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Clinical efficacy and safety of secukinumab in patients with psoriasis and comorbidities: pooled analysis of 4 phase 3 clinical trials

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ABSTRACT

Background: The influence of comorbidities on the efficacy and safety of biologic therapies in psoriasis has not been rigorously explored.

Objective: To assess the incremental burden of comorbidities on clinical efficacy and safety of secukinumab vs. etanercept and placebo among patients with plaque psoriasis pooled from 4 phase 3 trials.

Methods: Efficacy was assessed at week 12 according to achievement of Psoriasis Area and Severity Index (PASI) and Investigator's Global Assessment (IGA; modified 2011) responses. Efficacy comparisons between treatment arms stratified by comorbidity status were made using logistic regression analysis with nonresponder imputation. Relationships between baseline characteristics and clinical responses were evaluated by χ^2 tests.

Results: Of 2401 patients, 1469 (61.2%) had $\geq$1 active baseline comorbidity. Regardless of comorbidity status, patients receiving secukinumab were more likely to achieve PASI and IGA responses than those receiving etanercept or placebo at week 12 ($p < .05$ for all comparisons). Body weight of $\geq$90 kg was consistently associated with a decreased likelihood of achieving PASI and IGA responses ($p < .01$ for all comparisons). Safety was comparable across treatment arms stratified by comorbidity.

Conclusions: Secukinumab improved clinical outcomes and was well tolerated in patients with concomitant baseline comorbid conditions.

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KEYWORDS
Plaque psoriasis; comorbidities; secukinumab

Introduction

Psoriasis is a chronic inflammatory disease characterized in many patients by erythematous, scaly papules and plaques and affecting approximately 2% of the population (1). Given the systemic nature of the disease, in addition to cutaneous symptoms, patients with psoriasis often experience a spectrum of extracutaneous pathologies, comorbidities, and complications (1,2). Comorbidities frequently associated with psoriasis include obesity (3–5), metabolic syndrome (6,7), cardiovascular disease (8–10), and psoriatic arthritis (PsA) (11,12), and these comorbidities are factors in selection of the ideal therapy. A holistic approach is required to address the varied and systemic manifestations of psoriatic disease.

The presence of comorbidities represents a clinical challenge for the management of psoriasis, especially when initiation of a systemic therapy is considered. Although systemic therapies may improve comorbidities of psoriasis by reducing overall inflammation, the potential effect of psoriasis treatments on comorbidities remains poorly understood, and treatment-emergent adverse events (TEAEs) may adversely interfere with some comorbidities (2). Biologics selectively targeting interleukin 17A (IL-17A) are increasingly prescribed due to established efficacy in skin and joints, as well as a favorable safety profile compared with tumor necrosis factor inhibitors (TNFis) (13,14). Secukinumab, a fully human monoclonal antibody that selectively binds to and neutralizes IL-17A, has shown long-lasting efficacy and safety in treating the complete spectrum of manifestations of psoriatic disease, including psoriasis vulgaris (14,15); palmoplantar (16), nail (17), and scalp psoriasis (18); all PsA disease domains, including enthesitis and dactylitis (19–23); and ankylosing spondylitis (24,25). Preliminary results from ongoing studies confirm the effectiveness, persistence, and safety of secukinumab in the real world for up to 2 years (26–28). However, the safety profile and effect of biologic treatments on disease activity in patients with specific comorbidities may not be similar to those for all patients with psoriasis (2), as randomized clinical trials often exclude patients with relevant comorbidities. In the phase 3 clinical trials ERASURE (14), FIXTURE (14), FEATURE (29), and JUNCTURE (30), the efficacy and safety of secukinumab were characterized in patients with moderate to severe psoriasis. However, the effect of active baseline comorbidities on these parameters was not studied.

In this secondary analysis of patients pooled from these 4 phase 3 studies, the efficacy and safety of secukinumab were compared with those of etanercept and placebo in patients with and without active baseline comorbidities. Relationships between patient characteristics and comorbidities, as well as

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the effect of comorbidities on treatment response, were also observed.

Patients and methods

Study design and population

This analysis included pooled data from patients treated with secukinumab, etanercept, or placebo in 4 randomized, double-blind, placebo-controlled, phase 3 trials: ERASURE (NCT01365455) (14), FIXTURE (NCT01358578) (14), FEATURE (NCT01555125) (29), and JUNCTURE (NCT01636687) (30) (Figure 1). All studies included adult patients with plaque psoriasis that was poorly controlled with topical therapy, phototherapy, and/or systemic therapy and had been diagnosed ≥6 months prior to randomization. All patients had moderate to severe psoriasis as defined by a composite Psoriasis Area and Severity Index (PASI) score of ≥12, an Investigator's Global Assessment modified 2011 (IGA mod 2011) score of ≥3, and total affected body surface area of ≥10% at baseline. In the trials pooled for this analysis, patients were not randomized on the basis of the presence of comorbidities. For this study, one patient each from ERASURE and FIXTURE was excluded from the analysis due to protocol deviations; both patients signed the corresponding informed consent form after starting the study procedures.

