Dermatology Practical & Conceptual

A Real-Life 208 Week Single-Centred, Register-Based Retrospective Study Assessing Secukinumab Survival and Long-Term Efficacy and Safety Among Greek Patients with Moderate to Severe Plaque Psoriasis, Including Difficult-to-Treat Manifestations Such as Genitals and Scalp

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ABSTRACT

Introduction: Psoriasis is a chronic inflammatory disease with multiple skin manifestations, and in case of lesions affecting the genital area, sexual health impairment and psychological distress can furthermore impair the patients quality of life. Secukinumab is a fully humanized immunoglobulin G1 kappa antagonist of IL-17A and is indicated for the treatment of moderate-to-severe psoriasis, since it shows a significant efficacy in clinical outcomes, with rapid onset of remission, prolonged treatment response rate, advantageous safety profile and a valuable improvement of the patients quality of life.

Objectives: This study was conducted in order to gather retrospective real-world data regarding the efficacy of secukinumab in treating patients with moderate-to-severe plaque psoriasis in Greece. To

fill the relevant literature gap, we included difficult-to-treat manifestations in our analysis, specifically regarding the efficacy in the genital area and on the skin folds where relevant data are missing both from the drug clinical program as well as from the real-world setting.

Methods: All adult patients receiving 300 mg secukinumab and attending follow-up visits on a regular basis, according to routine medical practice were included. The timeline of the study was from 2015 to 2020. Primary endpoint of the study was the percentage of patients who achieved a psoriasis area and severity index (PASI) 75 response rate at week 16 and week 52 post baseline. Secondary endpoints were the evaluation at baseline (week 0), week 4 (±1), week 16 (±1), week52 (±1), and week 104 (±1), week 156 (±1), week 208 (±1) of clinical outcomes, incidence of adverse events and potential predictive variables influencing response rate.

Results: Ninety-nine patients were included in the study population, from whom sixty six patients (66.67%) were bio-naive, whereas 33 patients had never received systemic treatment. Regarding difficult-to-treat manifestations, we recorded scalp involvement in 74.74% (74/99) of our patients, genital psoriasis in 27.27% (27/99) and skin folds involvement (psoriasis inversa) in 17% (17/99). At week 16, PASI75/PASI90/PASI100 were observed in 87.5%/69.8%/49%, respectively. At week 4 lesions affecting the genital area and patients with skin fold involvement experienced a rapid regression and 84.1% of patients achieved sPGA 0/1 (Physician Global Assessment). Treatment with secukinumab during the 208 weeks of observation did not reveal any major adverse event or systemic infection and generally it was well tolerated.

Conclusions: According to our outcomes secukinumab is an effective treatment choice for treating chronic plaque psoriasis, but, additionally, it can be efficacious in the subgroups of patients with difficult-to-treat manifestations, as our patients experienced great improvement starting even 5 weeks after treatment initiation. This real-life study offers information about clinical efficacy, retention and safety profile of secukinumab in patients from everyday clinical practice over a long-term, 4-year, follow-up period in Greece.

Introduction

Psoriasis is a chronic inflammatory disease with multiple skin manifestations and from epidemiological studies in the United States it is estimated that 3% of adult population shows signs of psoriatic disease [1]. 90% of patients with psoriasis have chronic plaque psoriasis, whereas less common psoriasis can affect the nails (23%-27%), face (49%) palms and soles (12%-16%), or intertriginous folds (21%-30%). Quality of life is impaired in patients with psoriasis, especially when sites of aesthetic significance are affected like the scalp and palms [2]. Moreover psoriasis affecting the genital area can be the cause of sexual health impairment and psychological distress, despite the fact that it only affects ≤ 1% of the body surface area (BSA) [3].

