A prospective multicenter study assessing effectiveness and safety of secukinumab in a real-life setting in 158 patients

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Background: Secukinumab is a first-in-class interleukin 17A monoclonal antibody that has demonstrated an excellent safety and efficacy profile in phase 3 studies.

Objective: To evaluate the effectiveness of secukinumab in daily clinical practice and to understand the clinical and epidemiologic characteristics of patients treated with secukinumab in clinical settings.

Methods: In this multicenter prospective observational study, we recruited adult patients with moderate-to-severe plaque psoriasis from 12 hospitals in Spain during January-December 2016. These patients were treated with secukinumab and prospectively followed at 12-week intervals for 52 weeks.

Results: In total, 158 patients were recruited to the study. A Psoriasis Area and Severity Index (PASI) score improvement ≥75% over baseline (PASI-75) was achieved by 57%, 83.5%, 89%, and 78.5% of patients at weeks 4, 12, 24, and 52, respectively. PASI-90 was achieved in 27.8%, 62%, 64.6%, and 63.2% of patients at weeks 4, 12, 24, and 52, respectively; PASI-75 and PASI-90 responders were significantly more common among patients with a body mass index <30 kg/cm^2 and patients without previous biologic therapy failures.

Limitations: Observational study. Time from onset of psoriasis was not evaluated.

Conclusion: Secukinumab is a safe treatment with effectiveness rates similar to those found in its phase 3 studies. These rates endure up to a year from start of treatment. (J Am Acad Dermatol 2019;81:427-32.)

Key words: biologic therapy; IL-17; psoriasis; secukinumab.

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Secukinumab is a first-in-class interleukin (IL) 17A monoclonal antibody that has demonstrated excellent safety and efficacy profiles in phase 3 studies.[1] Nevertheless, patient profiles in real-life settings have differed from those seen in clinical studies.[2,3] Some studies have demonstrated that patients treated with secukinumab in the clinical setting are more heterogeneous, are more frequently obese, and have more previous treatment failures than the participants in the phase 3 studies.[4,5] However, these studies were retrospective, and thus, the results might be less reliable than results from prospective studies. The aim of our study was to evaluate the effectiveness of secukinumab in daily clinical practice and to understand the clinical and epidemiologic characteristics of patients treated with secukinumab in this setting.

CAPSULE SUMMARY

- Secukinumab (an interleukin 17A antibody) has demonstrated good efficacy in clinical trials. Nevertheless, among patients in real clinical settings, effectiveness rates can vary.
- Patients were more heterogeneous than in clinical trials but effectiveness rates were similar. Main predictors of treatment failure were high body mass index (>30 kg/cm^2) and multiple previous treatment failures.

METHODS AND MATERIALS

In this multicenter prospective observational study, we recruited adult patients with moderate-to-severe plaque psoriasis from 12 hospitals in Spain during January-December 2016. Patients included in the study were treated with secukinumab. Treatment criteria were moderate-to-severe psoriasis failing to respond to ≥1 systemic therapy (biologic or nonbiologic). Consecutive sampling was used to select all patients who met the treatment criteria during the sampling period. All sampled patients were provided with and signed an informed consent form for participation in the study.

All patients received secukinumab 300 mg subcutaneously weekly for 4 weeks and then every 4 weeks. All patients were screened with the appropriate tests before starting treatment (basic metabolic panel, hemogram, viral serologies, and interferon γ release assay).

Demographic data on patients (age, sex, body mass index [BMI], comorbidities, psoriatic arthritis, and alcohol and smoking habits) were obtained via clinical interviews and from hospital databases. Baseline Psoriasis Area and Severity Index (PASI) scores were recorded at the start of treatment. Patients were prospectively followed at 12-week intervals through week 52 (1 year). The main outcome variable was percentage of patients achieving a ≥75% (PASI-75) or ≥90% (PASI-90) reduction in their baseline PASI score at weeks 4, 12, 24, and 52. As a secondary outcome, percentage of patients achieving a target response of ≤1% body surface area affected was assessed, as proposed by Armstrong et al.[6] Reasons for patient withdrawal from the study were classified as lack of treatment efficacy, adverse effects, and other causes.

This study was conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects and was approved by the institutional review board of the General Hospital of Valencia's Investigation Foundation.