Patients were assigned to cohorts based on the presence or absence of active baseline comorbidities. Those patients with active baseline comorbidities had ≥1 of the following common comorbid conditions: angina pectoris, arthritis, cardiac failure, coronary artery disease, depression, diabetes, gout, hyperlipidemia, hypertension, osteoarthritis, and rheumatoid arthritis as defined by Medical Dictionary for Regulatory Activities questionnaires; obesity, defined as a medical history of obesity or baseline body mass index (BMI) of ≥30 kg/m^2; or PsA, as reported by the patient and indicated by the principal investigator in the electronic case report form. The studies from which these data were pooled were conducted in accordance with the Declaration of Helsinki principles and were approved by institutional review boards or independent ethics committees.

Study objectives

The objective of this secondary analysis was to assess the incremental burden of comorbidities on clinical efficacy and safety of secukinumab vs. etanercept after 12 weeks of treatment among patients with moderate to severe plaque psoriasis pooled from 4 phase 3 trials (14,29,30). Additionally, this analysis assessed the association between comorbidities and baseline demographics, as well as the effect of specific baseline characteristics on overall treatment response.

Statistical analysis

Efficacy comparisons between secukinumab 150 mg and secukinumab 300 mg vs. etanercept and placebo within patient groups stratified by presence or absence of comorbidities were made using logistic regression analysis with nonresponder imputation for missing patient data. Efficacy was assessed at week 12 according to the proportion of patients who achieved PASI75, PASI90, and PASI100, and IGA mod 2011 0 (clear) and 0/1 (clear/almost clear). Relationships between baseline demographics and clinical responses were evaluated by χ^2 tests. The frequencies of TEAEs, treatment-emergent serious adverse events, and TEAEs leading to discontinuation were summarized for each treatment arm stratified by presence of active baseline comorbidities.

Patients pooled in this secondary analysis were not randomized by presence vs. absence of baseline comorbidities in the original phase 3 trials. Statistical comparisons are for hypothesis generation only; analyses were not adjusted for multiple comparisons.

Results

Patient population and comorbidities at baseline

Of the 2401 patients included in this analysis, 1469 (61.2%) had ≥1 active baseline comorbidity (Table 1). Across all treatment arms, the most frequent diagnosed comorbidities included obesity (37.2% of patients), hypertension (24.6%), PsA (18.0%), hyperlipidemia (15.9%), and diabetes (8.4%) (Table 1). Other comorbidities affecting <6% of the overall patient population

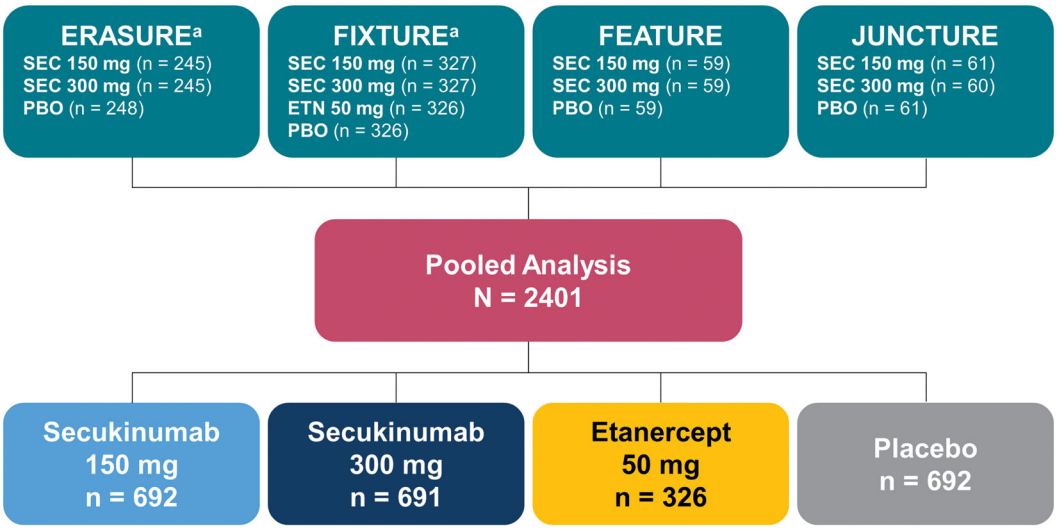

Figure 1. Study population for *post hoc* analysis. ETN: etanercept; PBO: placebo; SEC: secukinumab. [a]One patient from each study was excluded from the pooled analysis as a result of protocol deviations.