Although the exact pathogenetic mechanism of psoriasis has been under investigation until now, it seems that both genetic and environmental factors lead to an immune mediated hyperproliferation of the epidermal keratinocytes, an aberrant inflammatory infiltration of the dermis and an increased angiogenesis in the psoriatic lesions. Recently, the interleukin-23/T helper 17 (IL-23/Th17) pathway has been recognized as a key axis in the pathogenesis of psoriasis, which leads to the overexpression of the proinflammatory cytokine interleukin 17A (IL-17A). Secukinumab is a fully humanized immunoglobulin G1 kappa antagonist of IL-17A and is indicated for the treatment of moderate-to-severe psoriasis, moderate-to-severe paediatric plaque psoriasis, psoriatic arthritis (PsA), axial spondyloarthritis, juvevile idiopathic arthritis (enthesitis-related arthritis and juvenile psoriatic arthritis) and hidradenitis suppurativa [1-9]. Namely for the treatment of moderate-to-severe plaque psoriasis in adults, secukinumab is indicated as first line treatment. Secukinumab shows a significant efficacy in clinical outcomes, with rapid onset of remission, prolonged treatment response rate, advantageous safety profile and a valuable improvement of patients quality of life, not only from phase-III clinical trials but from real-life data as well [4,5].

Objectives

This study was conducted in order to gather retrospective real-world data regarding the efficacy of secukinumab in treating patients with moderate-to-severe plaque psoriasis at the psoriasis clinic of the Second Dermatology Department of the Aristotle University of Thessaloniki, “Papageorgiou” General Hospital.

Methods

In order to fill the relevant literature gap, we included difficult-to-treat manifestations in our analysis, specifically regarding the efficacy in the genital area and on the skin folds where relevant data are missing both from the drugclinical program as well as from the real-world setting. Frequency of follow-up visits was determined by attending physicians according to routine medical practice, however data were collected at 4, 16, 52, 104 and 208 weeks with a time window (± 1 week) after secukinumab treatment initiation.

Study Design

The Psoriasis Outpatient Clinic Registry of our clinic was reviewed and all adult patients receiving 300 mg secukinumab and attending follow-up visits on a regular basis, according to routine medical practice, were included. The timeline of the study was from 2015 to 2020. Written informed consent was obtained from each patient. Patients, aged ≥18 years, with a clinical diagnosis of chronic (≥6 months) moderate-to-severe plaque psoriasis, and candidates for systemic therapy who were receiving secukinumab (as per local label indication and according to routine medical practice) for at least for 16 weeks were included. Patients with a baseline Psoriasis Area and Severity Index (PASI) <10 were also included if the baseline Dermatology Life Quality Index (DLQI) was ≥10 or if there were symptoms in the scalp, genitals, palms, and feet or if onycholysis of at least 3 fingernails was characterized as persistent manifestation according to local and global guidelines. Use of concomitant anti-psoriatic agents (systemic or topical) was permitted as per everyday clinical practice.

Patients were excluded if the medical file data of interest was incomplete for eligibility evaluation and if there were any contradictions to IL-17/secukinumab intake as per label.

Primary endpoint of the study was the percentage of patients who achieved a PASI75 response rate at week 16 and week 52 post baseline. Secondary endpoints were the evaluation at baseline (week 0), week 4 (±1), week 16 (±1), week52 (±1), and week 104 (±1), week 156(±1), week 208 (±1) of:

a. absolute PASI; percentage of patients who achieved PASI75, PASI90, PASI100 response rates,
b. percentage of patients achieving scalp PGA 0/1 (sPGA)
c. percentage of patients achieving full/almost full genitals clearing;
d. percentage of patients achieving full/almost full folds clearing;
e. incidence of adverse events (AE) and serious adverse events (SAEs) and identification of AE leading to drug discontinuation;
f. potential predictive clinical variables influencing response at week 52, and 104.

Assessments were collected only when available in routine clinical practice, and they were not prerequisites for study participation.

Statistical Analysis

Frequencies and percentages are given for qualitative variables, while means and standard deviations, as well as medians and interquartile ranges, are given for quantitative variables. Since there were limited cases of loss to follow-up (<5% of the study sample), effectiveness data were analyzed using an 'as observed analysis'. Descriptive statistics were performed using relevant Descriptive statistics tests (for example Shapiro–Wilk/Shapiro–Francia test). For the comparison of categorical variables, Chi-Squared and Fisher Exact tests were used, while, depending on the distribution of continuous variables, unpaired t-test and Mann–Whitney U-test were applied. The Chi-Square test was applied to analyze differences in PASI Scores between subgroups of patients, such as PsA and bio-naïve patients. Univariable logistic regression analysis considering all variables collected was also performed in order to identify potential links and clinical factors of interest associated with the efficacy as per other similar RWE studies. Multivariable analysis could not be performed due to the high number of independent variables, along with the sample size of present study. All statistical analyses were done with IBM SPSS 27.0 (IBM). Alpha level of significance was set at 0.05.