Descriptive statistics were calculated for each variable; frequencies and percentages were provided for categorical variables. Quantitative variables were represented as mean and standard deviation (SD). Differences between responders and nonresponders were compared by using a bivariate logistic regression and a χ^2 test. Patients with missing effectiveness values were imputed as nonresponders.

RESULTS

In total, 158 patients were recruited during the study. Clinical epidemiologic characteristics of the patients are summarized in Table I. The mean (SD) age was 46.5 (12) years, 90 (57%) were male, and 71 (44.9%) had a BMI >30 kg/cm^2 (defined as obesity). Alcohol intake was reported by 54 (34.2%) patients, smoking by 66 (41.8%) patients, and psoriatic arthritis was present in 55 (34.8%) patients. All patients had been treated with ≥1 conventional systemic treatment, and 106 (67.1%) had been treated with ≥1 (mean ± SD, 1.3 ± 1.2) biologic treatment. The mean (SD) baseline PASI was 12.5 (6.9).

At week fifty-two, 131 (82.9%) patients were still undergoing secukinumab therapy and 27 (17.1%) patients had discontinued treatment. Of these 27 patients, 8 discontinued treatment because of lack of efficacy, 15 because of loss of efficacy, and 4 were lost to follow-up.

The proportions of patients achieving PASI-75 at weeks 4, 12, 24, and 52 were 57%, 83.5%, 89%, and 78.5%, respectively, while the proportions achieving PASI-90 at the same time points were 27.8%, 62%, 64.6%, and 63.2% (Fig 1). The proportion of absolute PASI <3 achievers and mean absolute PASI reduction

Abbreviations used:

BMI: body mass index
IL: interleukin
PASI: Psoriasis Area and Severity Index
PASI-75: ≥75% reduction in PASI
PASI-90: ≥90% reduction in PASI
SD: standard deviation

are shown in Table II. At week twelve, 109 patients (70%) had achieved the target response of body surface area affected <1%. None of the patients had any change in secukinumab dose or received any other systemic treatment.

PASI-75 and PASI-90 achievement was significantly higher among patients with BMI <30 kg/cm^2 (Fig 2) and patients without previous biologic therapy failures (Fig 3). Multivariate analysis showed that PASI-75 and PASI-90 rates were unrelated to baseline PASI, age, sex, smoking habit, liver disease, dyslipidemia, psoriatic arthritis, or alcohol intake.

During the course of the study, adverse events were experienced by 28 patients (17.7%). The most frequent adverse events were headache (9 patients, 5.7%), nasopharyngitis (9 patients, 5.7%), hypertension (6 patients, 3.8%), oral candidiasis (5 patients, 3.2%), and diarrhea (2 patients, 1.3%). Any adverse event led to the modification or suspension of secukinumab treatment.

DISCUSSION

We present a prospective cohort of patients treated with secukinumab 300 mg daily in clinical practice that were followed for up to 1 year. PASI-75 and PASI-90 response rates found in our study are similar to those found by Langley et al in phase 3 clinical studies of secukinumab.[1] Of interest, our patients had more previous failures to biologic therapies (67% vs 12%).

According to the exclusion criteria of the ERASURE study,[1] 44 (28.2%) patients from our study would have been ineligible for participation (ie, PASI <12, uncontrolled hypertension, HIV positive, and previous use of IL-17 inhibitors). This finding is in agreement with studies showing that up to 30% of patients treated in a daily practice setting meet the exclusion criteria for most clinical trials.[7]

Our results are also similar to those of Notario et al,[5] who retrospectively studied 136 Spanish patients with moderate-to-severe psoriasis treated with secukinumab.[5] However, we found a higher response rate than Notario et al (PASI-75 83.5% vs 66% and PASI-90 62% vs 53%, respectively, at week 16)[5]; both cohorts had similar baseline PASI values and demographic characteristics. Our higher response rate might be due to the higher adherence to treatment found in our study (82.9%, vs 73.5% in Notario et al, at week 52), the exclusion of patients treated with 150 mg of secukinumab (vs 14% in their study), and the prospective basis of our study.[5] Doses <300 mg has been proposed to be less effective, with less cumulative benefit.[8]