Table 1. Patients with active baseline comorbidities of psoriasis pooled from the ERASURE, FIXTURE, FEATURE, and JUNCTURE studies (full-analysis set).

Comorbidity, *n* (%)	Secukinumab 150 mg (*n* = 692)	Secukinumab 300 mg (*n* = 691)	Etanercept 50 mg (*n* = 326)	Placebo (*n* = 692)	Overall (*N* = 2401)
Any	432 (62.4)	437 (63.2)	188 (57.7)	412 (59.5)	1469 (61.2)
Obesity[a]	259 (37.4)	274 (39.7)	108 (33.1)	251 (36.3)	892 (37.2)
Hypertension	195 (28.2)	177 (25.6)	68 (20.9)	150 (21.7)	590 (24.6)
Psoriatic arthritis[b]	120 (17.3)	130 (18.8)	44 (13.5)	137 (19.8)	431 (18.0)
Hyperlipidemia	119 (17.2)	124 (17.9)	41 (12.6)	97 (14.0)	381 (15.9)
Diabetes	62 (9.0)	63 (9.1)	26 (8.0)	51 (7.4)	202 (8.4)
Depression	46 (6.6)	39 (5.6)	13 (4.0)	40 (5.8)	138 (5.7)
Osteoarthritis	33 (4.8)	21 (3.0)	8 (2.5)	28 (4.0)	90 (3.7)
Coronary artery disease	16 (2.3)	17 (2.5)	3 (0.9)	10 (1.4)	46 (1.9)
Gout	5 (0.7)	8 (1.2)	4 (1.2)	7 (1.0)	24 (1.0)
Arthritis	4 (0.6)	6 (0.9)	4 (1.2)	4 (0.6)	18 (0.8)
Rheumatoid arthritis	5 (0.7)	4 (0.6)	1 (0.3)	7 (1.0)	17 (0.7)
Cardiac failure	5 (0.7)	4 (0.6)	0	3 (0.4)	12 (0.5)
Angina pectoris	1 (0.1)	0	1 (0.3)	0	2 (0.1)

[a]Defined as a medical history of obesity or baseline body mass index of $\geq$30 kg/m^2.
[b]As reported by the patient and indicated by the investigator in the electronic case report form.

included depression, osteoarthritis, coronary artery disease, gout, arthritis, rheumatoid arthritis, cardiac failure, and angina pectoris.

Relationships among comorbidities and baseline characteristics

Baseline disease characteristics were balanced across treatment arms, as previously published, and all patients had moderate to severe psoriasis regardless of comorbidity status (Table 2) (14,29,30). As patients were not randomized by presence vs. absence of baseline comorbidities in the original studies, imbalances existed between baseline characteristics of patients with and without active baseline comorbidities. Compared with patients with no active baseline comorbidities, those with active baseline comorbidities were older, heavier (as measured by weight and BMI), more likely to be biologic experienced, and more likely to have lived with a diagnosis of psoriasis for a longer time (Table 2). Specific associations were found between individual comorbidities and imbalances in baseline characteristics. Linear regression analysis identified that both higher weight and older age were associated with the presence of specific comorbidities, including obesity, hypertension, hyperlipidemia, and diabetes ($p < .05$ for all comparisons) (Table 3). Additionally, patients with concomitant PsA were more likely to have previous exposure to biologics ($p < .05$) (Table 3). These relationships may influence clinical response to secukinumab.

Efficacy

At week 12, secukinumab treatment significantly improved clinical outcomes regardless of comorbidity status in this cohort of patients with moderate to severe psoriasis. All patient groups receiving any dose of secukinumab were more likely to achieve PASI responses than patients with corresponding comorbidity status receiving etanercept or placebo ($p < .05$ for all comparisons) (Figure 2). Similarly, all patient groups receiving any dose of secukinumab were more likely to achieve IGA mod 2011 0/1 or IGA mod 2011 0 responses than patients with corresponding comorbidity status receiving etanercept or placebo ($p < .05$ for all comparisons) (Figure 3). Furthermore, patients treated with secukinumab 300 mg were more likely to achieve all PASI and IGA mod 2011 responses than those receiving secukinumab 150 mg, regardless of comorbidity status ($p < .05$ for all comparisons) (Figures 2 and 3). Numerical differences in achievement of PASI and IGA mod 2011 endpoints were observed between patients with and without comorbidities receiving any dose of secukinumab (Figures 2 and 3).

