ORIGINAL ARTICLE

Improvements in patient-reported outcomes in patients with psoriasis receiving etanercept plus topical therapies: results from REFINE

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Abstract

Background The REFINE study examined the efficacy and safety of adding topical corticosteroid therapy to etanercept when stepping down from the initial dose of etanercept to the maintenance dose. Clinical responses were shown to be similar in patients who remained on etanercept 50 mg twice weekly (BIW) and those who received etanercept 50 mg once weekly (QW) plus topical therapies through week 24.

Objective The purpose of this analysis was to evaluate the effect of treatment on health-related quality of life (HRQoL) for patients in REFINE.

Methods All patients received etanercept 50 mg BIW for 12 weeks and were then randomized to etanercept 50 mg BIW or etanercept 50 mg QW plus topical corticosteroid as required to clear through week 24. HRQoL measures included the Dermatology Life Quality Index (DLQI), Treatment Satisfaction Questionnaire for Medication (TSQM) and the Economic Implications of Psoriasis Patient Questionnaire. No comparative testing was performed for this descriptive analysis. Missing data were imputed using the last observation carried forward.

Results For 287 randomized patients (144 etanercept; 143 etanercept plus topical), the mean change [standard deviation (SD)] in DLQI from baseline to week 24 was 10.7 (7.8) for etanercept and 9.9 (6.9) for etanercept plus topical. Mean change (SD) in TSQM effectiveness, convenience, side-effects and global satisfaction was 27.1 (36.1), 14.8 (25.9), −0.7 (22.0) and 26.7 (32.5) for the etanercept arm and 32.5 (40.3), 18.5 (29.0), 1.3 (19.4) and 28.4 (35.9) for etanercept plus topical. Economic implications, including healthcare visits, employment status, work productivity, ability to perform daily activities and out-of-pocket expenses were similar between treatment arms.

Conclusion At week 24 of REFINE, measures of HRQoL were numerically similar in patients who stayed on etanercept 50 mg BIW and patients who received etanercept 50 mg QW plus topical therapies.

Conflicts of Interest

K.A.P. has done consulting work for AbbVie Inc., Akros Pharma Inc., Amgen Inc., Astellas Pharma Inc., Baxter Healthcare Corp., Boehringer Ingelheim Ltd., Celgene Corp., Centocor Ortho Biotech, Inc., Cipher Pharmaceuticals, Inc., Eli Lilly and Co., Forward Pharma A/S, Galderma S.A., Genentech, Inc., Gilead, Isotechnika Pharma Inc., Janssen Biotech, Inc., Kataka, Kyowa Hakko USA, Inc., LEO Pharma Inc., Merck & Co., Novartis AG, Pfizer Inc., Regeneron Pharmaceuticals, Inc., Stiefel Laboratories, Inc., Takeda Pharmaceutical Co. Ltd, UCB, Vertex Pharmaceuticals Inc., Wyeth Inc. and Xoma Corp. K.B. has served as a consultant/advisory board member for or has received research grants or speaker honoraria from AbbVie Inc., Actelion Pharmaceuticals Ltd., Amgen Inc., Galderma S.A., Janssen Biotech, Inc., LEO Pharma Inc., Eli Lilly and Co., Novartis AG, Pfizer Inc. and Valeant Pharmaceuticals International, Inc. R.B. has been an investigator, advisory board member, consultant and/or speaker and has received grants and/or honoraria from AbbVie Inc., Amgen Inc., Novartis AG, Janssen Biotech, Inc., Pfizer Inc., Tribute Pharmaceuticals Canada Inc., Eli Lilly and Co., Merck & Co., Astellas Pharma

Introduction

Etanercept is a tumour necrosis factor (TNF) blocker that is approved for the treatment of moderate to severe plaque psoriasis and other autoimmune diseases.[1] The recommended initial dose of etanercept for adult patients with psoriasis is 50 mg administered twice weekly (BIW) 3 or 4 days apart for 12 weeks followed by a maintenance dose of 50 mg once weekly (QW). REFINE, the Randomized, blinded assessor study to Evaluate the efFIcacy and safety of etanercept 50 mg QW plus as Needed topical agent vs. Etanercept 50 mg BIW in patients with moderate to severe plaque psoriasis, was designed to evaluate the efficacy and safety of adding topical corticosteroid therapy as required to clear to etanercept when patients step down from the initial dose to the maintenance dose. Results from REFINE showed that response to etanercept, as measured by improvements in Psoriasis Area and Severity Index (PASI), was similar in patients who used topical therapies as required to clear with etanercept at 50 mg QW and those who received etanercept at 50 mg BIW.[2]

