	50.2 (46.6)	51.9 (47.7)	55.0 (49.7)	40.9 (48.3)	43.9 (46.0)	50.0 (50.0)
Cracking	50.9 (55.8)	66.7 (52.4)	83.3 (32.4)	52.1 (62.1)	71.0 (38.2)	80.9 (35.3)
Flaking	54.9 (40.5)	64.6 (36.6)	85.0 (21.1)	55.9 (43.8)	69.0 (36.0)	86.3 (23.9)
Pain	52.0 (50.7)	60.2 (45.7)	76.7 (41.7)	42.8 (61.1)	57.8 (47.2)	59.4 (49.1)

PASI Psoriasis Area Severity Index; PSI Psoriasis Symptom Inventory; SD Standard deviation

12 and 56.8% (36.2), 62.9% (37.8), and 73.5% (35.3) at week 24, respectively. Pain improved by 52.0% (50.7), 60.2% (45.7), and 76.7% (41.7) at week 12 and 42.8% (61.1), 57.8% (47.2), and 59.4% (49.1) at week 24, respectively. A similar pattern of response was seen across the other items of the PSI (Table 3).

DISCUSSION

Patient-reported symptoms and their impact on quality of life are important outcomes in psoriasis management and treatment. In this open-label study of patients with moderate-to-severe plaque psoriasis who had received apremilast but did not have adequate response in the opinion of the investigator, meaningful improvements were achieved in the PRO measures of PSI, DLQI and patient satisfaction at weeks 12 and 24 of etanercept therapy. In addition, a correlation was observed between the degree of PRO improvement and higher levels of PASI achievement for those patients who achieved PASI 50, 75, or 90 when treated with etanercept 50 mg SC twice weekly for 12 weeks followed by 50 mg SC once weekly for an additional 12 weeks. Patients who achieved PASI 50 and above experienced greater improvement in signs and symptoms of psoriasis measured by the PSI than in the overall study population. PSI total score mean (SD) percent improvement at week 12 was 45.1% (39.0) in the overall study population and 57.0% (30.1) among patients who achieved PASI 50. The degree of PSI improvement tended to rise with the level of PASI response from PASI 50 to PASI 75 to PASI 90. This finding was consistent across each of the 8 individual PSI component scores and improvements were observed in all signs and symptoms measured by the PSI. Additionally, PSI appeared to respond more rapidly to etanercept treatment than clinical outcomes using the PASI. Of note, PSI responses were similar at weeks 12 and 24, even as the etanercept dosing decreased from twice weekly to once weekly between weeks 12 and 24.

The majority of patients had an improvement in PRO response on DLQI and satisfaction at PASI 50 at weeks 12 and 24. Nearly 70% of patients who achieved PASI 50 were DLQI responders and nearly 80% of those who achieved PASI 50 were either very satisfied or satisfied with their treatment. Consistent with the PSI responses, DLQI improvement increased with higher levels of PASI response. Patients receiving etanercept tended to experience a greater degree of improvement by patient-reported satisfaction than by the clinical measure of PASI. These results highlight the importance of coupling PROs with clinical assessments.

Psoriasis is a multifactorial disease associated with predominant skin symptoms but also potential comorbid conditions characterized by chronic inflammation, cardiovascular disease, diabetes mellitus, hypertension and psychosocial impacts. Advancements in the understanding of psoriasis has led to development of new therapies. Along with these advancements, PRO measures including HRQoL have become increasingly important when determining treatment effectiveness, with impairments to HRQoL representing a large part of the patient's disease burden. National survey findings report that the majority of patients with psoriasis experience emotional as well as physical symptoms, with 63% reporting that psoriasis negatively impacts their emotional well-being. Therefore, a key component to treatment effectiveness should be assessing symptom impacts and satisfaction through PROs in conjunction with the degree of clinical response. Indeed, this recognition has led to acknowledgement and greater emphasis placed on HRQoL assessments during the design of current clinical studies where HRQoL tools such as the PSI, DLQI), and Psoriasis Symptoms and Sign Diary (PSSD) are utilized.

While the negative impact of psoriasis on a patients' PROs is well documented, the relationship between the degree of improvement in psoriasis and PROs has not always been clear. Unlike other autoimmune conditions, psoriasis may have a disproportionally larger negative effect on the patient's mental health and PROs due to its visible presentation and outward appearance, which may help explain some of the inconsistencies between PRO and PASI assessments. Several studies have demonstrated that the correlation between PROs and PASI was not always high. This suggests that developing a comprehensive patient care plan by coupling PRO and clinical measures may more accurately capture therapy effectiveness in assessing the full spectrum of the patient's well-being.

Strengths and Limitations

The single-arm, open-label nature of this phase 4 study as well as the small sample size may limit the interpretations that can be made from these findings.

One of the major strengths of this analysis is demonstrating that the patient's perspective on their symptoms via PRO instruments can be considered in evaluating the treatment effect along with traditional clinical measures.

CONCLUSION

This study found that patients with moderate-to-severe psoriasis who received etanercept therapy after not adequately responding to apremilast, experienced meaningful improvements in symptoms and quality of life as assessed by PRO measurements, including PSI, DLQI and patient assessment of treatment satisfaction. Furthermore, PROs tended to increase with the level of PASI response. Patient-reported improvements in psoriasis and satisfaction with psoriasis treatment should be considered along with traditional clinical measures when assessing patients.

DISCLOSURES

JB, Clinical Trials- Amgen, Celgene, SUN, Eli-Lilly, Novartis,

Janssen, BMS, Abbvie, LEO, Pfizer, Dermavant, BI, Ortho-Dermatologic. Speaker- Abbvie, Celgene, Novartis, Eli-Lilly, Janssen, Ortho-Dermatologic.

BS, YY, and GK are employees of Amgen and own shares of Amgen.

LK has served either as an investigator, speaker, consultant or advisory board member for Amgen, BMS, Celgene, Novartis, Eli Lilly, BI, Abbvie, Pfizer, Ortho Dermatologic, Leo, Sun, Dermavant, Arcutis, Janssen.

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Data Sharing Statement: Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/

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AUTHOR CORRESPONDENCE

Jerry Bagel MD
E-mail:..... dreamacres1@aol.com