Real-World Insight on Apremilast Therapy in Patients with Plaque Psoriasis: Indian Experience

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Abstract

Introduction: Psoriasis is an immune-mediated inflammatory skin disorder, which follows a chronic course. Apremilast is a novel phosphodiesterase 4 (PDE4) inhibitor, approved by US-FDA for the treatment of moderate to severe plaque psoriasis and psoriatic arthritis. A majority of the data related to the effectiveness and safety of apremilast use in psoriasis is extracted from clinical trials. The present study was planned to get an insight into real-world experience with the use of apremilast in patients with moderate-to-severe plaque psoriasis related to its effectiveness and safety in India. Materials and Methods: The present study was a retrospective one, wherein a review of the medical records of patients with psoriasis was conducted at one center in Kolkata, who were prescribed apremilast for 16 weeks in a community dermatology practice, from December 2017 to May 2018. Results: Out of 39 patients, two patients discontinued treatment due to diarrhea. Only three patients were treatment naïve; the rest had taken some form of systemic therapy before apremilast. At the end of 16 weeks of treatment with apremilast, PASI 100 was achieved in one patient (2.7%), PASI 90 in one (2.7%), PASI 75 in 18 patients (48%), while 14 patients (38%) achieved PASI 50. Eighteen (46%) experienced adverse events, diarrhea being the most common (29.7%). Conclusion: The findings of the present study indicate that apremilast is effective in a real-world setting, as compared with clinical trials in achieving certain endpoints like PASI 75, as was found in other real-world studies in other countries, as well.

Key Words: Apremilast, India, psoriasis

Introduction

Psoriasis is an immune-mediated inflammatory skin disorder which follows a chronic course. It is estimated to affect 2% of the global population. Psoriatic skin lesions are scaly, erythematous and are frequently pruritic and may be associated with joint pain. Apart from these, the lesions are marring and add to the psychological stress of the patients. Adding fuel to the fire is the presence of comorbidities/complications of psoriasis such as cardiovascular disease, psoriatic arthritis, etc. All these factors collectively play a vital role in adversely affecting the physical and emotional health of those affected with psoriasis, which are reflected by significant distortion in the health-related quality of life.

Pathologically, psoriasis is typified by excess production of partially differentiated keratinocytes, infiltration of leucocytes in the papillary layer of the dermis and increased blood flow to the cutis. This happens due to an imbalance between anti-inflammatory and pro-inflammatory intercessors. Cyclic AMP (CAMP) is a major secondary messenger known to supervise the inflammation homeostasis and is degraded by a group of enzymes known as phosphodiesterase (PDE). Psoriasis is characterized by increased expression of PDE4 isoenzyme in the skin.

Psoriasis is managed by a variety of topical and systemic drugs. Systemic agents include conventional agents like methotrexate, cyclosporine, and biologics, like infliximab, ustekinumab, etc., However, patient adherence to these systemic drugs may be poor and this is attributed to several factors, such as long-term efficacy and safety concerns regarding activation of infections, malignancies, painful injections, etc. Thus, it was the need of the hour to explore for a novel systemic agent that would circumvent the shortcomings encountered with the existing systemic agents.

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Apremilast, a novel PDE4 inhibitor, is to be taken orally. It was approved by US-FDA in 2014 for the treatment of moderate to severe plaque psoriasis and psoriatic arthritis as twice daily administration.\(^\text{[10]}\) It is known to explicitly wedge down the synthesis of pro-inflammatory molecules that play a key role in the causation of psoriasis that include interferon-\(\gamma\), tumor necrosis factor-\(\alpha\) interleukins-12, 17, 23.\(^\text{[11]}\) It has been found to effectively attenuate the magnitude and sternness of nail, palmoplantar and moderate-to-severe psoriasis.\(^\text{[10]}\)

However, a majority of data related to the efficacy and safety of apremilast used in psoriasis is extracted from clinical trials. The present study was planned to get an insight into real-world experience with the use of apremilast in patients with moderate-to-severe plaque psoriasis related to its effectiveness and safety. To the best of our knowledge, this study is the first real-world study of the use of apremilast in the treatment of psoriasis in India.

**Materials and Methods**

The present study was a retrospective one, wherein a review of the medical records of patients of psoriasis was conducted at one center in Kolkata, who were prescribed apremilast for an entire 16 weeks period in a community dermatology practice from December 2017 to May 2018. A prevalidated questionnaire was used to conduct this analysis. The questionnaire was designed to assess the efficacy and tolerability of apremilast in the management of plaque psoriasis.