Schwensen et al studied 69 patient records obtained from a multicentric database.[4] At week 12, they found PASI-75 and PASI-90 rates of 66.7% and 52.9%, respectively.[4] These results are also similar to

Table I. Comparison of baseline characteristics of patients included in this study and ERASURE study[1]

Characteristic	Included patients, n = 158	ERASURE study[1]
Age, y, mean ± SD	28 ± 17.7	44.5 ± 13.2
Male sex	90 (57)	(68.5)
Weight, kg, mean ± SD	86 ± 20.1	83 ± 21.6
BMI, kg/m^2, mean ± SD	30.8 ± 7	28.4 ± 6.4
Alcohol intake	54 (32.2)	NA
Smoking habit	66 (41.8)	NA
Dyslipidemia	45 (28.5)	NA
Hypertension	19 (12)	NA
Cardiovascular disease*	15 (9.5)	
Diabetes	23 (14.6)	
Liver disease	69 (43.7)	
Psoriatic arthritis	55 (34.8)	(15.3)
Baseline PASI, mean ± SD	12.5 ± 6.9	22.5 ± 9.2
Baseline DLQI, mean ± SD	12.8 ± 3.9	13.3
Previous no. biologic treatment		(11.6)
Any	106 (67.1)	
1	48 (30.4)	
2	27 (17.1)	
3	22 (13.9)	
4	6 (3.8)	
≥5	3 (1.9)	
Drug		
Etanercept	18 (11.4)	TNF inhibitor (19.6);
Infliximab	14 (8.9)	IL-12/23 inhibitor
Adalimumab	33 (20.9)	(13.1)
Ustekinumab	25 (15.8)	
Golimumab	3 (1.9)	
Brodalumab	2 (1.3)	

Values are n (%) unless indicated otherwise.
BMI, Body mass index; *DLQI*, Dermatology Life Quality Index; *IL*, interleukin; *NA*, not applicable; *PASI*, Psoriasis Area and Severity Index; *SD*, standard deviation; *TNF*, tumor necrosis factor.
*Includes coronary artery disease, stroke, and peripheral artery disease.

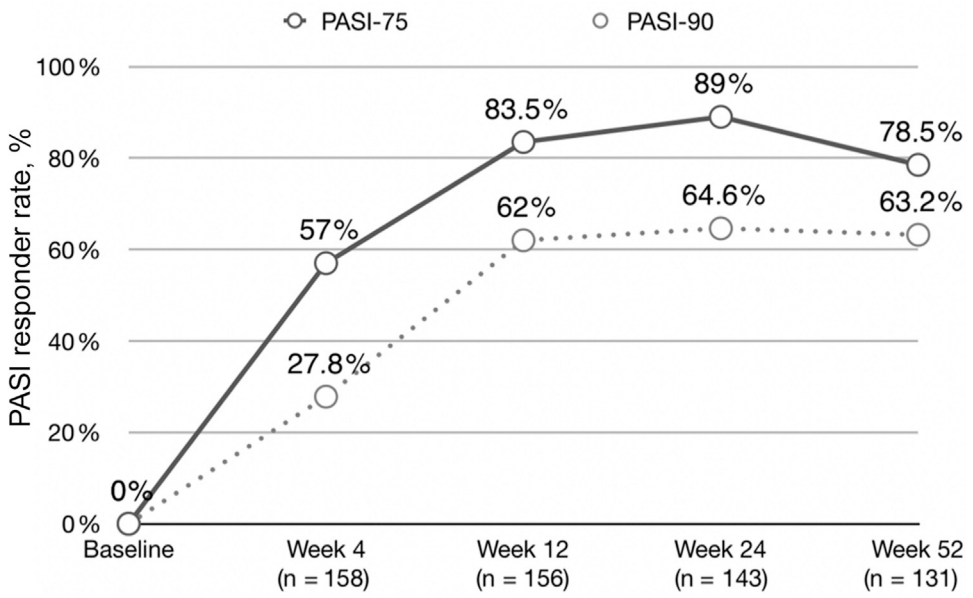

Fig 1. PASI-75 and PASI-90 responder rates at weeks 4, 12, 24, and 52. *PASI-75*: ≥75% reduction in Psoriasis Area and Severity Index; *PASI-90*: ≥90% reduction in Psoriasis Area and Severity Index.