The effect of comorbidities on clinical response to treatment was not significant by χ^2 tests (Table 4). However, this same analysis identified that increased body weight ($\geq$90 kg) was associated with a decreased likelihood of achieving all PASI and IGA mod 2011 clinical responses ($p < .01$) (Table 4). No other covariate was consistently associated with decreased likelihood of achieving all PASI and IGA mod 2011 responses, although previous exposure to biologics was associated with decreased likelihood of achieving PASI90 and IGA mod 2011 0/1, and greater age was associated with decreased likelihood of achieving PASI100 responses ($p < .05$ for all comparisons).

Safety

The frequency of TEAEs was comparable across treatment arms stratified by comorbidity (Figure 4(A)). Few patients experienced serious adverse events or TEAEs leading to discontinuation (Figure 4(B,C)), and no new safety signals were identified.

Discussion

In this *post hoc* analysis of patients pooled from 4 phase 3 studies of secukinumab in patients with moderate to severe psoriasis, the majority of patients had comorbidities at baseline. The top 5 most frequent comorbidities included obesity, hypertension, PsA, hyperlipidemia, and diabetes. Imbalances in baseline characteristics existed between patients with and without comorbidities. Those with comorbidities were older, heavier, and more biologic experienced than those without. Additionally, patients with PsA were more likely to have had previous exposure to biologic agents. Consistent with the primary analyses, patients receiving any dose of secukinumab were more likely to achieve PASI and IGA mod 2011 clinical responses compared with those receiving etanercept or placebo. Numerical differences in treatment response were observed between patients with and without comorbidities receiving secukinumab, although the effect of

Table 2. Baseline demographics, treatment histories, and disease characteristics of patients with psoriasis stratified by presence vs. absence of active comorbidities[a].

	Secukinumab 150 mg		Secukinumab 300 mg		Etanercept 50 mg		Placebo	
Characteristic	Comorbidities ($n = 432$)	No comorbidities ($n = 260$)	Comorbidities ($n = 437$)	No comorbidities ($n = 254$)	Comorbidities ($n = 188$)	No comorbidities ($n = 138$)	Comorbidities ($n = 412$)	No comorbidities ($n = 280$)
Age, mean (SD), years	48.5 (12.9)	39.5 (12.2)	48.0 (13.0)	39.6 (12.2)	47.1 (12.9)	39.3 (11.7)	47.5 (12.1)	40.6 (12.7)
Male, *n* (%)	286 (66.2)	199 (76.5)	294 (67.3)	183 (72.0)	131 (69.7)	101 (73.2)	280 (68.0)	204 (72.9)
White, *n* (%)	335 (77.5)	164 (63.1)	341 (78.0)	164 (64.6)	142 (75.5)	77 (55.8)	329 (79.9)	180 (64.3)
Weight, mean (SD), kg	93.7 (24.6)	74.8 (14.2)	94.6 (24.1)	72.8 (12.9)	92.4 (21.3)	73.8 (13.3)	94.7 (23.5)	73.2 (13.4)
BMI, mean (SD), kg/m^2	32.0 (7.5)	25.1 (3.1)	32.1 (7.1)	24.7 (2.9)	31.3 (6.2)	25.1 (2.9)	32.1 (7.3)	24.7 (3.0)
Time since first diagnosis of psoriasis, mean (SD), years	20.0 (13.0)	14.6 (10.7)	18.8 (12.9)	14.1 (9.6)	18.7 (12.6)	13.4 (10.5)	18.6 (12.7)	15.9 (11.3)
Previous exposure to systemic psoriasis therapy, *n* (%)	292 (67.6)	155 (59.6)	289 (66.1)	149 (58.7)	122 (64.9)	92 (66.7)	250 (60.7)	170 (60.7)
Previous exposure to biologic systemic psoriasis therapy, *n* (%)	125 (28.9)	36 (13.8)	121 (27.7)	25 (9.8)	25 (13.3)	20 (14.5)	104 (25.2)	44 (15.7)
PASI (0–72), mean (SD)	22.7 (10.0)	22.8 (10.1)	22.1 (9.1)	23.7 (9.7)	23.1 (9.8)	23.4 (9.9)	22.3 (9.5)	22.7 (9.9)
PASI $>$ 20, *n* (%)	200 (46.3)	124 (47.7)	197 (45.1)	140 (55.1)	94 (50.0)	69 (50.0)	197 (47.8)	130 (46.4)
BSA, mean (SD), % involvement	32.5 (18.8)	34.8 (19.0)	31.3 (18.5)	35.9 (18.9)	33.0 (18.3)	34.4 (17.5)	31.4 (17.7)	33.3 (17.9)
IGA mod 2011 (0–4) category, *n* (%)								
Moderate (IGA = 3)	269 (62.3)	170 (65.4)	274 (62.7)	162 (63.8)	113 (60.1)	82 (59.4)	242 (58.7)	182 (65.0)
Severe (IGA = 4)	163 (37.7)	90 (34.6)	163 (37.3)	92 (36.2)	75 (39.9)	56 (40.6)	170 (41.3)	98 (35.0)
Current PsA, *n* (%)[b]	120 (27.8)	–	130 (29.7)	–	44 (23.4)	–	137 (33.3)	–
Time since first diagnosis of PsA, mean (SD), years	7.2 (7.5)	–	8.1 (8.3)	–	9.5 (11.6)	–	9.9 (9.0)	–
DLQI score, mean (SD)	12.9 (7.2)	13.3 (6.7)	13.7 (7.4)	13.3 (7.0)	14.0 (7.5)	12.5 (6.9)	12.9 (7.4)	12.1 (6.7)

