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Original Research Article

An institution-based non-randomised prospective study to estimate the efficacy and adverse effect profile of apremilast for moderate to severe refractory palmoplantar psoriasis

Nisha Agrawal, Sabina Liangom Joanna Rongong, Saswati Halder, Jayanta Kumar Barua, Param Satsangi, Asim Kumar Halder, Prabal Samanta*

Department of Dermatology, School of Tropical Medicine, Kolkata, West Bengal, India

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***Correspondence:**
Dr. Prabal Samanta,
E-mail: prabalnbmc90@gmail.com

ABSTRACT

Background: Psoriasis is an immune-mediated inflammatory papulo-squamous disorder presenting as chronic plaque, pustular, erythrodermic, nail, scalp, drug induced, inverse, guttate etc. Palmoplantar psoriasis causes significant functional, cosmetic and psychological disability. Apremilast is a relatively newer drug being PDE-4 inhibitor, having negligible adverse effects with minimum blood monitoring.
Methods: It is an institution-based, non-randomised, prospective study conducted over a period of 3 months. 42 patients of moderate to severe disease (assessed using PPPASI), refractory to conventional line of therapy (for atleast 3 months) or had contraindications for the same were selected from our Dermatology OPD. Follow up was done monthly for 6 months.
Results: 42% of the patients were good responders. 1 patient did not respond and 2 had progression of the disease. There was a decrease in the mean DLQI from a baseline of 25 to less than 15 by the end of 1st month and around 5 by the end of 6th month.60% of patients showed onset of response by the 1st month. 45% of the patients showed adverse effects, mostly being nausea followed by dizziness.
Conclusions: From our study and those in the existing literature, it can be inferred that apremilast is a promising drug for palmoplantar as well as other forms of psoriasis, especially in patients with comorbidities or treatment refractory psoriasis.

Keywords: Psoriasis, Palmoplantar, Apremilast, Adverse effect

INTRODUCTION

Psoriasis is an immune mediated genetically determined common dermatological disorder which affects skin, nails, and joints and has various systemic associations. There is evidence that the disease is associated with a high impact on health-related quality of life and considerable cost. There are different types of psoriasis like chronic plaque, inverse, erythrodermic, scalp, nail, drug induced, pustular, guttate etc. Palmoplantar involvement can occur in isolation but often occurs with psoriasis elsewhere in body. Though only small body surface area is affected but because of the disabling sequelae, it carries a definite significance. It also leads to cosmetic disfigurement causing psychological morbidity to the patient. It can occur in the form of scaly plaques or pustular lesions which can present as palmoplantar pustulosis or acrodermatitis continua of Hallopeau. Several topical and systemic treatment are currently available for its management like topical steroids, topical calcineurin inhibitors, coal tar, keratolytic agents, methotrexate, psoralens, NBUVB

therapy, cyclosporine, systemic retinoids etc. Each of the treatment options present with its own set of advantages and adverse effect profile.

Table 1: Starter kit.

Day	Morning	Evening
Day 1	10 mg	-
Day 2	10 mg	10 mg
Day 3	10 mg	20 mg
Day 4	20 mg	20 mg
Day 5	20 mg	30 mg
Day 6 and thereafter	30 mg	30 mg

Apremilast is an orally administered small molecule inhibitor of Phosphodiesterase 4(PDE4). It was approved by USFDA on March 21, 2014 for the management of active psoriatic arthritis in adults. Soon, on September 23, 2014, FDA approved apremilast for treating patients of moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.[1] It has got marketing approval from Drug Controller General of India in 2017. As a result of PDE4 inhibition, the levels of pro-inflammatory cytokines like TNF-a and IL-23 decrease and those of anti-inflammatory mediators like IL-10 increase.[2] The absolute bio-availability of apremilast is around 73%. Its concentration in the plasma peaks (Cmax) in a median of around 2.5 hours. Food intake does not affect its clinical activity. Mild to moderate renal dysfunction or moderate to severe hepatic dysfunction do not change the pharmacokinetics of apremilast to a significant level clinically.

