Secukinumab sustains early patient-reported outcome benefits through 1 year: Results from 2 phase III randomized placebo-controlled clinical trials comparing secukinumab with etanercept

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Background: Psoriasis is a chronic condition with negative impact on patients' quality of life that most often requires lifelong effective and safe treatment.

Objective: This analysis focused on the effect of secukinumab treatment on patient-reported health-related quality of life as assessed by the Dermatology Life Quality Index (DLQI) in patients with moderate to severe psoriasis.

Methods: The proportion of subjects achieving DLQI score 0/1 response at week 24, time to DLQI score 0/1 response, and sustained DLQI score 0/1 response up to week 52 were compared between secukinumab and etanercept.

Results: Of 1470 subjects, 1144 received secukinumab and 326 received etanercept. DLQI score 0/1 response rates were significantly higher for secukinumab than for etanercept at week 24. The median time to DLQI score 0/1 response was significantly shorter for secukinumab versus etanercept (12 vs 24 weeks; $P < .01$). The majority of secukinumab-treated subjects achieved DLQI score 0/1 response at week 24 and

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sustained it through week 52 along with a 90% to 100% reduction in the Psoriasis Area and Severity Index total score response.

Limitations: Placebo comparisons are limited during the maintenance period because of rerandomization at week 12.

Conclusion: Secukinumab treatment provided faster and greater sustained improvements in quality of life than etanercept over 52 weeks, consistent with greater clinical response. (J Am Acad Dermatol 2017;76:655-61.)

Key words: Dermatology Life Quality Index; patient-reported outcome; psoriasis; secukinumab.

CAPSULE SUMMARY

- Psoriasis is a chronic condition that negatively impacts quality of life (QOL).
- Secukinumab led to faster and more sustained QOL improvement than etanercept; for most secukinumab-treated patients with Psoriasis Activity and Severity Index response at week 24, QOL improvement was maintained through 1 year.
- For treating moderate to severe psoriasis, secukinumab offers sustained QOL benefits.

Psoriasis is a chronic relapsing disease of the skin characterized by variable clinical features. Commonly, patients experience diffuse red, elevated, and hyperkeratotic (scaly) plaques affecting any area of the body. Psoriatic plaques may be symptomatic, often involving pruritus, burning, and soreness. Accumulating evidence indicates that psoriasis is a multifactorial disorder caused by the concerted action of multiple disease genes, triggered by environmental factors, in a single patient. Genetic factors influence the pattern of psoriasis, severity, and age of onset.[1] Psoriasis usually represents a lifelong burden for the patient.

Effective treatments for psoriasis not only treat the symptoms and signs of the disease, but also enhance patients' self-esteem and their ability to carry out daily personal and professional activities. In addition to dermatologic care, attention must be given to the emotional problems that may affect the patient and the family.[2,3]

Patient-reported outcome assessments are essential to understanding the full effect of psoriasis and its treatment on patients' lives. The Medical Advisory Board of the National Psoriasis Foundation acknowledged the importance of including the patient perspective when measuring psoriasis symptoms and their impact on well-being.[4] The impact of psoriasis on patients' health-related quality of life (QOL) can be substantial, even similar to that seen in cancer, arthritis, hypertension, heart disease, diabetes, and depression.[5,6]

Although many patients with psoriasis, particularly those with a limited form of the disease, may be treated with topical therapy, those with extensive (moderate to severe) psoriasis eventually require phototherapy or systemic or biologic therapy to adequately suppress the systemic, immunopathophysiologic process.[7] In 2 patient surveys, substantial proportions of patients reported being frustrated (40%) or dissatisfied (24%-42%) with traditional therapies.[8] Biologic therapies may provide safe and effective alternatives to conventional systemic agents for the treatment of moderate to severe psoriasis.[9,10]