Only those records were included for analysis, whose data were available for complete 16 weeks. Most of the patients in our analysis had been previously treated with a systemic agent and switched to apremilast either due to the lack of efficacy or the side effects of the previous treatment.

The primary endpoint was the assessment of clinical response in terms of the percentage of patients achieving PASI 75 at 16-week after treatment initiation. The secondary endpoints consisted of:

(i) Changes in mean PASI from baseline to weeks 4, 10 and 16;

(ii) Changes in mean BSA from baseline to week 4, 10 and 16;

(iii) Percentage of patients who achieved PASI 50, PASI 90 and PASI 100;

(iv) Adverse events reported during the therapy.

**Statistical analysis**

Statistical analysis was done using SPSS (Statistical Package for Social Sciences) version 18.0. Continuous and categorical data were expressed in terms of mean and percentage, respectively. To compare changes in mean scores at weeks 4, 10 and 16, repeated measure ANOVA was applied. \(P\) value < 0.05 was considered as statistically significant.

**Results**

Records of 39 patients who were given apremilast during the study period were included in the study. Out of them, 30 were taking methotrexate prior to apremilast, 3 patients had prior biologic therapy, 2 patients were taking cyclosporine, 1 patient was taking acitretin and 3 were treatment naïve. Of these 39 patients, 18 (46\%) developed side effects with apremilast and 2 discontinued apremilast due to diarrhea before completion of 4-week therapy. Further analysis was carried out on the records of the rest 37 patients.

**Effectivity results**

At the end of 16 weeks of treatment with apremilast, PASI 100 was achieved in one patient (2.7\%), PASI 90 in 1 patient (2.7\%), PASI 75 in 18 patients (48\%), whereas 14 patients (38\%) achieved PASI 50, and three patients (8\%) achieved PASI <50. Thus, 34 (92\%) patients had achieved PASI ≥50 [Figure 1].

On analyzing the week-wise progress in PASI score in the patients, it was found that only 4.8\% of the patients had achieved PASI 75 at week 4, which increased to 45.2\% at week 10 and 51.2\% at week 16 and 26.2\% of the patients achieved PASI 50 at week 4, which increased to 47.6\% at week 10 and 35.5 at week 16 [Figure 2]. The fall in PASI 50 between weeks 10 and 16 was due to shift of the patients from PASI 50 to PASI 75 during this time.

After analyzing mean PASI scores over the study period, it was found that the mean score at baseline was 13.6, which gradually reduced to 7.3 at week 4, 5 at week 8, and 4 at week 16, and this improvement was statistically significant \((P < 0.001)\). Mean body surface area affected (BSA) at baseline was 17.2, which got reduced to 10.32 at week 4, 8.24 at week 8 and 7.23 at week 16, which was statistically significant \((P < 0.001)\) [Figure 3].

**Safety analysis**

On analyzing the occurrence of adverse events, it was found that 18 patients (46\%) experienced adverse events. Out of these 18 patients, 10 patients had only 1 adverse event, 6 patients had 2 adverse events, whereas 1 patient reported 3 adverse events making a total of 25 adverse events [Figure 4]. Most of these adverse events were mild and temporary and resolved over time with pharmacotherapy. The most common adverse event was diarrhea, which was found in 11 patients (28.2\%), followed by headache and nausea while gastritis and vomiting were least commonly encountered. Two patients discontinued the apremilast therapy; the reason cited was diarrhea.
Discussion

The safety and efficacy data of apremilast in India is currently available only from clinical trials or real-world evidence from a few other countries. \([12,13]\) Although trial data have been encouraging, there is a paucity of data related to real-world experience with the use of apremilast in the treatment of psoriasis. \([12]\) Apremilast was found to be effective in achieving the said endpoints.

Primary endpoints

The results obtained in the present study are better than those obtained in landmark ESTEEM-1 and 2 trials, where 28.8 and 33% of the patients achieved PASI 75 at the end of 16 weeks as compared with 48% patients achieving the same parameter. \([14,15]\) Although due to the retrospective study design we could not analyze the Dermatology Quality of Life, the majority of the patients continuing the full course of treatment indirectly points towards improvement in patient compliance and quality of life. Although the percentage of patients achieving PASI 75 was high in the present study, a real-world study done by Papadavid et al. on apremilast use in moderate-to-severe psoriasis reported this percentage to be even higher (i.e., 60%). \([12]\) This may be due to the mean PASI score in that study was 10 as compared with 13.6 in this study. Thus, the severity of psoriasis in that study was less; hence it is quite logical to anticipate that a positive response will be obtained in more number of patients compared to more severe psoriatic lesions. Overall, the PASI 75 responses reported in various clinical studies at the end of 16-week treatment with apremilast ranged from 30% to 41%. \([14,16,17]\)