BMI: body mass index; BSA: body surface area; DLQI: Dermatology Life Quality Index; IGA: Investigator's Global Assessment; PASI: Psoriasis Area and Severity Index; PsA: psoriatic arthritis.
[a]Patients with active baseline comorbidities had ≥1 comorbidity.
[b]As reported by the patient and indicated by the investigator in the electronic case report form.

Table 3. Relationships between comorbidities and baseline demographics and treatment histories of patients with psoriasis pooled from the ERASURE, FIXTURE, FEATURE, and JUNCTURE studies.

	Comorbidity[a]				
Covariate, OR (95% CI)	Obesity	Hypertension	Psoriatic arthritis	Hyperlipidemia	Diabetes
Previous exposure to biologic systemic psoriasis therapy, yes vs. no	0.89 (0.39–1.24)	1.10 (0.81–1.32)	**2.03 (1.88–2.14)**	**1.72 (1.53–1.86)**	1.05 (0.61–1.35)
Weight	**1.17 (1.15–1.19)**	**1.03 (1.02–1.04)**	1.01 (1.00–1.01)	**1.01 (1.01–1.02)**	**1.02 (1.02–1.03)**
Age	**1.03 (1.02–1.04)**	**1.09 (1.08–1.10)**	1.02 (1.01–1.03)	**1.07 (1.06–1.08)**	**1.06 (1.05–1.07)**

OR: odds ratio.
[a]Bold values indicate $p < .05$.

comorbidities on treatment was not found to be significant by χ^2 tests. Body weight of ≥90 kg was consistently associated with decreased achievement of PASI and IGA mod 2011 clinical responses. The imbalances in baseline body weight between those with and without comorbidities likely explain the observed numerical differences in treatment response between these 2 groups. Secukinumab appeared to be safe in patients with comorbidities; the frequency and severity of TEAEs were comparable across all groups studied and were aligned with long-term safety data (31–34). Secukinumab treatment was not associated with increased likelihood of TEAEs in patients with comorbidities.

In patients with psoriasis, body weight and BMI are known to influence clinical response to treatment with biologics, with increased BMI being a predictor of poorer response and reduction of body weight in obese patients associated with increased effectiveness of biologic therapy (35). TNFis have been found to be less effective in patients with higher BMI than in those with normal BMI (36,37). Further, a meta-analysis of patients with immune-mediated inflammatory diseases, including psoriasis, found that obese patients were approximately 60% more likely than patients with normal BMI to experience TNFi failure (38). Higher BMI or body weight also correlated with poorer outcomes and response to treatment with the IL-12/23 biologic ustekinumab, which is reflected by the approved dosing regimen that accounts for body weight: patients weighing ≤100 kg receive 45 mg of ustekinumab, and those weighing >100 kg receive 90 mg (39). In pharmacokinetic studies, patients weighing >100 kg were found to have faster clearance and greater volume of distribution of ustekinumab than those weighing ≤100 kg (40,41). Additionally, one cohort study of Italian patients receiving a new systemic treatment for plaque psoriasis found an inverse relationship between BMI and achievement of PASI75 (42), suggesting that these relationships may be common across systemic therapies for psoriasis. In general, increased