Table II. PASI scores at weeks 4, 12, 24, and 52 of patients with moderate-to-severe psoriasis included in study

Outcome	Week 4, n = 158	Week 12, n = 156	Week 24, n = 143	Week 52, n = 131
PASI-75, n (%)	90 (57)	132 (83.5)	139 (89)	124 (78.5)
PASI-90, n (%)	44 (27.8)	98 (62)	102 (64.6)	100 (63.2)
Absolute PASI <3, n (%)	84 (53.2)	120 (75.9)	109 (69)	94 (59.5)
Absolute PASI score	4.2	2.1	1.8	1.9
Target response, <1% BSA affected, n (%)	47 (29.7)	109 (70)	113 (79)	102 (77.9)

BSA, Body surface area; *PASI*, Psoriasis Area and Severity Index; *PASI-75*, ≥75% reduction in PASI; *PASI-90*, ≥90% reduction in PASI.

ours. During our study we found no serious adverse events. This is in-line with the many other studies that have not found a significant risk associated with secukinumab. The long-term safety profile of secukinumab remains to be confirmed in longer prospective studies.[9]

Interestingly, patients with higher BMIs (>30 kg/cm^2) had considerably worse responses than nonobese patients. This result is supported by an investigation by Bruin et al that demonstrated that weight directly affects the pharmacokinetics of secukinumab.[10] This suggests that standard doses of biologic treatments might be insufficient in patients with large body surface areas and indicates the need to investigate alternative regimens with higher drug doses in obese patients. This approach has been tested with other biologic therapies, such as ustekinumab.

Another response modifier was previous failure of biologic therapies other than IL-17 blockers. We propose 2 hypotheses to explain multiple target resistance: patients with severe and resistant psoriasis might have different pathways involved than the classic T helper 17 cells (such as type I interferons or tumor necrosis factor pathways)[11] and patients treated with biologic therapies might have immunologic shifts that alter the classical psoriasis pathogenesis paradigm.[3] Patients with multiple previous failures typically have a longer duration of disease, which might be the main predictor of failure.[2,3]

Our study showed a treatment adherence of 95% at week 52. This finding is discordant with those of Egeberg et al, who found an adherence rate of <50% at week 25.[12] These differences might be due to the high censor rate among patients treated with secukinumab in their study (with short follow-up time for most patients). Also, the prospective design of our study might have improved patient treatment compliance. Furthermore, other real-life studies