Results

Ninety-nine patients were included in the study population and their demographic and baseline characteristics are summarized in Table 1. More precisely, 74 (74.75%) patients had scalp involvement, genitals and skin folds were affected in 27 (27.27%) and 17 (17.17%) respectively, and 32 (32.32%) of the studied population had psoriatic arthritis. Sixty-six patients (66.67%) were bio-naive, whereas 33 patients had never received systemic treatment. In the bio-experienced group, 12 patients had received one biologic agent, 12 patients had received two biologic agents and 5 patients had experienced treatment failure of any reason in 3 or more biologic agents. Moreover out of all the studied population 17.17% (17/99), 11.11% (11/99), 12 (12/99), 10.10% (10/99), 2.02% (2/99) had received adalimumab, etanercept, infliximab, ustekinumab and golimumab respectively. PDE4 inhibitors had been prescribed in 14.14% (14/99) of them. Mean BMI index in our study population was 29.3.

Regarding comorbidities 15 patients (15.15%) were obese (BMI>30), 42 patients (42.42%) had Hashimoto disease, 19 patients (19.19%) were diagnosed with depression or anxiety disorder and 8 patients (8.08%) had diabetes mellitus. Overall 53 patients (53.54%) had no comorbidities,

Table 1. Epidemiological and clinical characteristics at baseline (N = 99).

Characteristics	N	N	%
Age (yr, median, range)	99	50 (23-76)	
Sex male	99	53	53.5
Weight (kg, mean [SD])	99	87.78 [17.98]	
BMI (mean, [SD])	99	29.3 [4.88]	
BSA (mean [SD])	99	27.14 [12.01]	
PASI baseline (mean [SD])	99	12.7 [3.94]	
DLQI baseline (mean [SD])	99	11.68 [2.95]	
Psoriatic arthritis (N, %)	99	32	32.32
Previous systemic treatment	99	66	66.67
Conventional treatment	61/99	61	61.61
Previous Biological therapy	33		
Biologic naive	99	66	66.67
Psoriasis genital involvement	99	27	27.27
Psoriasis scalp	99	74	74.74
Psoriasis involving folds	99	17	17.17
Psoriasis nails	99	49	49.49
Comorbidity	N	n	%
Hashimoto disease	99	42	42.42
Obesity (BMI>30)	99	15	15.15
Depression	99	12	12.12
Diabetes mellitus	99	8	8.08
Anxiety disorder	99	7	7.07
Hypertension	99	6	6.06
Coronary disease	99	3	3.03
Dyslipidemia	99	3	3.03
Smoking	99	17	17.17
Patients comorbidities			
None	99	53	53.53
1-2	99	35	35.05
>3	99	11	11.11

BMI = Body Mass Index; BSA = Body Surface Area; DLQI = Dermatology Quality of Life Index; SD = standard deviation.

5 patients (5.05%) had one comorbidity, 30 patients (30.30%) had two comorbidities and 11 (11.11%) patients had 3 or more comorbidities. 17.17% of the patients were active smokers (> 10 cigarettes/day).

All patients started receiving secukinumab as monotherapy together with topical steroids and vitamin D analogues. Topical treatment was discontinued by almost all patients (92/99, 93%) by the first follow up visit at week 4. Cyclosporine was added as additional therapy for two patients, for 12 weeks (week 4-week 16) and for 24 weeks (week 60-week 84) respectively. Four patients received methotrexate additionally, two at week 8, one at week 84 and one at week 116 respectively.

Baseline mean PASI, BSA, sPGA and DLQI scores are 12.7, 27.14, 2.2 and 11.68 respectively. Addressing the efficacy of secukinumab at week 16, PASI75 was achieved by 84/96 (87.5%) patients, PASI90 by 67/96 (69.8%) and PASI100 by 47/96 (49%) (Table2). By week 52 PASI75/PASI90/PASI100 was achieved by 86.4%/77.8%/43.2%, by week 104 PASI75/PASI90/PASI100 was achieved by 94.5%/78.2%/47.3% and in 9 patients having completed 208 weeks of therapy PASI100/PASI90 was achieved in a percentage of 88.9%/100% respectively (Table 2).