Patient-reported outcomes (PROs) are commonly used in clinical trials to understand the patient's perspective. PROs can be used to assess health-related quality of life (HRQoL), impacts and burdens of disease and treatment satisfaction. In patients with moderate to severe plaque psoriasis, PRO measures generally correlate with clinical outcomes.[3,4] We now report the results of PROs used to measure HRQoL using the Dermatology Life Quality Index (DLQI),[5] treatment satisfaction using the Treatment Satisfaction Questionnaire for Medication (TSQM)[6] and health resources utilization (HRU) using the Economic Implications of Psoriasis Patient Questionnaire[7] for patients enrolled in REFINE.

Materials and methods

Study design
REFINE was a phase 3b, multicentre, open-label study and has been described previously.[2] Briefly, all patients enrolled in the study received etanercept 50 mg BIW for the first 12 weeks of the study. Patients were then randomized (1:1) to either remain on etanercept 50 mg BIW or to etanercept 50 mg QW with topical therapies used as required to achieve a static physician global assessment of 0 (clear) or 1 (almost clear) for an additional 12 weeks. Topical agents included hydrocortisone 2.5%, beta-methasone valerate 0.1%, betamethasone dipropionate 0.05%, clobetasol 0.05%, calcitriol, or calcipotriol plus betamethasone dipropionate 0.05% and were selected by the investigator. Change in topical agent was allowed.

Patients
To be eligible, patients had stable moderate to severe plaque psoriasis for $\geq$ 6 months, psoriasis-affected body surface area (BSA) $\geq$ 10%, PASI score $\geq$ 10, and qualified as a candidate for systemic therapy or phototherapy. Patients could not have guttate, erythrodermic or pustular psoriasis or significant concurrent medical conditions.

Outcome measures
For this analysis, PRO measures included the DLQI, the TSQM and the Economic Implications of Psoriasis Patient Questionnaire. The DLQI is a validated, 10-question, self-reported questionnaire to evaluate the patient's perception of the impact of psoriasis on HRQoL.[5] The DLQI is rated on a 4-point Likert scale (0 = not at all to 3 = very much). The highest possible total score for the DLQI is 30, and higher scores indicate more severe impact on HRQoL. The TSQM is a validated measure of the major dimensions of patients' satisfaction with medicine.[6] The TSQM comprises 13 items that assess treatment effectiveness (three items), convenience (three items), side-effects (four items) and global satisfaction (three items). Higher scores on the TSQM indicate greater levels of satisfaction. The Economic Implications of Psoriasis Patient Questionnaire evaluates healthcare visits, assistance with daily activities, employment, productivity at work, domestic activities and out-of-pocket expenses. PASI assessments for efficacy, reported previously for REFINE,[2] were also used in the analyses of PROs.

Statistical considerations
This analysis was descriptive and no comparative testing between treatment arms was performed. Missing data were imputed using the last observation carried forward. Exploratory analyses to assess the correlations of the TSQM and DLQI with efficacy as measured by PASI score were performed. Multivariate models were fit at baseline, week 12, and week 24, adjusting for treatment at week 24 and stratification factors of body mass index (BMI) and prior use

of TNF blockers for psoriasis. No adjustment was made for multiplicity. All *P*-values are descriptive.

Results

Patients

The patient population of REFINE has been described previously.[2] Briefly, 310 patients enrolled in the study, 144 were randomized to etanercept 50 mg BIW, 143 were randomized to etanercept 50 mg QW plus topical therapy and 23 patients discontinued from the study before week 12 and were therefore not randomized to further treatment. The patient population was 88% white, 65% were males and the mean [standard deviation (SD)] age was 45 (14) years.