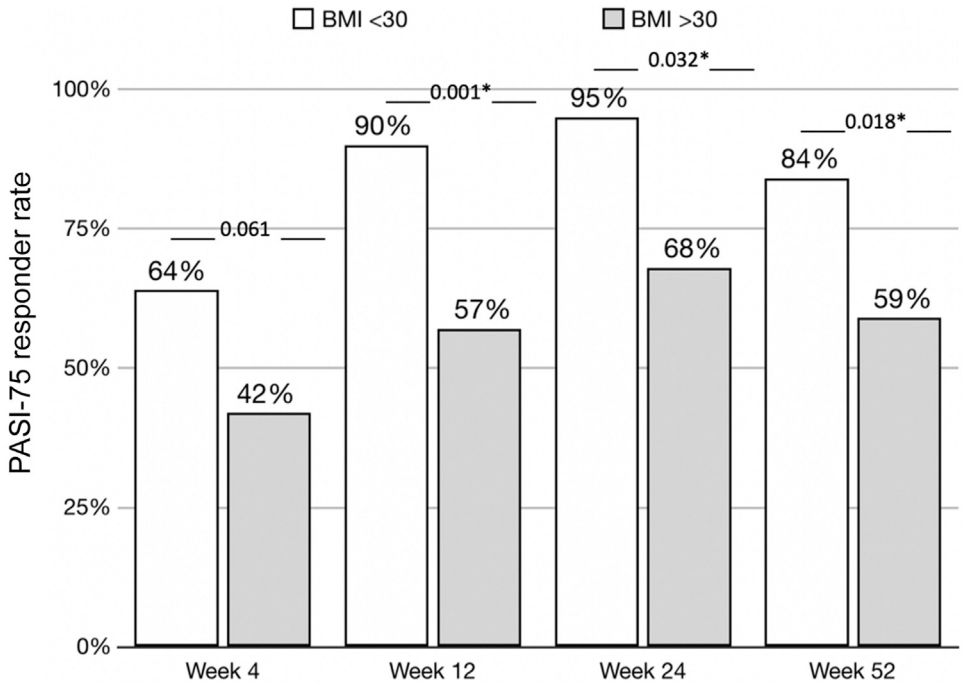

Fig 2. PASI-75 responder rates in patients with BMI <30 kg/cm^2 (white) and BMI >30 kg/cm^2 (gray) at weeks 4, 12, 24, and 52. **P* values of χ^2 test comparing responder rates are given above each pair of columns. *BMI*, Body mass index; *PASI-75*: ≥75% reduction in Psoriasis Area and Severity Index.

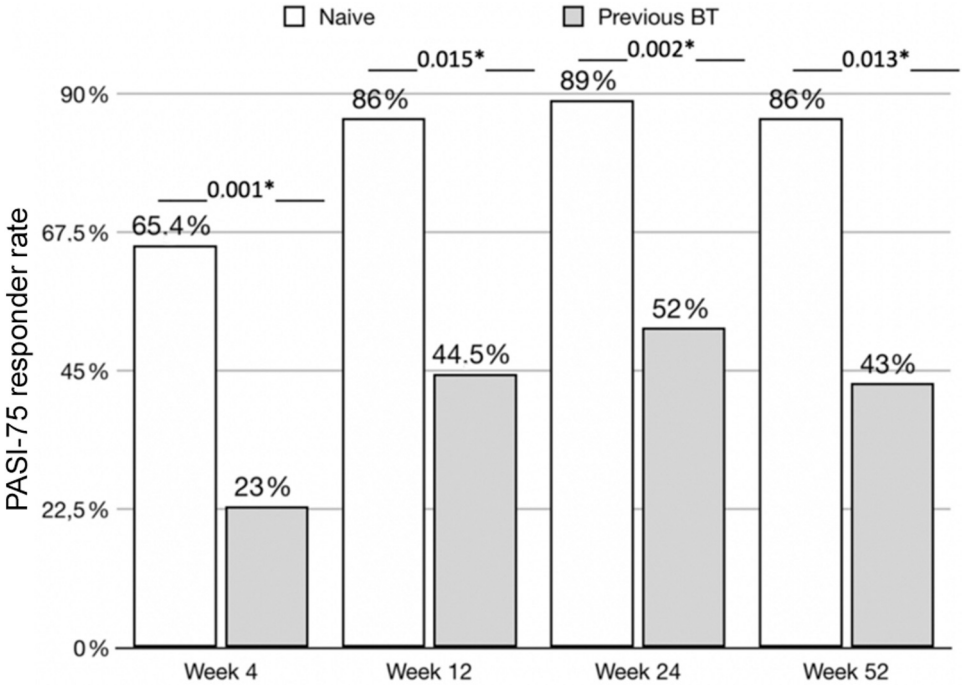

Fig 3. PASI-75 responder rates in patients with (gray) and without (white) ≥1 previous biologic treatment failure at weeks 4, 12, 24, and 52. **P* values of χ^2 test comparing responder rates are given above each pair of columns. *BT*, Biologic therapy; *PASI-75*: ≥75% reduction in Psoriasis Area and Severity Index.

have found survival rates similar to those we found.[4,5,13]

Our study is not without limitations. At the time of data collection (2016), some IL-17 antagonists (ixekizumab and brodalumab) and IL-23 p19 antibodies (guselkumab and tildrakizumab) that are now in use were not yet available for treatment of moderate-to-severe psoriasis in the clinical setting. Introduction of these medications might have an effect on drug survival of secukinumab. Another limitation is that time from psoriasis diagnosis was not studied. Other studies have proposed that this variable is relevant. It has also been hypothesized that early targeted treatments might alter disease evolution.[13] Thus, the role of IL-17 blockers in early onset psoriasis remains to be elucidated.[14,15]

In conclusion, patients in a real-life scenario might be more heterogeneous than those studied in clinical trials. Secukinumab is a safe and effective treatment, with effectiveness rates similar to those found in the phase 3 studies. These rates endure up to 52 weeks from the beginning of treatment.

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