Secukinumab (Novartis Pharma AG, Basel, Switzerland), a fully human monoclonal antibody that selectively neutralizes interleukin (IL)-17A, has been shown to have significant efficacy in the treatment of moderate to severe psoriasis and psoriatic arthritis, demonstrating a rapid onset of action and sustained responses with a favorable safety profile.[11-17] Results from a phase II study provided evidence that secukinumab treatment provided early improvement in QOL response.[14] Two multicenter phase III studies, ERASURE (NCT01365455) and FIXTURE (NCT01358578), evaluated the efficacy, safety, and tolerability of secukinumab in patients with moderate to severe chronic plaque-type psoriasis.[15] In the FIXTURE trial, secukinumab demonstrated superior efficacy versus etanercept with a similar safety profile.[15] Furthermore, using the pooled ERASURE and FIXTURE data, evidence of superior cumulative clinical benefit was found over 52 weeks of treatment for secukinumab versus etanercept using an area under the curve analysis.[18] More recently, secukinumab demonstrated superior efficacy to ustekinumab in the 16-week primary analysis of the CLEAR study (NCT02074982).[19]

The objective of this analysis was to evaluate the long-term effect of secukinumab using

Abbreviations used:

DLQI: Dermatology Life Quality Index
IL: interleukin
PASI: Psoriasis Activity and Severity Index
QOL: quality of life

patient-reported health-related QOL as measured by the Dermatology Life Quality Index (DLQI) in a large data set. Specifically, the analysis focused on the speed and sustainability of response (ie, whether early benefits remained up to 1 year).

METHODS

Clinical trials

Patient enrollment criteria and study design for the 2 randomized, double-blind, placebo-controlled, parallel-group, multicenter phase III trials (ERASURE and FIXTURE) have been described in detail.[15] The trials were conducted between June 2011 and July 2013 and were designed to assess the efficacy and safety of subcutaneous secukinumab in subjects with moderate to severe chronic plaque psoriasis. There were 4 periods: screening (1-4 weeks), induction (12 weeks), maintenance (40 weeks), and follow-up (8 weeks).

Eligible subjects aged 18 years or older were randomized into the treatment arms stratified by geographic region and body weight (<90 or ≥90 kg). In ERASURE, subjects were randomized 1:1:1 to subcutaneous treatment groups (secukinumab 300 mg, secukinumab 150 mg, and placebo). In FIXTURE, subjects were randomized 1:1:1:1 (including an etanercept 50 mg group). All treatments were administered subcutaneously (secukinumab: weekly for 4 weeks, then once every 4 weeks; etanercept: twice weekly for 12 weeks, then once weekly).

Patient-reported outcome assessment

Assessment of health-related QOL was included as an additional secondary end point in each trial. Health-related QOL was assessed using the DLQI, which was administered at baseline and weeks 4, 8, 12, 24, 36, and 52.

The DLQI is a 10-item general dermatology disability index designed to assess health-related QOL in adults with skin diseases such as eczema, psoriasis, acne, and viral warts.[20] The measure is self-administered and includes domains of: (1) daily activities, (2) leisure, (3) personal relationships, (4) symptoms and feelings, (5) treatment, and (6) work/school.

Each item has 4 response categories, ranging from 0 (no impact at all on patient's life) to 3 (very much impact). The DLQI total score is a sum of the 10 questions. Scores range from 0 to 30, and higher scores indicate greater impairment of health-related QOL. DLQI response was defined as a DLQI total score of 0 or 1, implying that the patient's QOL was no longer affected by psoriasis.[21]

Statistical analysis

All analyses were conducted on the full analysis set (ie, all randomized subjects according to the treatment assigned at randomization) for subjects with baseline and at least 1 postbaseline DLQI score. Missing DLQI scores from scheduled visits were imputed from the last nonmissing score at a previous visit. Because of the rerandomization of patients in the placebo group who had not achieved PASI 75 (75% or greater improvement in Psoriasis Area and Severity Index score from baseline) at week 12, placebo was excluded from the sustained response analyses.

Time to DLQI score 0/1 response was defined as the period from randomization to the week when a prespecified response in DLQI (total score of 0 or 1) first occurred. Median time to DLQI score 0/1 response was estimated using Kaplan-Meier methods; treatment groups were compared using an unstratified log-rank test. Hazard ratios were computed using a Cox proportional hazards regression model accounting for baseline score as a continuous covariate. The percentage of subjects with DLQI score 0/1 response was presented by time point, and treatment groups were compared using the Pearson χ^2 test.