DLQI results

Mean DLQI total scores [SD] were similar between treatment groups at baseline (14.3 [7.0] and 13.1 [6.4] for etanercept and etanercept + topical respectively), at randomization at week 12 (4.3 [4.9] and 3.2 [3.8]), and at week 24 (3.9 [5.8] and 3.2 [4.5]) (Fig. 1a). Change from baseline in mean DLQI total score (SD) to week 24 was 10.7 (7.8) for the etanercept group and 9.9 (6.9) for the etanercept + topical group (Table 1). DLQI and PASI outcomes at week 12 and week 24 were slightly correlated, with r^2 values of 0.26 and 0.23, respectively, whereas changes from baseline in DLQI and PASI were less correlated with r^2 values of 0.10 and 0.11. There was no evidence of any interaction with the treatments or stratification factors. Patients with a DLQI score of 0 or 1 at week 12 or week 24 had greater PASI improvements than those with higher DLQI scores (Fig. 1b).

TSQM results

Mean TSQM scores for effectiveness, convenience, side-effects and global satisfaction were similar between treatment groups at baseline (Fig. 2). Mean TSQM scores for effectiveness (Fig. 2a), convenience (Fig. 2b) and global satisfaction (Fig. 2d) improved from baseline for both treatment groups. Mean TSQM scores for side-effects (Fig. 2c) were unchanged throughout the study. Mean change from baseline (SD) to week 24 for the etanercept and etanercept + topical groups, respectively, was 27.1 (36.1) and 32.5 (40.3) for effectiveness; 14.8 (25.9) and 18.5 (29.0) for convenience; −0.7 (22.0) and 1.3 (19.4) for side-effects; and 26.7 (32.5) and 28.4 (35.9) for global satisfaction. An improvement in PASI from baseline to weeks 12 and 24 coincided with overall satisfaction (weeks 12 and 24, $P < 0.0001$) and effectiveness (weeks 12 and 24, $P < 0.001$) (Fig. 3). No evidence of
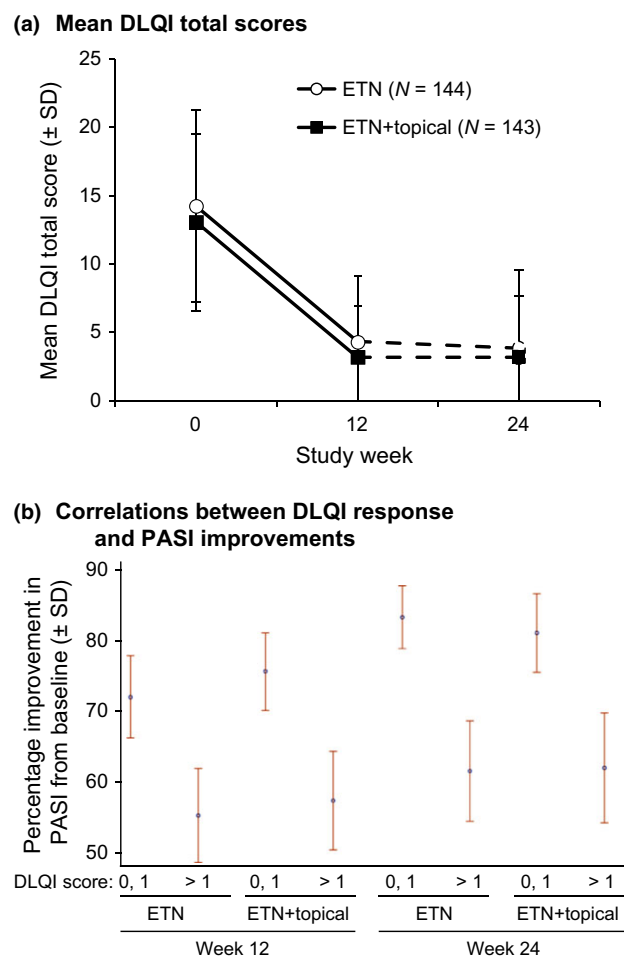
(a) Mean DLQI total scores

(b) Correlations between DLQI response and PASI improvements

Figure 1 DLQI Outcomes. (a) Mean DLQI total scores for patients receiving etanercept (open circles) or etanercept + topical therapy (closed squares) are shown. Solid lines represent the first 12 weeks when all patients received ETN 50 mg BIW and dashed lines represent the period after randomization when patients received their assigned treatment. Error bars represent standard deviations. (b) Correlations between DLQI response categories (scores of 0,1 and > 1) and percentage improvement in PASI scores at weeks 12 and 24 are shown. Error bars represent standard deviations. DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; ETN, etanercept; BIW, twice weekly; SD, standard deviation.