Secondary endpoints

Apart from PASI 75 as the primary endpoint, we analyzed certain secondary endpoints as well, that is, PASI 50, 90, and 100, changes in mean PASI and BSA. The percentage of patients achieving PASI 50 in this study was comparable with that of other real-world clinical studies. \([12,18]\) However, ESTEEM-1 and 2 trials reported that 55% and 58% of the patients achieved PASI 50 at the end of 16 weeks. \([14,15]\) This might be due to the differing baseline mean PASI scores in the study populations of ESTEEM trials and that of the present study.

It is interesting to note that PASI 100 was not reported in ESTEEM trials, which can be attributed to some extent to the high-baseline PASI values in the patients of ESTEEM trials. The number of patients achieving PASI 50 increased from baseline to week 10 and then it reduced to week 16. This change should be logical since
more number of patients in PASI 50 at week 10 will achieve PASI 75, 90 or 100 afterwards. The patients in the present study showed rapid improvement in mean PASI score and this trend was seen continuously up to 16 weeks. The mean PASI score in this study got reduced from 13.6 at baseline to 7.3 at week 4, which was comparable with change of mean PASI from 10.8 at baseline to 4.9 at week 16 in real-world clinical study by Papadavid et al.[12]

The mean BSA involvement in the recent study at baseline was 17.2, which changed to 7.23 at week 16, that is, -59% changes in BSA involvement were seen. This improvement was more than that observed in the ESTEEM-1 trial, which reported -~47.8% changes/improvements in BSA involvement. It is noteworthy to mention that baseline BSA in ESTEEM-1 trial was more than that in the present study.

Safety analysis
Eighteen patients (46.2%) experienced adverse events in the present study. Other studies including ESTEEM trials reported these adverse events in around 60%-70% of the patients.[12,14,15] The most common adverse event in the present study was diarrhea, and this finding was corroborated in various clinical studies.[11,14,15,18] It was the only reason for drug discontinuation in the present study. However, this incident was more in the study reported by Mayba et al.[18] Also, the incidence of diarrhea was higher than that found in ESTEEM-1 (18.7%)[14] as chances of recall bias are always a problem in such cases and there are chances that over-reporting of specific adverse effects. Headache and nausea and their rates of occurrence were comparable with that found in other clinical studies.[12,18]

The total drug discontinuation rate in this study was 5.1%. This was found to be higher in real-world studies and clinical trials, wherein drug discontinuation rates were reported in the range of 30% to 40%.[12,14,15,18,20] Interestingly, the major reason cited for drug discontinuation in some of these studies was drug failure, although apremilast was used in combination with other systemic agents in those studies.[12,18] Thus, the finding of the present study that the discontinuation of apremilast was not due to drug failure, despite its monotherapy is a welcome sign, further strengthening its evidence of effectiveness though in a small number of cases. Also, the increased incidence of diarrhea might be due to the lack of compliance with instructions given by physicians, to combat diarrhea.[12]

The reasons for drug discontinuation in ESTEEM trials (adverse events) and real-world studies by Mayba et al. and Papadavid et al. (drug failure) were attributed to strict vigilance in clinical trials compared to real-world studies.[12] Finally, appropriate patient counseling may also play a vital role in shaping the patient compliance to therapy, because it is important to align the expectations of the patients, in terms of relief from the disease with the use of drug, to the real-world settings.[21]

Another noteworthy finding in the present study was that many of the patients had taken some form of systemic therapy before apremilast monotherapy, which is in contrast to LAPIS-PSO real-world study by the American Association of Dermatologists and ESTEEM trials, wherein half of the patients were treatment naive.[20] Thus, apremilast is effective in both systemic therapy experienced patients and treatment naïve patients. The findings of the present study are a valuable addition to the existing scant real-world data, and to the best of our knowledge, the first of its kind from India.

The present study had certain limitations. Firstly, the sample size was small, so that a generalization of the results of this study to a larger population cannot be carried out. Secondly, due to the study design, chances of recall bias cannot be ruled out. Thirdly, the quality of life was not a part of the study because of its retrospective nature.

Conclusion
The findings of this study verify those of previous clinical trials and real-world studies, which support apremilast monotherapy as an effective and safe treatment option for the management of moderate-to-severe plaque psoriasis.

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Conflicts of interest
Dr Dhiraj Dhoot is an employee of Glenmark Pharmaceuticals Ltd, India, that has a brand of apremilast.

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