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Original Article

Efficacy and safety of secukinumab in the treatment of chronic plaque psoriasis: A 52-weeks follow up study

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Abstract

Background Psoriasis is a chronic inflammatory skin disease and other multiple chronic conditions are observed with it, including depression, cardio-metabolic disorders and diminished quality of life. Interleukin (IL)-17A has a fundamental role in the pathogenesis of psoriasis. Secukinumab is a monoclonal anti-IL-17A antibody and it is recommended to be used in plaque psoriasis of moderate to severe intensity.

Objective To determine efficacy and safety of secukinumab in the treatment of chronic plaque psoriasis.

Methods Twelve patients with chronic plaque psoriasis, fulfilling the inclusion and exclusion criteria, were enlisted in this study. Secukinumab (300 mg) subcutaneously at weekly intervals was given to patients for two consecutive weeks followed by 150 mg dose at weekly intervals for three weeks and then a dose of 150 mg at monthly intervals until week 24. Each patient was followed up for 52 weeks. Primary end points for establishing the efficacy of the treatment was achievement of PASI 75 and DLQI score of 0-1, at week 12. Safety of secukinumab was assessed by observing any side effects in the patients on each follow up visit.

Results Both primary efficacy end points were achieved in our study. PASI 75 was attained in 11 (91.7%) patients at week 12. DLQI score of 0-1 was observed in 11 (91.7%) patients at week 12. There were no significant side effects seen in any of the patients.

Conclusion Secukinumab showed excellent efficacy in the treatment of moderate to severe chronic plaque psoriasis with a very good safety profile.

Key words
Psoriasis; Secukinumab; PASI.

Introduction

Psoriasis clinically presents as erythematous scaly plaques, mainly affecting extensor surfaces of the skin and scalp. It is a chronic inflammatory dermatosis mediated by the immune system.[1,2] Around 1-3% of the world's population is affected with psoriasis. Almost 60 million people have psoriasis globally.[3,4] Psoriasis is a long-standing dermatological disease and manifests as various clinical types i.e. plaque, pustular, flexural, guttate or erythrodermic.[2]

The exact etiology is unknown. Autoimmune disease mediated by T lymphocytes is

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considered to be the main etiological factor in psoriasis. In many patients, association with HLA antigens is seen. Genetic predisposition of the disease is suggested by familial occurrence. A bi-model age of onset is seen in psoriasis. First peak of psoriasis occurs from 15 to 20 years of age and the second peak is seen from 55 to 60 years. Both males and females are affected with psoriasis but it begins at an early age in females.[3]

The pathogenesis of psoriasis is multifactorial. An aberrant T cell mediated immune response is considered to be essential in the development of plaque psoriasis. This altered immune response principally involves substantial inflammation and abnormal keratinocytes differentiation. Keratinocytes produce several cytokines namely interleukin (IL)-23, IL-22, IL-17A and tumor necrosis factor-α (TNF-α). These cytokines are highly upregulated in psoriatic skin.[5] The pro-inflammatory cytokine, IL-17A, that plays a major role in etiopathogenesis of psoriasis is increasingly expressed in this disease. The cytokines IL-17A is produced by T helpers 17 (Th17) cells, mast cells, neutrophils and T cytotoxic 17 cells, which in turn triggers keratinocytes to secrete chemokines and other pro-inflammatory mediators and also causes increased production of antimicrobial peptides that leads to enhanced and sustained immune responses in the skin.[5-7]

There are numerous extracutaneous comorbidities and complications associated with moderate to severe psoriasis. Cardio metabolic disorders, obesity and joints involvement are most commonly observed with psoriasis. It causes significant morbidity and is associated with substantial impairment of physical and psychological wellbeing of the patients and decreased quality of life.[1,8,9]

Standard treatments of psoriasis include topical therapies, light therapy and systemic therapy (methotrexate, cyclosporin and acitretin). These conventional treatment options have not completely fulfilled the requirements of patients.[10] Biological therapies (TNF-α and IL-23 inhibitors) are recently being used to manage psoriasis of moderate to severe intensity. These biologic treatments are quite effective and generally well tolerated, however the safety profile of these drugs in the long run is still unknown. Biologics, selectively targeting IL-17A, are increasingly used due to proven efficacy as well as satisfactory safety profile compared with TNF-α inhibitors.[11]