Sustained DLQI score 0/1 response was defined as no QOL impact as a result of psoriasis (DLQI score of 0 or 1) at week 24 that was maintained through week 52 in addition to a 90% to 100% reduction in the PASI total score from baseline to week 24. Sustained DLQI score 0/1 response was also assessed by no psoriasis impact on QOL (DLQI score of 0 or 1) at week 24 that was maintained through week 52 in addition to a 100% reduction in the PASI total score from baseline to week 24. Secukinumab and etanercept treatment groups were compared using the Pearson χ^2 test. All analyses were considered exploratory, therefore no adjustment for multiple comparisons were done.

RESULTS

Of the 2042 patients randomized to both studies, 1470 (72%) received active treatment (secukinumab 300 mg, 572; secukinumab 150 mg, 572; etanercept, 326; and placebo, 572). The baseline demographic and clinical characteristics were similar across treatment groups (Table I). The subjects were predominantly male, and the mean age of subjects ranged

Table I. Psoriasis: baseline demographic and clinical characteristics

Demographics and characteristics	Secukinumab 300 mg n = 572	Secukinumab 150 mg n = 572	Etanercept n = 326	Placebo n = 572
Male, n (%)	393 (68.7)	404 (70.6)	232 (71.2)	407 (71.2)
Age, y, mean (SD)	44.5 (13.5)	44.8 (13.0)	42.9 (12.9)	44.8 (12.9)
Body weight, kg, mean (SD)	85.5 (22.8)	85.1 (21.5)	84.6 (20.5)	85.3 (22.8)
BSA score, mean (SD)	33.7 (19.2)	34.0 (19.3)	33.6 (18.0)	32.9 (18.0)
PASI score, mean (SD)	23.3 (9.7)	23.1 (10.2)	23.2 (9.8)	22.9 (10.0)
IGA, n (%)				
Moderate [level = 3], n (%)	357 (62.4)	367 (64.2)	195 (59.8)	352 (61.5)
Severe [level = 4], n (%)	215 (37.6)	205 (35.8)	131 (40.2)	220 (38.5)
DLQI total score, mean (SD)	13.6 (7.3)	13.4 (7.1)	13.4 (7.3)	12.8 (7.1)

BSA, Body surface area; *DLQI*, Dermatology Life Quality Index; *IGA*, Investigator Global Assessment; *PASI*, Psoriasis Area and Severity Index.

from 42.9 to 44.8 years (secukinumab 300 mg, 44.5 years; secukinumab 150 mg, 44.8 years; etanercept, 42.9 years; and placebo, 44.8 years). Mean PASI scores at baseline were similar across treatment groups and ranged from 22.9 to 23.3. Based on the modified 2011 Investigator Global Assessment, the majority of subjects in each group had moderate disease (ie, 3 based on a 0-4 scale). Baseline DLQI total scores were similar across groups showing moderate effect on QOL (ie, ranged from 12.8-13.6). The majority (97.7%) of randomized patients completed the DLQI at baseline. Missing data for DLQI varied from 6.2% to 15.8% between weeks 24 and 52.

Patient-reported treatment effect

Fig 1 presents the proportion of subjects achieving DLQI score 0/1 response over time by treatment group. Response rates for secukinumab treatment groups were consistently higher than for etanercept and placebo. All comparisons with placebo through week 12 were significant at P less than .0001. Significantly higher DLQI score 0/1 response for secukinumab compared with etanercept started as early as week 4 and was sustained through week 52 (with 2 exceptions for secukinumab 150 mg vs etanercept: at week 4 [P = .0553] and at week 52 [P = .0843]).

Through week 52, DLQI score 0/1 response occurred in 456 of the 571 subjects (79.9%) in the secukinumab 300 mg group and 404 of the 571 subjects (70.8%) in the secukinumab 150 mg group versus 193 of the 325 subjects (59.4%) in the etanercept group (Table II). The Kaplan-Meier estimated median time to response was week 12 for both secukinumab 300 mg and secukinumab 150 mg, and week 24 for etanercept (P < .01) (Fig 2 and Table II).

After adjusting for the DLQI total baseline score as a continuous variable in a Cox model, differences in time-to-response curves for secukinumab versus etanercept and secukinumab versus placebo remained significant (P < .0001 for each placebo and etanercept hazard ratio comparison), indicating shorter time to DLQI score 0/1 response for secukinumab. Specifically, the Cox model showed that subjects taking secukinumab 300 mg were 2.32 times more likely than those taking placebo and 1.94 times more likely than those taking etanercept to achieve DLQI score 0/1 response (hazard ratio 1.94, 95% confidence interval 1.61-2.32).