However, dose reduction is recommended in those with severe renal dysfunction. [3] The recommended dose of apremilast in adults for psoriasis and psoriatic arthritis is 30mg twice daily. It is started with 10mg morning dose with daily increment of 10mg until day 6 when the recommended dose of 30mg BD for adults is reached and continued as such thereafter. Such dose titration reduces gastrointestinal side effects.

A new nail lacquer formulation for nail psoriasis has also been developed, though not yet available commercially.[4] The efficacy and safety of apremilast were established through well-conducted clinical trials which showed superior efficacy over placebo. Unlike the clinical trials that followed strict protocols in patient follow-up and treatment plan, the real world data have revealed even better efficacy with the achievement of Psoriasis Area and Severity Index (PASI-75) in half of the studied population.[5,6] Evidence from various clinical studies has established the efficacy of apremilast monotherapy irrespective of previous exposure to the systemic agents.[5-9]

Aim and objectives

Aim and objective of current study was to estimate the efficacy and adverse effect profile of apremilast for moderate to severe refractory palmoplantar psoriasis.

METHODS

This institution- based Non-randomised prospective clinical trial was conducted over a period of 3 months from 1 December 2021 to 28 February 2022 in the dermatology department of school of tropical medicine, Kolkata. The study population comprised of moderate to severe palmoplantar psoriasis patients who were refractory to conventional line of treatment, attending the Dermatology OPD. A total of 42 patients were taken in the study.

A written informed was presented to the patients followed by detailed history taking and clinical examination. The diagnosis of palmoplantar was mainly clinical and histopathological confirmation was done wherever applicable. Severity of palmoplantar psoriasis was assessed using Palmoplantar psoriasis area and severity index (PPPASI). It is a point-based system quantifying the area and quantity of palmoplantar psoriasis. It takes into account erythema, induration and desquamation on scale of 0-4, 4 being the most severe. Scores between 2-4 were labelled as moderate to severe and thus included in the study. Refractory cases were the once who did not respond to conventional line of therapy for atleast 3 months or had contraindications for the same.

Inclusion and exclusion criteria

Inclusion criteria for current study were; Patients of age 20-60 yrs, Patients with moderate to severe palmoplantar psoriasis (Measured using PPPASI).PPPASI scores 2-4 were taken, Patients who were refractory to Conventional therapy, Patients who had contraindications for conventional therapy. Severely ill or pregnant patients and those unwilling to participate in the study were excluded.

In case of treatment, patients were weaned off the previous systemic medications, then they were given starter kit for 7 days. Maintenance dose was 30 mg twice daily for 6 months. Then, follow up was done monthly for 6 months. The investigator's scoring was done using PPPGA score (Palmoplantar psoriasis physician global assessment) in which the scores were 0,1,2,3 and 4, lower scores indicating good response. Weak response is reduction by 1 score. Moderate and good responses are represented by reduction in scores by 2 and 3 or more respectively. Subject's scoring was done using DLQI (dermatology life quality index). The score brackets being 0-1, 2-5, 6-10, 11-20 and 21-30. Lower scores indicated good response.

RESULTS

In our study, we had 30 male patients while the rest 12 were females. There were no transgender patients (Table 2). 64% of the patients were Hindus while 12% of them were Muslims, rest 3% belonged to other religions (Table 3). Majority (36%) belonged in the age group of 30-40 yrs, 28% belonged in the group of 40-50 yrs while 12% belonged in the group of 50-60 yrs (Table 4). In terms of residence, 60% belonged to urban areas while rest 40%

belonged to rural areas (Table 5). In our study, 42% of patients (17) were good responders where they showed a decrease in PPPGA by 3 or more scores. 31% were moderate responders (12) who showed a decrease in PPPGA by 2 scores. 1 patient did not show any response while 2 patients showed progression of disease despite treatment (Figure 1).

Table 2: distribution according to gender.