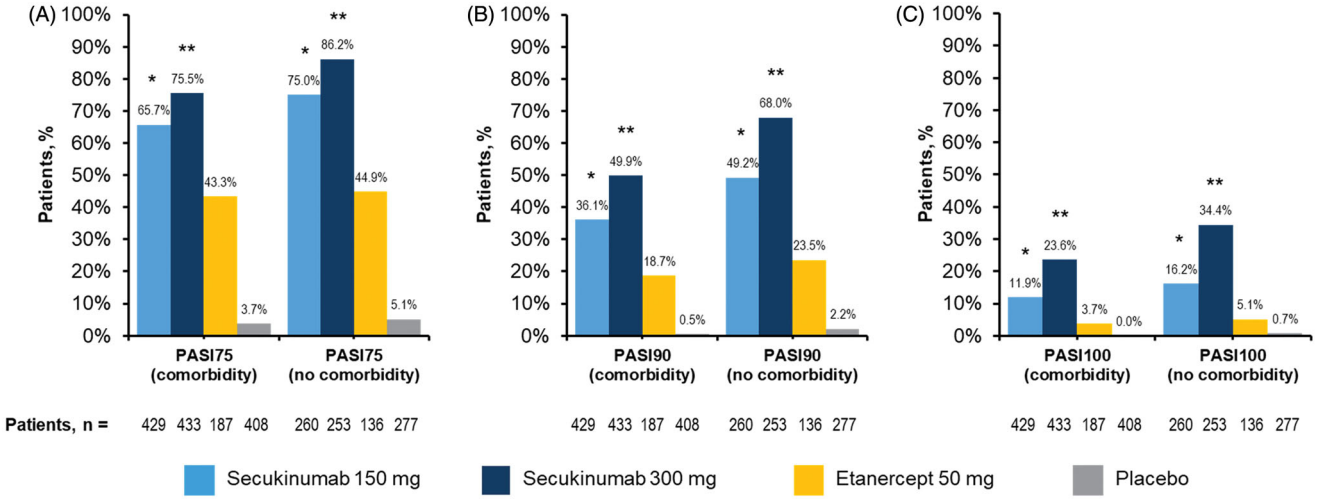

Figure 2. Efficacy as measured by (A) PASI75, (B) PASI90, and (C) PASI100 among patients with psoriasis stratified by presence or absence of active baseline comorbidities. PASI: Psoriasis Area and Severity Index. *$p<.05$ compared with etanercept and placebo. **$p<.05$ compared with secukinumab 150 mg, etanercept, and placebo.

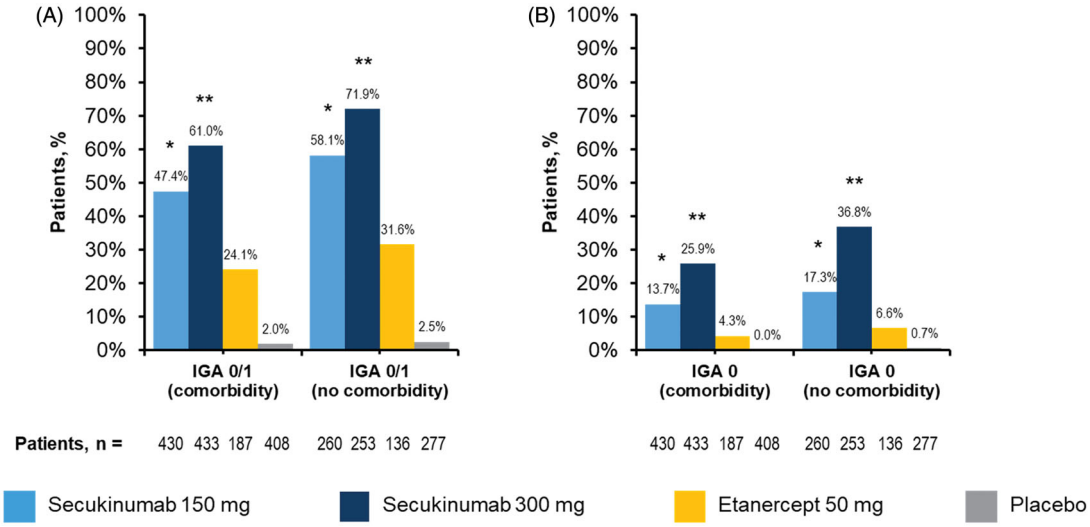

Figure 3. Efficacy as measured by (A) IGA mod 2011 0/1 or (B) IGA mod 2011 0 among patients with psoriasis stratified by presence or absence of active baseline comorbidities. IGA mod 2011, Investigator's Global Assessment modified 2011. *$p<.05$ compared with etanercept and placebo. **$p<.05$ compared with secukinumab 150 mg, etanercept, and placebo.