Table 1 Change in DLQI and PASI scores from baseline (full analysis set, LOCF imputation)

	ETN (N = 144)	ETN+Topical (N = 143)
Change in DLQI score, mean score change (SD)		
Baseline to week 12	10.0 (7.0)	9.7 (6.2)
Baseline to week 24	10.7 (7.8)	9.9 (6.9)
Change in PASI score, mean % (SD)		
Baseline to week 12	62.1 (28.6)	65.5 (28.6)
Baseline to week 24	71.7 (27.6)	72.6 (27.8)

DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; LOCF, last observation carried forward; ETN, etanercept; SD, standard deviation.
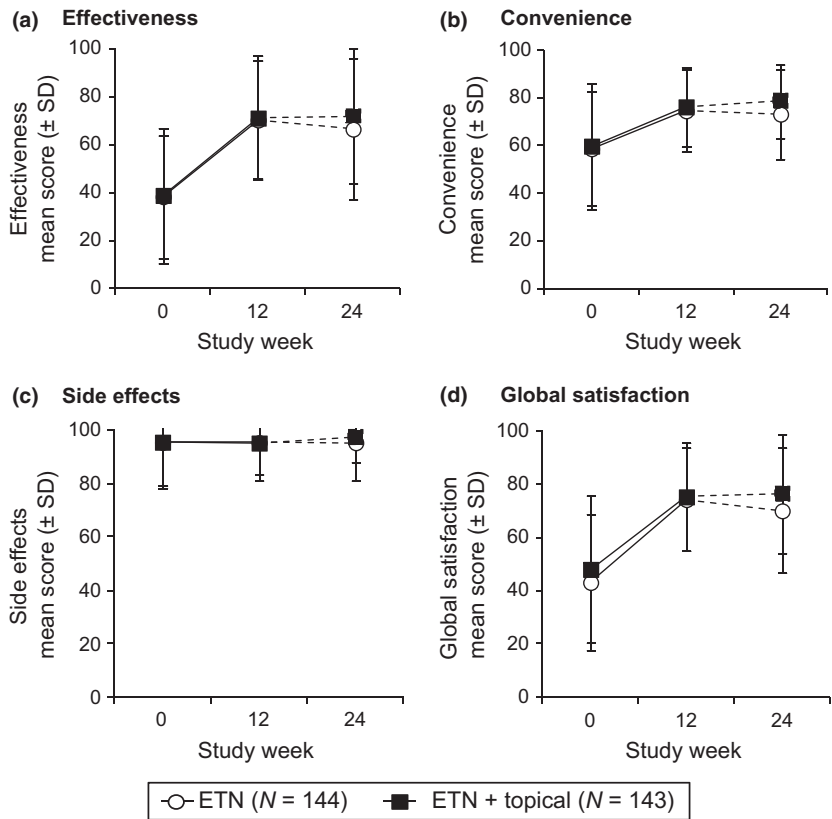
Figure 2 TSQM Scores. Mean TSQM scores for (a) effectiveness, (b) convenience, (c) side-effects, and (d) global satisfaction are shown for patients receiving etanercept (open circles) or etanercept + topical therapy (closed squares). Solid lines represent the first 12 weeks when all patients received ETN 50 mg BIW and dashed lines represent the period after randomization when patients received their assigned treatment. Error bars represent standard deviations. TSQM, Treatment Satisfaction Questionnaire for Medication; ETN, etanercept; BIW, twice weekly; SD, standard deviation.