Aiming to identify potential predictive factors influencing response, univariable analyses were performed at weeks 52 and 104 taking into consideration various parameters, namely age, height, weight, BMI, BSA, disease/therapy duration, previous treatments (conventional/ biologic), special manifestations of psoriasis (scalp, nails, genitals, folds) and comorbidities (PsA, obesity, coronary disease, depression,

Table 2. Clinical efficacy of secukinumab.

PASI outcomes	AS OBSERVED		
	WEEK	N	N (%)
PASI 75	4	99	55/99 (55.6%)
	16	96	84/96 (87.5%)
	52	81	70/81 (86.4%)
	104	55	52/55 (94.5%)
	156	30	29/30 (96.7%)
	208	9	9/9 (100%)
PASI 90	4	99	25/99 (25.3%)
	16	96	67/96 (69.8%)
	52	81	70/81 (77.8%)
	104	55	43/55 (78.2%)
	156	30	24/30 (80.0%)
	208	9	9/9 (100%)
PASI 100	4	99	14/99 (14.1%)
	16	96	47/96 (49.0%)
	52	81	35/81 (43.2%)
	104	55	26/55 (47.3%)
	156	30	15/30 (50.0%)
	208	9	8/9 (88.9%)

PASI = Psoriasis Area and Severity Index.

diabetes mellitus, dyslipidemia, hypertension, Hashimoto disease, anxiety disorder, smoking). In a univariate analysis, no medical, sociodemographic and the assessed clinical biomarker was significantly associated with PASI responses.

Regarding difficult-to-treat manifestations, we recorded scalp involvement in 74.74% (74/99) of our patients, genital psoriasis in 27.27% (27/99) and skin folds involvement (psoriasis inversa) in 17% (17/99). After secukinumab initiation (week 4) lesions in the genital area and patients with skin fold involvement experienced a rapid regression which was evident in 37/44 (84.1%) of patients. Skin folds and genitals were remarkably cleared at week 5 (mean week of clearing 5.29 [SD 1.49], median week of clearing: 5, [IQR:2]), and sPGA 0/1 at week 4. Regarding drug retention, we report 11 patients that had to discontinue treatment throughout the observation period. 7 patients lost PASI75 within more than 2 years of the treatment and lost its effectiveness. 3 patients had to switch to other therapies because they did not respond to the drug by week 16 (Table 3).

Safety

Most of the adverse events (AE) recorded was characterized as low grade and did not require a treatment discontinuation. Actually 3 patients reported AE: two patients reported fatigue grade 1 CTCAE possibly drug-related and one reported headache grade 1 CTCAE probably not-drug related. Four patients had to discontinue the treatment up until week 16 due to lack of efficacy. Lastly, one patient was diagnosed with ulcerative colitis at week 108 and the treatment was discontinued. Up until the 208 weeks of the observation period no major adverse events were recorded.

During the observation period after week 16 and up until week 208, 11 patients discontinued the treatment due to lack of efficacy and this was observed mainly after 104 weeks of therapy, in bio-experienced patients and patients with multiple comorbidities (Table 3).

In three patients a quantiferon tuberculosis conversion was recorded, but a systematic infection was not confirmed. For safety reasons those patients underwent prophylactic antibiotic therapy.

Conclusions

Our study provides retrospective data of patients with chronic plaque psoriasis and their treatment outcomes after receiving secukinumab in real-life clinical practice in Greece. Additionally, we focused on difficult-to-treat areas, namely psoriasis affecting the skin folds and the genital area, mainly because data of the effect of secukinumab on these manifestations are limited. The studied population that was selected were patients with moderate to severe chronic plaque psoriasis that were treated with secukinumab at the recommended dose. Bio-naïve, as well as bio-experienced patients were included. Increased rates of comorbidities were recorded, with almost half of the patients reporting at least one; a factor that generally levels up the difficulty in managing the disease. Secukinumab accomplished to improve the disease burden in an impressively fast manner, with over half of the patients (55.6%) achieving PASI75 and one out of four patients (25.3%) achieving PASI90 at week 4. This improvement continued to increase to reach at week 16 PASI75/PASI90/PASI100 in 87.5%/69.8%/49% respectively.