Gender	N (%)
Male	30 (71)
Female	12 (29)

Table 3: Distribution according to religion.

Religion	N (%)
Hindu	27 (64)
Muslim	12 (29)
Christian	1 (2)
Others	2 (5)

Table 4: Distribution according to age.

Age group	N (%)
20-30	10 (24)
30-40	15 (36)
40-50	12 (28)
50-60	5 (12)

Table 5: Distribution according to residence.

Residence	N (%)
Urban	25 (60)
Rural	17 (40)

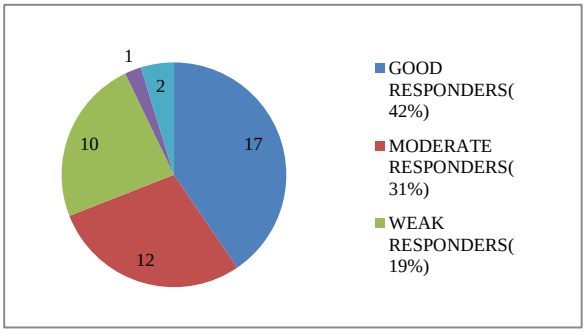

Figure 1: Percentage of patients according to extent of response.

In our study, there was a decrease in the mean DLQI scores of patients with progression of the months. By 1st month, it dropped to below 15 from 25. By the 3rd month, it dropped to below 10 while by the 6th month, it came to near around 5. This showed all over good improvement in the subjective parameter of the disease (Figure 2). In our study, out of 42 patients, 25 of them (60%) showed onset of response by 1st month, 4 patients (10%) each by the 2nd and 3rd month respectively while 1 patient (2%) each showed onset of response by the 5th & 6th month respectively. This showed that the speed of response of action varies according to different patients (Figure 3). In our study, majority (55%) of the patients showed no adverse effects while 45% of them showed various adverse effects (Figure 4). Among them, nausea seemed to be the most common adverse effect which was present in 59% of them, followed by dizziness (42%) and diarrhea (21%). Palpitations were noted in 3 patients for which Cardiological opinion was sought. 12% of the patients showed other adverse effects like coryza, weight loss, general feeling of discomfort etc. (Figure 5).

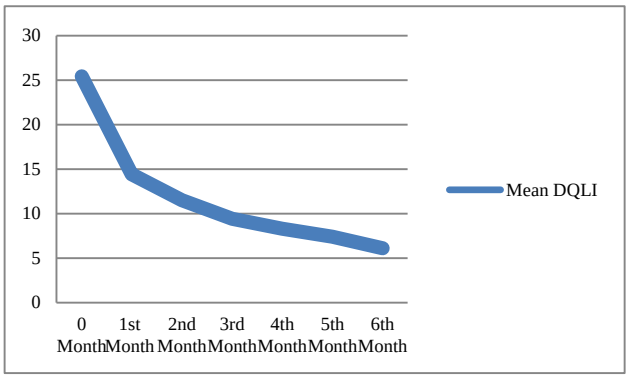

Figure 2: The mean DLQI in different months of follow up.

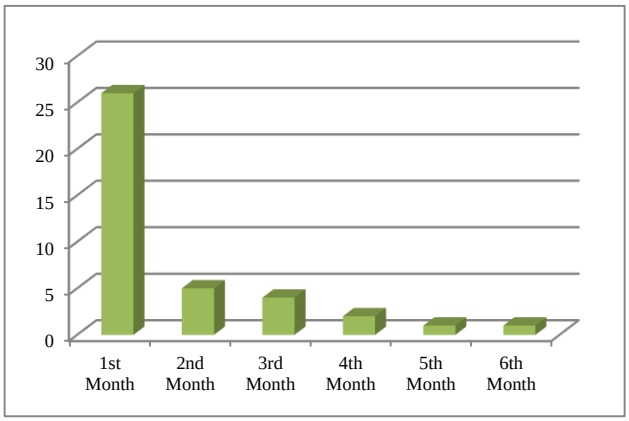

Figure 3: The onset of response.