Secukinumab is an anti IL-17A antibody that inhibits IL-17A. Secukinumab showed good safety and was tolerated well with promising clinical response as demonstrated by remarkable improvement in psoriasis area and severity index (PASI) score and dermatology life quality index (DLQI) scores in patients of psoriasis.[12-14]

The rationale of our study is that psoriasis is quite commonly seen in our population and it is associated with systemic manifestations and has negative effects on QOL of patients. Hence, there is a need to find an efficacious treatment modality with minimum side effects for the management of recalcitrant cases of psoriasis. Such research work is rarely conducted in this country as majority of the patients cannot afford this expensive treatment option. The scarcity of research data related to this topic warrants the need to evaluate long-term efficacy and safety of this drug in this setting.

Methods

The present study was carried out in the Department of Dermatology, Ameer-ud-Din Medical College/ LGH, after taking permission from the institutional review board. 12 patients were enrolled in this study having age ≥18 years, of either sex and with clinically diagnosed chronic plaque psoriasis of at least 6 months

duration. Patients provided written informed consent. All the selected patients were candidates for systemic treatment which means patients of plaque psoriasis having moderate to severe intensity (PASI score ≥10) and in which disease was not effectively controlled by topical treatment phototherapy and/or previous systemic treatment.

Patients having other clinical types of psoriasis (flexural, erythrodermic or guttate etc.), psoriasis caused by drugs (recently caused by medications or aggravated from beta-blockers, calcium channel blockers or lithium) and patients who received secukinumab or any other biologic drug in the past (directly targeting IL-17A/ or its receptor) were excluded from the study. Pregnant and lactating women, patients having history of hypersensitivity to secukinumab, patients with any other active inflammatory diseases or having underlying systemic conditions (hematologic, renal, hepatic, pulmonary infectious) were also excluded from the study.

Pre-treatment evaluation was conducted along with detailed history and clinical examination. The work-up included routine investigations, lipid profile, chest X-ray, hepatitis B and C serology and T-spot test. Patients were given 300mg of secukinumab subcutaneously at weekly intervals for two consecutive weeks (week 0 and week 1) followed by a dose of 150 every week for three weeks (week 2 to week 4) and then a dose of 150 mg at monthly intervals until week 24. Each patient was followed up for a total duration of 52 weeks. In case of start of relapse, patients were administered 150 mg secukinumab (subcutaneously) on monthly intervals for further three months.

Assessment of severity of psoriasis was done at baseline and at each follow up visit using PASI score. PASI score varies from 0 – disease absent to 72 - highest disease activity and it is measured by aggregating the severity of lesion and area affected by psoriasis into one score. The body is divided into four areas i.e. head, arms, trunk, and legs. The area multiplier for different parts are head – 0.1, arms – 0.2, body – 0.3 and legs – 0.4. To evaluate final PASI score, first each area is scored separately and then these scores are added. Measurement of individual part for involvement of surface area of skin affected is done from 0 (0%) to 6 (90-100%). Severity is assessed from 0 (none) to 4 (highest) for erythema thickness and scaling. For each area, surface area score is multiplied by severity score and area multiplier to get the final score. The final PASI is calculated by adding scores of all four areas.[15]

Quality of life of patients was assessed using DLQI at baseline and at week 12. DLQI is a questionnaire comprising of 10 questions from multiple domains of life (personal, social and work related). Each question is scored from 0 (not at all) to 3 (very much). Final DLQI score is a sum of the scores of all ten questions. DLQI scores are interpreted as; no effect at all (0-1), minimum effect (2-5), moderate effect (6-10), very large effect (11-20) and extremely large effect (21-30) on patient's quality of life.[16]

Safety was measured by observing any side effects seen in patients during treatment with secukinumab and the severity of these adverse effects was also recorded. The assessment conducted at each scheduled follow up visit included monitoring of hematology, blood chemistry and urine, assessment of vital signs, body weight and physical examination. The adverse effects noted were nasopharyngitis, URTI, rhinorrhoea, oral herpes, candidiasis, urticaria, GIT complaints (diarrhea, constipation, mucus or blood in stool), SOB, productive cough, weight loss and any other side effects if observed.