In accordance with the treatment outcomes of this study, secukinumab has shown high efficacy in managing psoriasis quickly. In fact in ERASURE, FEATURE and JUNCTURE clinical trials there was a PASI75/PASI90/PASI100 reduction rate at week 16 in 86.1%/69.8%/41.6% [5]. Similar were the results from Rompoti et al in Greece where, at week 16, a PASI75/PASI90/PASI100 reduction rate in 83.3%/70%/46.3% of the patients was recorded [6]. Our study population shares some characteristics with the abovementioned study in Greece. Namely both include overweight patients (mean BMI: 29.3; range: 18.4-45.2 versus 29.1; range: 17.3-50.2) and almost half of the studied population in both trials have at least one comorbidity (46% versus 49.4%). We report 32.3% patients with PsA whereas Rompoti et al report 43.2% (versus 20% in clinical trials). Bai et al conducted a systematic review with a network meta-analysis (NMA) of all randomized trials in order to determine the differences in efficacy and safety profiles of Il-17,

Table 3. Previous treatment, Adjuvant therapy, reason for discontinuation.

Patient (gender, age)	Previous treatment	Adjuvant therapy	Week of treatment	Reason for discontinuation	Discontinuation time
Female, 76y		acitretin	Week 52	Loss of effectiveness	Week 80
Male, 49y	Ustekinumab	Topical steroids	Week 24	Loss of effectiveness	Week 52
Male, 55y	Infliximab, Ustekinumab	Topical steroids	Week 48	Loss of effectiveness	Week 112
Male, 52y		Topical steroids	Week 108	Loss of effectiveness	Week 160
Male, 31y	Cyclosporine	Topical steroids	Week 52	Loss of effectiveness	Week 108
Female, 59y	Cyclosporine, Infliximab Methotrexate, Apremilast			Loss of effectiveness	Week 70
Female, 53y	Cyclosporine, Acitretin	Topical steroids	Week 52	Loss of effectiveness	Week 120
Male, 55y				No response	Week 16
Female, 47	Ustekinumab, Adalimumab			No response	Week 16
Male, 52y	Cyclosporine, Infliximab, Adalimumab, Methotrexate	Methotrexate	Week 0	No response	Week 20
Male, 42y				Ulcerative colitis	Week 152

IL12/23 and IL23 inhibitors used in treating moderate to severe plaque psoriasis. Regarding the short-term achievements amongst 19840 patients from 28 trials secukinumab ranked first in achieving sPGA 0/1 or IGA 0/1 or PGA 0/1, and second in achieving PASI75 at week 12 or 16 [7]. In agreement with that, and according to the results of our study, secukinumab is highly efficacious in managing the disease burden of chronic plaque psoriasis in a fast manner in real life clinical practice too. In phase II/III, clinical trials patients are selected according to specific inclusion criteria. It is reasonable to hypothesize that in a real-world setting, where patients differ at least in disease severity and comorbidities, treatment efficacy can vary vastly. Augustin et al designed a review of all available published studies of real-world evidence using secukinumab in treating plaque psoriasis from 1 January 2015 to 31 May 2019. This meta-analysis included 43 studies and the effectiveness results for PASI75/PASI90/PASI100 at 12 weeks were 72%/50%/36% respectively. The endpoint of clinical improvement of psoriasis in our real-life population complies with this data, supporting additionally the consistency secukinumab offers in fast treatment efficacy.

With regard to the durability of response, secukinumab presented long-lasting and went as far as to improve the efficacy at subsequent timepoints in this study, with almost 100% of patients maintaining PASI 75 response, 78.2% achieving PASI 90 response and 47.3% achieving PASI 100 response at week 104, whilst these efficacy rates were further sustained until the end of the observation period (week 208). These findings are in agreement with clinical trials reporting 5-year data, as well as other long-term real-life studies for Secukinumab [8-10].