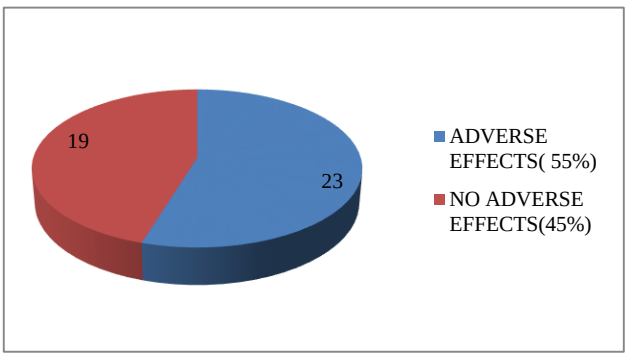

Figure 4: Percentage of patients showing adverse effects.

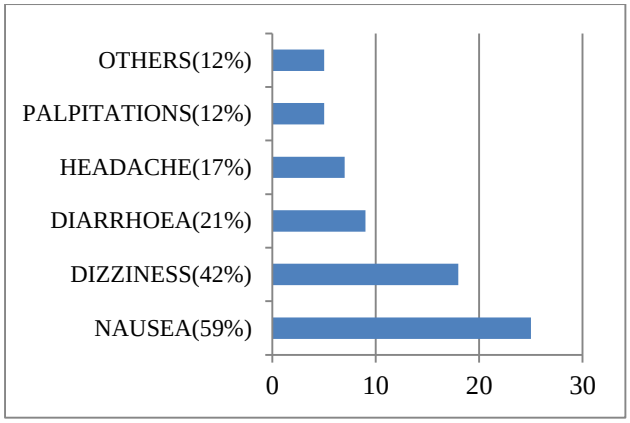

Figure 5: Percentage of patients experiencing individual adverse effects.

DISCUSSION

Psoriasis is an immune mediated inflammatory papulo-squamous disorder which has various clinical subtypes like chronic plaque, scalp, inverse, guttate, erythrodermic, drug-induced, nail psoriasis etc. Palmoplantar psoriasis is also one such variant in which hyperkeratotic lesions chiefly affect the palm and sole and which causes significant morbidity and disability to the patient as it hampers with their daily activities. Apremilast is a relatively newer drug which is a Phosphodiesterase-4 inhibitor (PDE4) which suppresses production of proinflammatory cytokines like IL-17, TNF-a and IFN-g and promotes production of anti-inflammatory cytokines like IL-10.

In our study, 42% of patients were good responders while 31% were moderate responders, wherein they showed reduction in the PPPGA scores by 2 or 3 and more respectively by the end of 6 months. In a study conducted by Stander et al out of 6 patients with severe and refractory PPP, all patients showed improvements in their PGA scores from their baseline of 3 or 4 to 1 (almost clear) or 0(clear) after 12 weeks of use.[10] Among patient related outcome measurements, there was significant reduction in mean DLQI of the patients from baseline of 25 to less than 15 after 1st month, less than 10 after 3rd month and around 6 at the end of 6th month in our study. These indicators provide a more comprehensive view of the impact that psoriasis and its treatment can have on patients. [11] The durability of improvement in PROs requires longer term monitoring and analyses beyond 32 weeks as shown in the study by Thaci et al. [11] A study by Bissonnette et al suggests apremilast may have a role in the treatment of moderate to severe palmoplantar psoriasis.[12] In a report by Eto et al. 3 patients with palmoplantar pustulosis achieved near complete symptom resolution after 2 weeks while being followed for 8 months.[13] In our study, adverse effects were reported in 55% of the patients. More than a single adverse effect was present in the same patient in some cases. Nausea and dizziness were the most common which were present in 59% and 42% of those affected, followed by diarrhea and headache in 21% and 17% respectively. Secretory diarrhea, nausea and vomiting were thought to be induced by PDE4 inhibition; a similar mechanism is implicated in caffeine-induced diarrhea. [14] In a study by Crowley et al 21.9% patients sustained weight loss >5% of their baseline body weight.[14] PDE inhibition can affect other organ systems like adipose tissue, which may contribute to weight loss, this was shown in a study by Zhang et al.[15] Nausea induced by PDE-4 inhibitors appears to be triggered by central and peripheral mechanisms as shown in a study by Li et al.[16] This adverse effect has been associated with lack of selectivity of PDE-4 inhibitors for the different isoforms (A,B,C,D) expressed in different cell types.[16] Specifically, the PDE-4 isoform is expressed in neurons of the area postrema, where the chemoreceptor trigger zone that links with the vomiting centre is located. The increase in intracellular levels of cAMP in neurons of area postrema ultimately triggers the emetic response as shown in the study by Raker et al.[17] Among these non-pharmacological interventions, frequent smaller meals as well as limited liquid intake during meals may help reduce the sensation of nausea as described in a study by Langley et al.[18] A phase 4, multicentre, randomised controlled trial in patients with low BSA involvement (5-10% BSA) known as Evaluating Apremilast in a phase IV trial of efficacy and safety in patients with moderate plaque psoriasis (UNVEIL) demonstrated significantly better patient satisfaction with the safety, efficacy and convenience of apremilast compared with placebo.[19] In studies of patients taking biological agents and small molecule inhibitors like apremilast, latent TB reactivation is not associated with apremilast use. [20]