Two primary end points were defined for

establishing the efficacy of the treatment. First, at least 75% decrease in PASI score (PASI 75) from baseline at week 12. Second, attainment of DLQI score of 0-1 at week 12. Secondary end points of study were at least 90% decrease in PASI score (PASI 90) till week 24 and maintenance of PASI 90 from week 24 through week 52. Safety of secukinumab was assessed by observing any above-mentioned side effects, in the patients on each follow up visit.

Results

This study was carried out on 12 patients of chronic plaque psoriasis. Mean age of patients was 41.75±9.18 years. Number of male patients was 8 (66.7%) and female patients was 4 (33.3%). The mean duration of disease was 14.17±7.66 years and the mean weight of patients was 74.42±15.15kg (**Figure 1**). Comorbidities such as hypertension was seen in 2 (17%) patients and arthralgia was present in 3 (25%) of patients.

Both primary efficacy end points were achieved in our study. PASI 75 was attained in 11 (91.7%) patients at week 12 (**Figure 2**). DLQI score of 0-1 (no effect at all on QOL) was observed in 11 (91.7%) patients at week 12. DLQI at baseline revealed that 8 (66.7%) patients had a score of 11-20 whereas, 4 (33.3%) patients had a DLQI score of 21-30 (**Table 1**). Secondary end point of PASI 90 was also achieved in 11 (91.7%) patients before week 24. PASI 100 was achieved in 4 (33.3%) patients at week 24. However, maintenance of PASI 90 from week 24 through week 52 was seen in 4 (33.3%) patients. Only one patient (8.3%) did

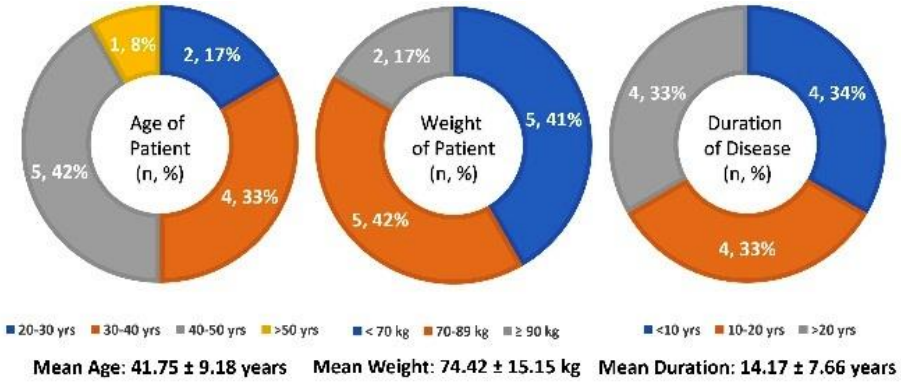


Figure 1 Distribution of patients by age, weight and duration of disease.

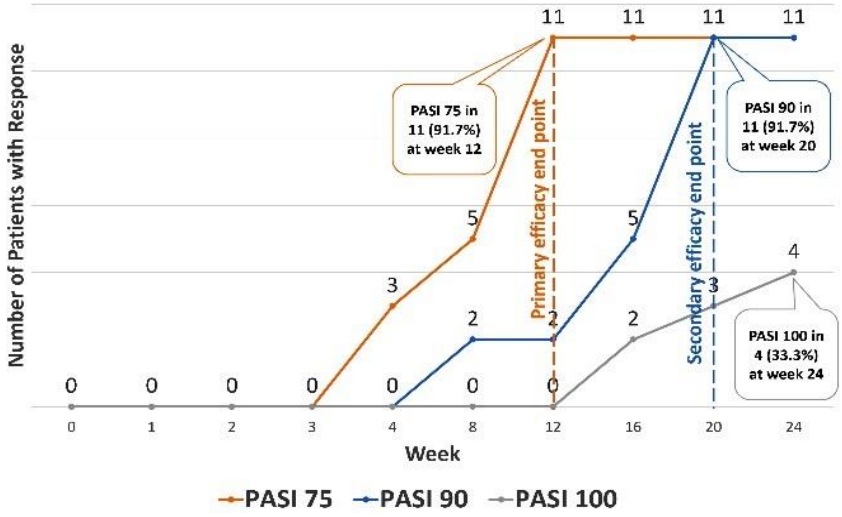


Figure 2 Efficacy of Secukinumab – PASI response

Table 1 Efficacy of Secukinumab – DLQI scores.