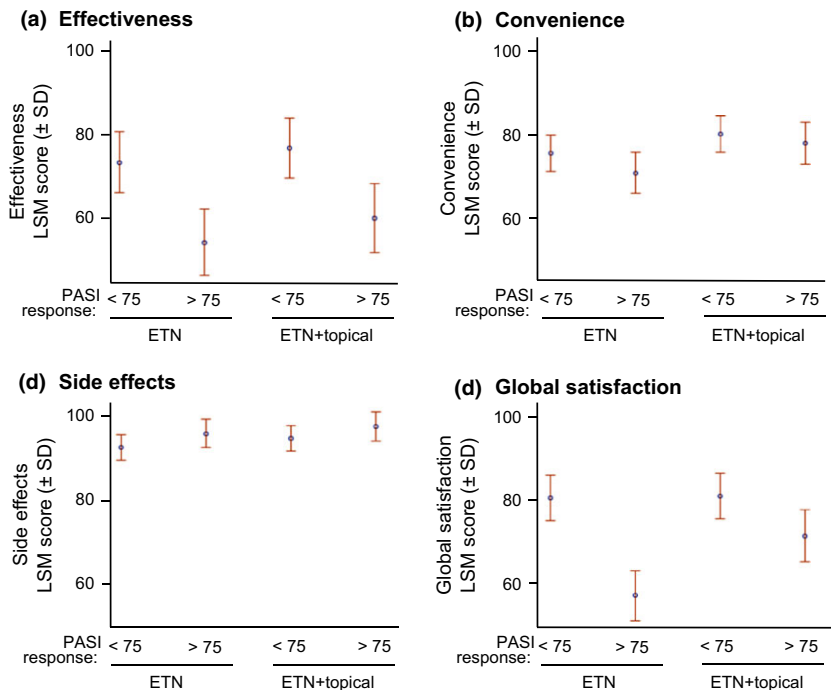**Figure 3** Correlations Between TSQM Improvements and PASI Responses. Correlations between TSQM least square mean values and PASI response categories of < 75% improvement (PASI < 75) and PASI > 75 are shown. Error bars represent standard deviations. TSQM, Treatment Satisfaction Questionnaire for Medication; PASI, Psoriasis Area and Severity Index; LSM, least square mean; ETN, etanercept; SD, standard deviation.

Table 2 Economic implications of psoriasis (full analysis set, LOCF imputation)

	ETN (N = 144)	ETN+Topical (N = 143)
Non-dermatologist office visits, n (%)		
Baseline		
0	85 (59.0)	90 (62.9)
1	30 (20.8)	23 (16.1)
2	16 (11.1)	10 (7.0)
3	1 (0.7)	7 (4.9)
4	5 (3.5)	2 (1.4)
≥5	0	3 (2.1)
Week 12		
0	107 (74.3)	95 (66.4)
1	20 (13.9)	27 (18.9)
2	5 (3.5)	5 (3.5)
3	2 (1.4)	1 (0.7)
4	0	1 (0.7)
≥5	2 (1.4)	3 (2.1)
Week 24		
0	103 (71.5)	99 (69.2)
1	18 (12.5)	22 (15.4)
2	6 (4.2)	3 (2.1)
3	3 (2.1)	0
4	1 (0.7)	0
≥5	0	0
Employment status, n (%)		
Baseline		
Employed full-time	81 (56.3)	72 (50.3)
Employed part-time	26 (18.1)	21 (14.7)
Unemployed	16 (11.1)	21 (14.7)
Retired	19 (13.2)	28 (19.6)
Week 12		
Employed full-time	84 (58.3)	73 (51.0)
Employed part-time	18 (12.5)	18 (12.6)
Unemployed	22 (15.3)	17 (11.9)
Retired	16 (11.1)	30 (21.0)
Week 24		
Employed full-time	81 (56.3)	67 (46.9)
Employed part-time	21 (14.6)	19 (13.3)
Unemployed	16 (11.1)	13 (9.1)
Retired	18 (12.5)	30 (21.0)
Productivity while working, n (%)		
Baseline		
A great deal	7 (4.9)	6 (4.2)
Quite a bit	16 (11.1)	13 (9.1)
Somewhat	37 (25.7)	28 (19.6)
Minimally	20 (13.9)	21 (14.7)
Not at all	26 (18.1)	25 (17.5)
Week 12		
A great deal	3 (2.1)	2 (1.4)
Quite a bit	4 (2.8)	6 (4.2)
Somewhat	14 (9.7)	6 (4.2)
Minimally	22 (15.3)	21 (14.7)
Not at all	58 (40.3)	57 (39.9)