Limitations

Limitations of current study were; we enrolled 42 patients in our study which was conducted over a period of 3 months. A larger sample size would provide more comprehensive details about the efficacy and adverse effect profile of the drug compared to our smaller sample size. Also, a longer study period could have provided more insight into the long-term effect of the drug on remission of the disease and whether any more relapses occurred while taking the drug. Also, any long-term adverse effect could have been observed in greater detail. The tools used for assessing response were the Physician Global Assessment and DLQI, both of which are observer dependent and subjective in nature. This could have led to bias in assessing the results. Inclusion of a more Objective nature study tool can lead to more clarity and perfection in the results.

CONCLUSION

Palmoplantar psoriasis though affects comparatively a smaller area of the body, has a huge impact on the normal daily functioning of the patient causing significant disability and psychological trauma to the patient, especially the cosmetic disfigurement. Several topical and

systemic treatment are available like topical steroids, keratolytic agents, topical calcineurin inhibitors, methotrexate, PUVA therapy, cyclosporine etc. Apremilast is a novel PDE-4 inhibitor in this regard which requires minimum blood monitoring and is safe to use in patients with other comorbidities. In our study, we have found several beneficial results of its use in palmoplantar psoriasis. A total of 42 patients of palmoplantar psoriasis were taken in our study. Majority (42%) showed good response at the end of 6 months wherein there was reduction in the PPPGA by 3 or more scores followed by 31% who showed moderate response in which there was reduction in PPPGA by 2 scores.1 patient showed disease progression while 2 had progression of disease. Mean DLQI of the patients was also decreased starting from a baseline of 25 to <15 by the end of 1st month to <10 by the end of 3rd month to near about 5 by the 6th month. This shows beneficial effect of the drug in most patients as has been seen in other studies and trials too. The drug showed early onset of action by 1st month in majority (60%) of the patients while 1 patient each had onset of action by the 5th and 6th month respectively. Majority of the patients (55%) did not show any adverse effect to the drug. However, among those who showed, more than 1 adverse effect was sometimes present in the same patient. Nausea and dizziness being the most common adverse effects present in 59% and 42% of those affected respectively. Palpitations were present in 5 patients for which Cardiological opinion was sought. But none of the patients had to be discontinued from our study and all completed the 6 months course of apremilast. Thus, Apremilast is emerging as a potent systemic agent for the management of palmoplantar psoriasis and its further research in other forms of psoriasis is also highly recommended. It has negligible serious adverse effects with minimum blood monitoring. It can be combined with other systemic agents like methotrexate and psoralens also.

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