DLQI Score	Interpretation	At Baseline		At Week 12	
		n	%	n	%
0-1	No effect at all	0	0 %	11	91.7 %
2-5	Minimum effect	0	0 %	0	0 %
6-10	Moderate effect	0	0 %	0	0 %
11-20	Very large effect	8	66.7 %	1	8.3 %
21-30	Extremely large effect	4	33.3 %	0	0 %

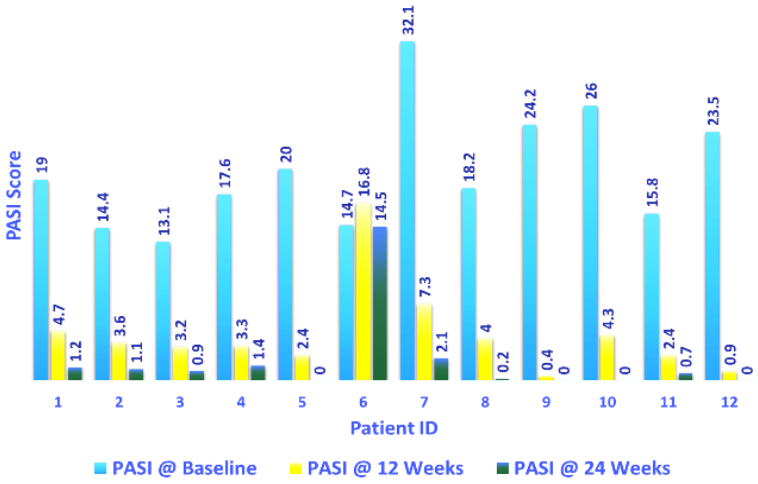


Figure 3 PASI scores of patients at baseline, week 12 and week 24.

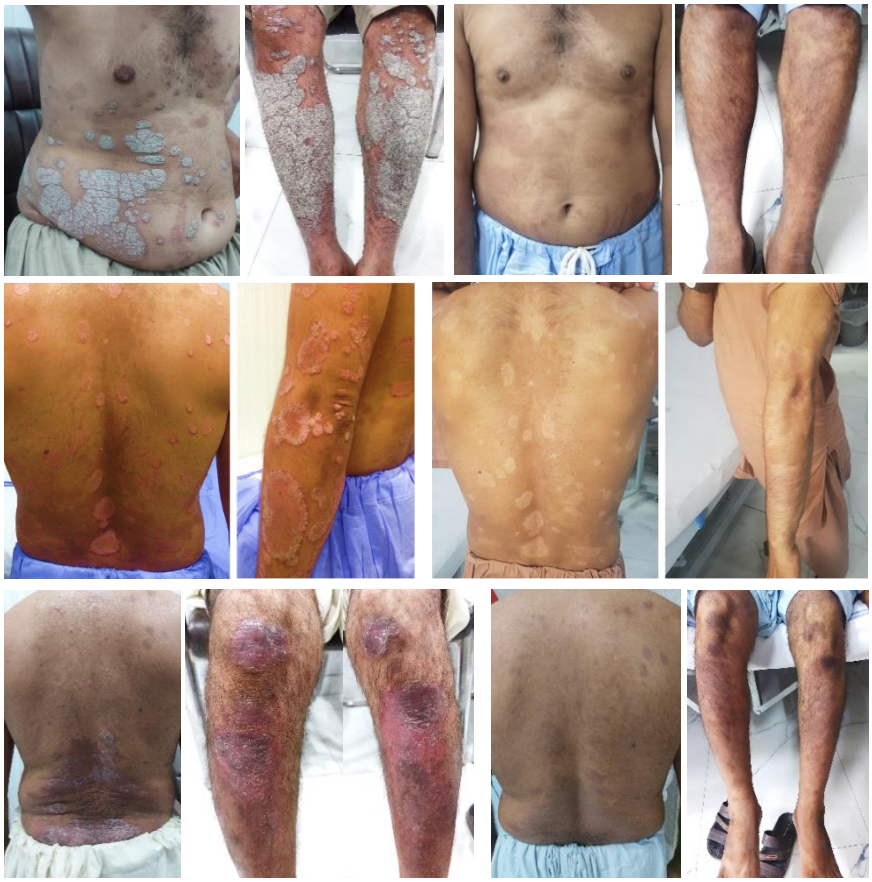
not show a favorable response to the treatment (**Figure 3**).