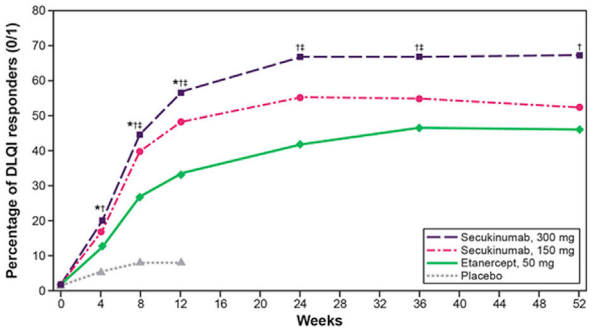

Fig 1. Psoriasis. Percentage of subjects with DLQI total score 0/1 response (ie, no psoriasis impairment in quality of life), by treatment group, from randomization up to 52 weeks. Patients in the placebo group who did not achieve Psoriasis Activity and Severity Index 75 at week 12 were rerandomized to secukinumab; analyses do not contain the placebo group beyond week 12. *P < .001, 150 mg versus placebo; 300 mg versus placebo. †P < .05, 300 mg versus etanercept. ‡P < .05, 150 mg versus etanercept. *DLQI*, Dermatology Life Quality Index.

Sustained response

Placebo sustained response comparisons were omitted because of the rerandomization of placebo at week 12. Response rates for sustained response as defined by DLQI score 0/1 response at week 24 and maintained through week 52 in addition to a 90% to 100% reduction in the PASI total score response at week 24 were higher for secukinumab treatment

Table II. Psoriasis: time to Dermatology Life Quality Index score 0/1 response up to week 52 (active treatment)

DLQI score 0/1 response*	Secukinumab 300 mg n = 572	Secukinumab 150 mg n = 572	Etanercept n = 326
N	571	571	325
No. of responders	456 (79.9%)	404 (70.8%)	193 (59.4%)
Median time to response, wk (95% CI)	12.0 (8.0-12.0)	12.0 (12.0-24.0)	24.0 (24.0-36.0)
P value for comparison with etanercept	<.0001	.0036	—

P values are from unstratified log-rank test.
CI, Confidence interval; *DLQI*, Dermatology Life Quality Index.
*No psoriasis impairment in quality of life.

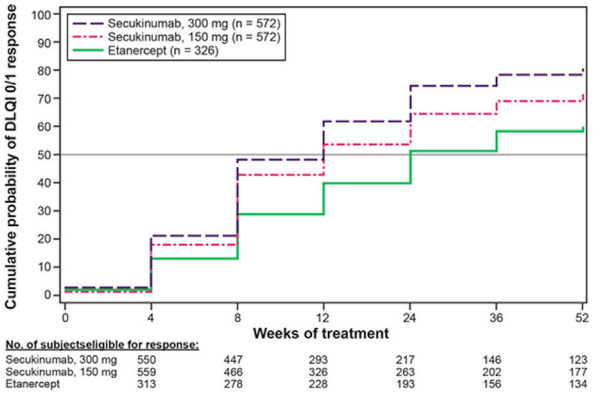

Fig 2. Psoriasis. Time to DLQI total score 0/1 response (ie, no psoriasis impairment in quality of life), by treatment (active treatment). Log-rank test *P* values for overall Kaplan-Meier curve comparison: <.0001, 300 mg versus etanercept; .0036, 150 mg versus etanercept. *DLQI*, Dermatology Life Quality Index.

groups than for etanercept; 85.8% (278/324) for secukinumab 300 mg, 79.4% (177/223) for secukinumab 150 mg, and 74.6% (50/67) for etanercept. In addition, response rates were higher for secukinumab 300 mg than etanercept among subjects who achieved DLQI score 0/1 response at week 24 and maintained through week 52 in addition to a 100% reduction in the PASI total score response at week 24: secukinumab 300 mg, 90.2% (174/193); secukinumab 150 mg, 81.1% (86/106); and etanercept 83.3% (20/24) (Table III).