Table 2 *Continued*

	ETN (N = 144)	ETN+Topical (N = 143)
Week 24		
A great deal	1 (0.7)	3 (2.1)
Quite a bit	4 (2.8)	1 (0.7)
Somewhat	7 (4.9)	12 (8.4)
Minimally	24 (16.7)	12 (8.4)
Not at all	64 (44.4)	57 (39.9)
Hours missed from work,* n (%)		
Baseline		
0	86 (59.7)	73 (51.0)
1	1 (0.7)	2 (1.4)
2	2 (1.4)	3 (2.1)
3	3 (2.1)	0
4	1 (0.7)	4 (2.8)
≥5	8 (5.6)	10 (7.0)
Week 12		
0	91 (63.2)	86 (60.1)
1	0	1 (0.7)
2	0	0
3	0	0
4	0	1 (0.7)
≥5	2 (1.4)	2 (1.4)
Week 24		
0	91 (63.2)	76 (53.1)
1	0	0
2	0	0
3	1 (0.7)	1 (0.7)
4	1 (0.7)	0
≥5	3 (2.1)	5 (3.5)
Ability to perform daily activities, n (%)		
Baseline		
A great deal	11 (7.6)	11 (7.7)
Quite a bit	14 (9.7)	16 (11.2)
Somewhat	23 (16.0)	27 (18.9)
Minimally	29 (20.1)	25 (17.5)
Not at all	34 (23.6)	30 (21.0)
Week 12		
A great deal	2 (1.4)	4 (2.8)
Quite a bit	2 (1.4)	9 (6.3)
Somewhat	9 (6.3)	6 (4.2)
Minimally	21 (14.6)	14 (9.8)
Not at all	61 (42.4)	71 (49.7)
Week 24		
A great deal	2 (1.4)	2 (1.4)
Quite a bit	5 (3.5)	6 (4.2)
Somewhat	9 (6.3)	7 (4.9)
Minimally	16 (11.1)	7 (4.9)
Not at all	56 (38.9)	64 (44.8)

*Only employed patients were included in the hours missed from work analysis.

ETN, etanercept; LOCF, last observation carried forward.

correlation between convenience or side-effects and PASI improvement from baseline to weeks 12 and 24 was observed ($P > 0.1$). Prior use of a TNF blocker was not statistically significant ($P > 0.05$). Patients with BMI ≥ 30 kg/m^2 at baseline had significantly higher ($P < 0.05$) average effectiveness and satisfaction scores at weeks 12 and 24 and higher average convenience score at week 24 than patients with baseline BMI < 30 kg/m^2. Specifically, overall satisfaction at week 24 differed for patients by treatment arm and PASI outcome. The opportunity to use a topical agent seemed to improve a patient's overall satisfaction regardless of PASI improvement. In addition, overall satisfaction was high for patients randomized to etanercept alone who also had improvement in PASI relative to those with less PASI improvement (Fig. 3).

Economic Implications of Psoriasis Patient Questionnaire results

Most patients in both treatment arms responded with 0 (none) to the following items in the questionnaire: number of visits to physician's office or urgent care clinic; number of visits to any healthcare professional (including nurse practitioner, physician assistant, psychologist, naturopath, acupuncturist or chiropractor); number of home visits by a healthcare professional; number of times that the patient paid another person for household chores; and number of hours that a friend or family member had to take time off from work to provide care or transportation to the patient. Employment status (full-time, part-time, unemployed, or retired) and hours missed from work were similar at baseline, week 12, and week 24 in both treatment arms (Table 2). The percentage of patients who reported that their psoriasis affected their productivity while working and ability to perform daily activities 'Not at all' was greater at weeks 12 and

24 than at baseline in both treatment arms. Out-of-pocket expenses were highly variable for both treatment arms; most patients had no out-of-pocket costs (minimum, first quartile, and median values were 0) but some had high costs (Fig. 4). Median costs were similar between treatment arms, and were lower at week 12 and week 24 than at baseline (excluding two patients who had > $10 000 in unknown non-drug expenses).

Discussion

Results from REFINE have shown that adding topical antipsoriatic agents from week 12 while decreasing the dose of etanercept to 50 mg QW appears to be as efficacious as maintaining etanercept 50 mg BIW without topicals.[2] In this analysis of PROs, no notable differences between treatment arms in DLQI and TSQM results were observed. Additionally, improvements in PASI appeared to correlate with improvements in PROs.