Relapse was observed in 7 (58.3%) patients after a mean duration of 3.0±0.41 months from discontinuation of the treatment (i.e. from week 24). A dose of 150 mg of secukinumab was given subcutaneously to all these patients (with relapse) for a duration of 12 weeks from the start of relapse. PASI 90 was again achieved in such patients with the monthly maintenance dose of secukinumab.

Safety of secukinumab, in our study, was established, as no significant adverse effects were observed in all the patients during and post treatment. Only 2 (16.7%) patients reported rhinorrhoea at week 2 and one (8.3%) patient reported GIT complaint at week 2. No other side effects were observed in any patient during treatment and in follow up visits till week 52 (**Table 2**).

Table 2 Adverse effects of secukinumab in the treatment of chronic plaque psoriasis (n).

Side Effects	2 Weeks	4 Weeks	8 Weeks	12 Weeks	24 Weeks	52 Weeks
NASOPHARYNGITIS	-	-	-	-	-	-
URTI	-	-	-	-	-	-
RHINORRHOEA	+ (2)	-	-	-	-	-
ORAL HERPES	-	-	-	-	-	-
ORAL CANDIDIASIS	-	-	-	-	-	-
URTICARIA	-	-	-	-	-	-
OTHER (SPECIFY)	-	-	-	-	-	-
GIT COMPLAINTS (Diarrhea, Constipation, Mucus or Blood in stool)	+ (1)	-	-	-	-	-
SOB, PRODUCTIVE COUGH, WEIGHT LOSS	-	-	-	-	-	-



Pre-Treatment Post-Treatment

Figure 4 Pre-Treatment and Post-Treatment Pictures.

Pre-treatment and post-treatment pictures of patients are given in **Figure 4**.

Discussion

The pathogenesis of psoriasis is being widely investigated and increased understanding of this disease led to availability of novel therapeutic drugs. The use of anti-TNF α drugs has tremendously enhanced the treatment choices to treat psoriasis but newer, more definite therapeutic modalities having lesser adverse effects and minimally affecting immune system are still required. IL-17A plays an integral part in the development of psoriasis and is a key therapeutic target. Secukinumab is an anti-IL 17A agent that showed encouraging results in different studies.[7,17] Very few studies are carried out on this drug in this population so this study was conducted to evaluate the long-term efficacy and safety of this drug.

In this study, PASI 75 was achieved in 91.7% of the patients at week 12 which is comparable to the study conducted by Yan Zhao *et al.*[17] on Chinese population where PASI 75 was achieved in 93.2% of the patients at week 12. In other studies, done by Neema S. *et al.*[18] on Indian population and Lin Cai *et al.*[19] on Chinese population. PASI 75 at 12 weeks was achieved in 85% and 87.2% of patients respectively. In all the above-mentioned studies the dose of secukinumab was 300 mg. In a study conducted in Pakistan by Tariq H *et al*,[20] PASI 75 was achieved in 36.36% patients at week 25, which is quite less as compared to this study. This difference may be attributed to lower dosage of secukinumab (150 mg) used, and the inclusion of other morphological forms of psoriasis (pustular psoriasis, psoriatic arthritis)

along with plaque psoriasis in their study. However, this study used 300mg as a loading dose in the initial two weeks and then weekly maintenance dose of 150 mg secukinumab to the patients of plaque psoriasis only.