Table 4. Relationships between treatment response and baseline covariates across all patients with psoriasis pooled from the ERASURE, FIXTURE, FEATURE, and JUNCTURE studies[a].

	Predictor of response							
	Effect of comorbidities on treatment response		Age		Weight ≥ 90 kg		Previous exposure to biologics	
Response	χ^2 (DF)	*p* Value	χ^2 (DF)	*p* Value	χ^2 (DF)	*p* Value	χ^2 (DF)	*p* Value
PASI75	3.48 (3)	.32	0.05 (1)	.83	15.69 (1)	<.01	3.19 (1)	.07
PASI90	2.92 (3)	.40	2.38 (1)	.12	25.02 (1)	<.01	5.43 (1)	.02
PASI100	2.89 (3)	.41	3.93 (1)	.05	24.98 (1)	<.01	0.01 (1)	.91
IGA mod 2011 0/1	0.13 (3)	.99	0.90 (1)	.34	14.17 (1)	<.01	9.67 (1)	<.01
IGA mod 2011 0	3.21 (3)	.36	2.20 (1)	.14	23.16 (1)	<.01	0.23 (1)	.63

DF: degrees of freedom; IGA mod 2011: Investigator's Global Assessment modified 2011; PASI: Psoriasis Area and Severity Index.
[a]Analysis is adjusted for age, weight, prior biologic exposure, and comorbidities.

doses of biologics are likely required to adequately treat patients with higher BMI (43).

Although secukinumab is considered effective in patients regardless of body weight, relationships between effectiveness and patient BMI are beginning to emerge. In a pooled analysis of patients receiving secukinumab in the phase 3 ERASURE and FIXTURE trials stratified by BMI into quartiles, secukinumab 300 mg was effective in all quartiles as determined by the

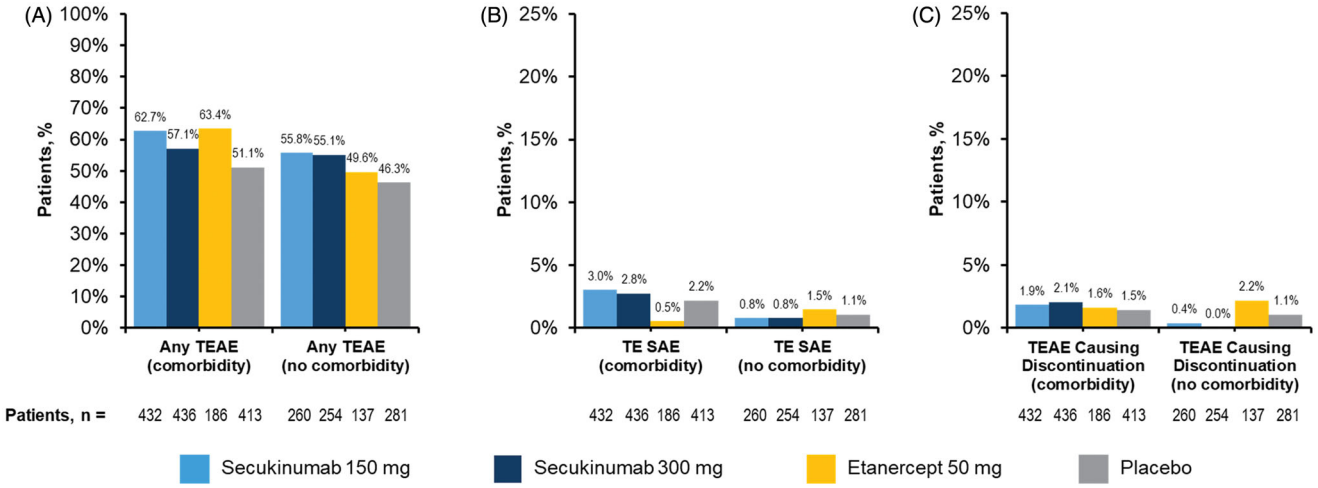

Figure 4. Safety as measured by (A) TEAEs, (B) TE SAEs, and (C) TEAEs leading to discontinuation among patients with psoriasis stratified by presence or absence of active baseline comorbidities. SAE: serious adverse event; TEAE: treatment-emergent adverse event.

proportion of patients achieving PASI75, PASI90, and IGA mod 2011 0/1, although a numerical trend of decreasing effectiveness with increasing patient body weight was observed (44). In the phase 3b OPTIMISE study, patients who achieved PASI75 but not PASI90 at week 24 of treatment with secukinumab were re-randomized to receive secukinumab 300 mg every 2 weeks or to continue receiving secukinumab 300 mg every 4 weeks (45). Patients in whom secukinumab was uptitrated every 2 weeks were numerically more likely to achieve PASI90 at week 52 than those receiving secukinumab every 4 weeks (57.0% vs. 46.5%) (45). The numerical benefit of decreased dosing intervals was greatest in patients weighing ≥90 kg (45).