Maintenance of response when adding a topical therapy while decreasing the etanercept dose was also observed in a similar, smaller trial.[8] In that study, patients received etanercept 50 mg BIW for 12 weeks followed by etanercept 50 mg QW up to 12 weeks. Patients used a topical calcipotriene 0.005% and betamethasone dipropionate 0.064% combination ointment for 4 weeks if their psoriasis-affected BSA increased by 2% after reducing the etanercept dose. Similar to results from REFINE,[2] addition of topical therapy to etanercept 50 mg QW resulted in significant improvements in PASI response.[8]

The correlation between PASI improvement and PRO improvement is also consistent with findings from other studies.[4,9] In a systematic review of 13 randomized, controlled trials of patients treated for their psoriasis, agents that were associated with a 75% improvement in PASI score (PASI 75) or better response to treatment were also associated with significant
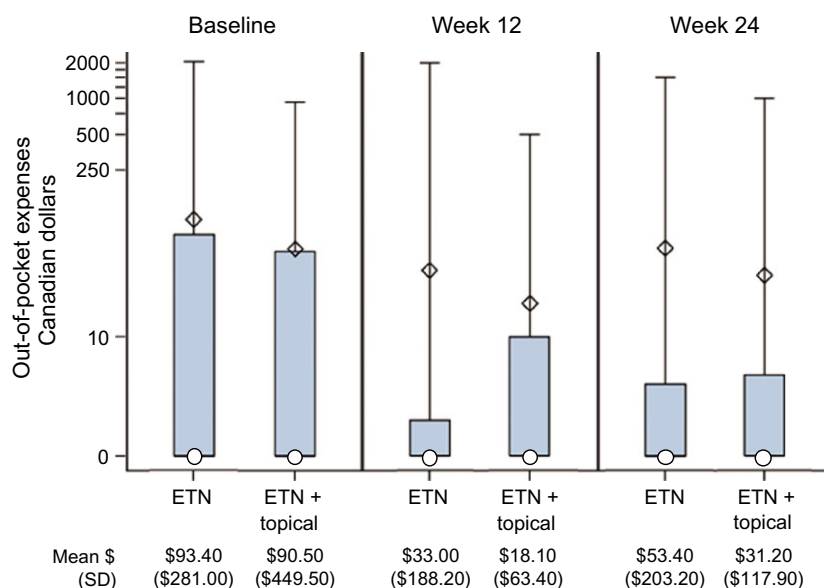

Figure 4 Out-of-Pocket Expenses. The lower edge of each box represents the first quartile, the upper edge of the box represents the third quartile, the diamond represents the mean, the circle represents the median and the whiskers represent the minimum and maximum values. Data are shown for all patients except two patients in the etanercept monotherapy arm, who had expenses > $10 000 for unknown non-drug costs. ETN, etanercept; SD, standard deviation.

	Baseline		Week 12		Week 24	
	ETN	ETN + topical	ETN	ETN + topical	ETN	ETN + topical
Mean $ (SD)	$93.40 ($281.00)	$90.50 ($449.50)	$33.00 ($188.20)	$18.10 ($63.40)	$53.40 ($203.20)	$31.20 ($117.90)

improvements in DLQI scores (r^2 = 0.898).[4] Similarly, in an analysis of data from two clinical trials of adalimumab in patients with plaque psoriasis (N = 1469), the percentage of patients with DLQI score of 0 was statistically higher for patients with PASI 90 to PASI 100 response compared with patients with lower PASI responses (P < 0.0001).[9] Correlations between effectiveness and global satisfaction subscales, but not convenience and side-effects subscales, of the TSQM with PASI improvements in our study were also observed in a cross-sectional study of systemic and topical therapies for moderate to severe plaque psoriasis.[10]

This study tested a 'real-world' strategy of using topical therapies to maintain clinical improvements while the dose of etanercept was reduced.[11,12] A limitation of the study was the provision of drugs (both etanercept and topical) to the patients at no cost, which may have introduced a bias towards using the topical therapies. Additionally, the duration of treatment with topical therapies was only 12 weeks; a longer duration may result in loss of efficacy as adherence to topical therapies may decrease with time.[13,14] While the cost of QW etanercept and topical may be a less costly option compared with BIW etanercept, access to etanercept via Canadian public and private drug plans is generally very good, and the cost of higher dose of etanercept may be covered. The analyses of efficacy and PRO data from REFINE were based on a non-inferiority trial design (without statistical testing); long-term hypothesis-testing clinical studies of biologic therapies used in combination with topical therapies with PROs as the primary endpoint are warranted.

In conclusion, measures of HRQoL, including DLQI and TSQM, were numerically similar in patients who stayed on etanercept 50 mg BIW and those who received etanercept 50 mg QW plus topical therapies when used as required to clear. Economic implications of psoriasis treatment, including out-of-pocket expenses, were similar between patients who remained on etanercept monotherapy and those who used concomitant topical therapies.

Acknowledgements

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