Addressing the difficult-to-treat psoriatic manifestations, in particular scalp psoriasis, nail psoriasis and palmoplantar psoriasis, secukinumab has shown a rapid and sustained response in improving psoriatic lesions and associated symptoms [11-15]. Likewise treatment response in our studied population showed significant improvement in difficult-to-treat specific locations. We recorded scalp involvement in 74,74% (74/99) of our patients, genital psoriasis in 27.27% (27/99) and skin folds involvement (psoriasis inversa) in 17% (17/99). After secukinumab initiation lesions in the genital area and patients with skin fold involvement experienced a rapid regression which was evident in 37/44 (84.1%) of patients. Skin folds and genitals were remarkably cleared at week 5 (mean 5.29 [SD 1.49], median: 5, [IQR:2]), and sPGA 0/1 at week 4. Data regarding secukinumab efficacy on areas with fold involvement as well as genital psoriasis are lacking from the drug clinical program, as well as the real-world setting. To our knowledge this is the first study that included skin fold improvement as a treatment endpoint for investigating the treatment efficacy of secukinumab in this difficult-to-treat area. However, patients of this study who had chronic plaque psoriasis and lesions affecting the skin folds and the genital area could be characterized as

secondary involvement. Burlando et al recently presented the superiority of anti-IL17 antibodies, in comparison to anti-IL12/23 and anti-TNFα drugs, in improving genital psoriasis in a small group of female patients [16].

With regard to drug retention, we report only 11 patients that had to discontinue the treatment. Seven patients lost PASI75 within more than 2 years of treatment and lost its effectiveness. Three patients had to switch to other therapies because they did not respond to the drug by week 16 (Table 3). These results adhere to what has been presented in other real-world studies assessing psoriasis patients treated with Secukinumab [6,10,17]. Additionally, it needs to be mentioned that, in our study, almost half of the patients who discontinued secukinumab (5/11, 45%) were bio-experienced with at least one biologic drug that failed in the management of the disease. Previous biologic experience has been already identified as a factor influencing drug survival [18].

Another key point to be mentioned is the fact that in January 2022, the local label of Secukinumab was updated to include an intensified dosing scheme (300 mg every 2 weeks, as maintenance dose) for adult patients with moderate to severe plaque psoriasis and body weight 90 kg or higher, based on clinical response. Since the observation period of this study started before this update, it is not known, whether the efficacy outcomes in patients who belong to this sub-population and show a sub-optimal response could have responded better, had this option been available at the time [19].

Treatment with secukinumab during the 208 weeks of observation did not reveal any major adverse events or systemic infections and it was generally well-tolerated. Only three patients reported AEs of low grade, which at no point was an adequate enough reason to discontinue secukinumab. These were characterized as self-limited without requiring any additional treatment.

One 42-year-old male patient was diagnosed with ulcerative colitis at week 152 of treatment. Personal and family history were negative of any inflammatory bowel disease, and he was a smoker. This is characterized as a paradoxical gastrointestinal effect of IL-17 inhibitors with a still unclear pathogenetic mechanism. It is believed that type I interferon might be involved and may be the reason for a hyperactive innate inflammatory pathway [20]. Furthermore, three of our patients had a quantiferon tuberculosis conversion and as per the guidelines they underwent prophylactic antibiotic therapy without clinical or radiographic evidence of TB infection.

We acknowledge the fact that this is a retrospective monocentric observational study and the data extracted were obtained from a small number of patients. This retrospective nature of this study could also explain the small number of reported AEs extracted from patient records that were used for this analysis.

According to our outcomes, secukinumab is an effective treatment choice for treating chronic plaque psoriasis, but, additionally, it can be efficacious in the subgroups of patients with difficult-to-treat manifestations. Especially, regarding lesions at the genital area, as well as psoriasis inversa, patients in our study experienced a great improvement and this occurred rapidly at a mean time of 5 weeks after therapy initiation. In addition, the already well described advantageous safety profile of secukinumab is confirmed by the results of this study, since we did not report any serious adverse events during the 208 weeks observational period. Consequently, this real-life study offers information about clinical efficacy, retention and safety profile of secukinumab in patients from everyday clinical practice over a long-term, 4-year, follow-up period in Greece.

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