Explanations for these observations may be rooted in both the pathophysiological mechanisms of psoriasis, including the potential inflammatory role of adipose tissue, and the pharmacokinetics of the biologic drugs themselves. Associations have been found among white adipose tissue, circulating levels of inflammatory adipokines released by adipose tissue, and the presence and severity of psoriasis (3,46). In pediatric patients with psoriasis, obesity seems to be associated with development and severity of psoriasis (47), with adiposity preceding the formation of psoriatic plaques (48). An ongoing trial is investigating the role of genes modulating adipokine and adipocyte activity in systemic inflammation and response to secukinumab (NCT03055494). As patients with greater body mass may require higher doses of biologics to achieve therapeutic serum concentrations (43), increased doses may be required to optimally treat heavier patients. A study of the safety and efficacy of higher doses of secukinumab in obese patients is currently underway (NCT03504852).

Studies comparing the effectiveness and safety of available biologic therapies in patients with comorbidities are important for informed shared decision-making in the treatment of psoriasis because relationships between psoriasis treatment and comorbidities remain poorly understood (2). Methodological shortcomings exist in previous studies evaluating the association between comorbidities and psoriasis; many epidemiological studies of psoriasis comorbidities do not use a validated comorbidities index (49). However, the presence of comorbidities has been found to be associated with more-advanced psoriatic disease, with the severity of comorbidities correlating directly to severity of psoriasis (50).

Although rigorous controlled trials are required to assess the effect of individual comorbidities on treatment response and safety of secukinumab, results presented here suggesting that secukinumab is safe and effective in patients with comorbidities are reinforced by evidence from clinical practice. Secukinumab has shown maintenance of therapeutic response over 5 years in an extension of the ERASURE and FIXTURE trials (NCT01544595), as well as the long-term monitoring study SCULPTURE (31), and has been used clinically for >5 years for the treatment of moderate to severe psoriasis. The safety of secukinumab has been demonstrated in patients with psoriasis, PsA, and ankylosing spondylitis over 5 years (31–34). True long-term safety of secukinumab, as with any drug, can be established only through real-world registry data. Despite intrinsic differences between clinical trials and clinical practice, including adherence to drug regimens and patient baseline characteristics (51), secukinumab retains a favorable safety profile in the real world (52), with approximately 80% drug survival after 1 year (27). As patients with psoriasis frequently experience comorbidities, the long-term use of secukinumab and its associated safety in real-world populations suggest that secukinumab is not widely contraindicated in patients with common comorbidities associated with psoriasis. The impact of secukinumab on comorbidities and in special populations should be considered as well (36,53).

Limitations

Some limitations are important to understand when considering the results of this study. Several common comorbidities of psoriasis were studied in this analysis, but others were not included, such as comorbid autoimmune diseases, demyelinating disease, inflammatory bowel disease, and concomitant chronic infection; these are additional factors that must be considered when selecting the optimal therapy for patients with psoriasis. In this *post hoc* analysis, patients were not randomized by presence or absence of specific comorbidities, and imbalances exist in baseline patient characteristics across treatment arms. The studies from which this patient population was pooled were not statistically powered to study the effects of individual comorbidities on treatment response, and analyses were not adjusted for multiple comparisons. As such, statistical comparisons presented here are for hypothesis generation only. Nonetheless, these findings suggest that the presence of

comorbidities appears to have little effect on the efficacy and safety of secukinumab, although the increased body weight of obese patients may decrease the likelihood of achieving optimal treatment response.

Conclusions

In this *post hoc* analysis of patients with moderate to severe psoriasis, secukinumab improved clinical outcomes and was well tolerated in patients with and without baseline comorbid conditions. Although comorbidity status did not significantly affect achievement of clinical response in patients treated with secukinumab, body weight of $\geq$90 kg was associated with decreased likelihood of achievement of clinical response for all PASI and IGA mod 2011 endpoints measured. This association could underlie observed numerical differences in treatment responses between patients with and without comorbidities. Further research is needed to test the effect of individual comorbidities on response to secukinumab; studies of secukinumab dosing in obese patients are currently underway to ensure that psoriasis treatment is optimized in these patients.

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