DISCUSSION

This study assessed the speed and sustainability of secukinumab's treatment benefit on patient-reported health-related QOL as assessed by the DLQI score 0/1 response. Psoriasis therapies, especially therapies with newer modes of action such as secukinumab, should be evaluated for both short-term (eg, primary end points usually planned for 12-16 weeks) and long-term (≥52 weeks) efficacy given patients must remain on therapeutics indefinitely for the management of this chronic incurable condition. Increasingly, patient-reported outcome assessments, such as the DLQI, the Psoriasis Symptom Diary,[22] or the Psoriasis Symptom Inventory[23] are viewed as complementary to objective assessments in understanding the full effect of psoriasis and its treatment on patients' lives.

Secondary treatment failure (after initial success) potentially is costlier both emotionally to the patient and financially to the health care system (drug switches, often necessitating higher costs the first year of therapy, are more expensive) and requires additional practitioner time and effort to switch therapy.[24] Therefore, sustained responses of more potent medications can reduce long-term negative consequences of treatment failure. However, there is little information regarding the sustainability of patient-reported outcome response for current treatments in psoriasis.

Results from phase III studies have shown secukinumab to be effective at targeting the IL-17A pathway in patients with moderate to severe plaque psoriasis.[15] IL-17A appears to represent a highly viable target for modern therapeutics, as its inhibition results in unprecedented short- and long-term efficacy.[15]

This analysis of DLQI showed consistently greater proportions of secukinumab-treated patients achieving DLQI response (score 0/1) than patients treated with etanercept or placebo (300 mg, 57.0%; 150 mg, 48.3%; etanercept, 33.7%; placebo, 8.0% at week 12). In addition, DLQI response was significantly faster for secukinumab than for etanercept treatment (12 vs 24 weeks, $P < .01$). Further, greater proportions of secukinumab-treated patients achieved DLQI score 0/1 response at week 24 and maintained through week 52 in addition to a 90% to 100% reduction in the PASI total score response at week 24. Results were similar for sustained DLQI score 0/1 response through week 52 for patients achieving 100% reduction in the PASI total score response at week 24. These results are further noteworthy because of the large sample size and minimal missing data for the patient-reported

Table III. Psoriasis: sustained Dermatology Life Quality Index score 0/1 response through 52 weeks (active treatment)

Response	Secukinumab 300 mg N = 572	Secukinumab 150 mg N = 572	Etanercept N = 326
PASI, % (n/N)			
PASI 90 response at wk 24	69.6 (398/572)	55.1 (315/572)	37.4 (122/326)
PASI 100 response at wk 24	39.7 (227/572)	22.9 (131/572)	10.7 (35/326)
P value vs etanercept	<.0001	<.0001	
DLQI total score 0/1,* % (n/m)			
Response at wk 24	81.4 (324/398)	70.8 (223/315)	54.9 (67/122)
P value vs etanercept	<.0001	<.0001	
Sustained response, % (n/m)			
Sustained DLQI total score 0/1* response through wk 52 in addition to PASI 90 at wk 24	85.8 (278/324)	79.4 (177/223)	74.6 (50/67)
P value vs etanercept	.0235	.4088	
Sustained DLQI total score 0/1* response through wk 52 in addition to PASI 100 at wk 24	90.2% (174/193)	81.1% (86/106)	83.3% (20/24)
P value vs etanercept	.3059	.8018	

P values are based on Pearson χ^2 test.
DLQI, Dermatology Life Quality Index; *m*, number of patients evaluable; *n*, number of patients with response; *PASI*, Psoriasis Activity and Severity Index; *PASI 90*, 90%-100% reduction in PASI total score; *PASI 100*, 100% reduction in PASI total score.
*No psoriasis impairment in quality of life.

outcomes, which provided a robust longer-term head-to-head comparison of the QOL benefit of secukinumab versus etanercept. Future research should consider replicating this evaluation using real-world long-term data and including other aspects of patient-centered outcomes such as work productivity and psoriasis-related symptoms.

Conclusion

The evaluation provided here extends previous head-to-head assessments of secukinumab and provides a long-term comparative analysis. These results replicate the findings that secukinumab provides significantly faster improvements in skin-specific QOL. Furthermore, the results show that this benefit over etanercept is sustained over 52 weeks. These QOL benefits add to the clinical improvement associated with secukinumab therapy in patients with moderate to severe plaque psoriasis. Future studies should be considered to evaluate other patient-reported outcomes beyond the QOL, such as symptom burden and work productivity.

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