In the current 91.7% of the patients achieved PASI 90 at week 20 that shows an early and rapid response of secukinumab in the management of plaque psoriasis. This is in accordance with the study done by Yan Zhao *et al.*[17] in which PASI 90 was achieved in 86.4% of the patients at week 24. In another study conducted by Topal IO *et al.*[14] PASI 90 was achieved in 69.8% of the patients at week 24. 33.3% of patients achieved PASI 100 at week 24 in the current study, whereas, in the studies conducted by Momose *et al.*[21] and Topal IO *et al.*[14] PASI 100 was achieved in 51.2% and 52.2% of the patients respectively at week 24. Different study population and the continuous usage of higher dose of secukinumab (300 mg) in these studies may be the reason of higher PASI 100 seen in their results.

Another secondary end point of the current study was maintenance of PASI 90 in patients from week 24 to week 52. PASI 90 was maintained till week 52 in 33.3% of the patients in this study (without monthly maintenance dose after week 24). In Topal IO *et al.*[14] PASI 90 was maintained in 49.3% of the patients till week 52 (with monthly maintenance dose). Relapse was observed in 7 (58.3%) patients in this study, after a mean duration of 3.0±0.41 months from discontinuation of the treatment (i.e. from week 24). A dose of 150 mg of secukinumab was given on monthly intervals to all these patients (with relapse) for duration of 12 weeks from the start of relapse. PASI 90 was again achieved in all such patients with the monthly maintenance dose of 150 mg secukinumab. Hence, we inferred from this experience that monthly maintenance dose of secukinumab till week 52 can be more beneficial in maintaining PASI score rather than flexible dosing regimen (treatment given at the start of relapse).

Similar observations were made in another study conducted by Gisondi P *et al.*[12] that maintenance dose of secukinumab on monthly interval (fixed interval treatment regimen) yields better maintenance of PASI score till week 52 as compared to a flexible dosing regimen. One of the trials conducted by Rich P *et al.*[22] investigated maintenance treatment strategies and the option of a regular dose (monthly) or variable dose of secukinumab was given to patients. Although, the maintenance period demonstrated a promising efficacy profile of regular dose (84.6% of patients) as compared to variable dose i.e. when required (67.2% of patients) in maintaining PASI score. In the ERASURE study by Langley RG *et al.*[1] PASI 75 from week 12 was maintained till week 52 with monthly maintenance therapy of secukinumab in 74.4% of the patients (secukinumab 300mg) and in 59.2% patients (secukinumab 150mg).

The DLQI score of 0-1 was achieved in 91.7% of patients in our study. Mean DLQI score before treatment was 18.92 which reduced by 17.5 points to the mean DLQI score of 1.42 at week 12. This demonstrated remarkable enhancement in the QOL of the patients after treatment. These results are comparable with the results of other studies. ERASURE study[1] showed mean DLQI score of 2.5 at week 12 with absolute change in mean score of -11.4. In a study conducted by Pariser D *et al.*[23] mean DLQI score at week 12 was 2.4 with absolute change in mean score of -12.7.

Interleukin-17A plays a crucial role in innate immune response and host defense, specifically in mucocutaneous microbial surveillance. Continued monitoring and examination for the risk of candida infection is necessary during use

of secukinumab.[12] Interleukin-17A also plays an important part in granulopoiesis and recruitment and activation of neutrophils so the risk of neutropenia should also be considered during the use of secukinumab.[12,24]

Very few side effects were seen in this study. Only two patients experienced rhinorrhoea and one patient had diarrhea after second dosage of secukinumab, that resolved spontaneously. The most commonly seen side effects in other studies were nasopharyngitis, headache, upper respiratory tract infections and candida infections.[1,14,25] Secukinumab is a generally well tolerated drug as also shown in other studies.[17, 25]

Both primary and secondary efficacy end points were achieved by secukinumab in this study and it was also very well tolerated. It is therefore expected that it will be more acceptable and the preferred therapeutic option for those patients of psoriasis who do not show response to or are unable to tolerate their previous or existing treatment modalities.

Limitations of Study There was no control group in this study and the sample size was small.

Strength of Study We believe that this study is the only study in Pakistan, on secukinumab therapy, with a year-long follow up of patients.

Conclusion

Secukinumab showed excellent efficacy in the treatment of moderate to severe chronic plaque psoriasis with a very good safety profile. It is highly effective in achieving early and rapid reduction of PASI score.

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