

Real-world Efficacy and Safety of Apremilast Monotherapy in the Management of Moderate-to-severe Psoriasis

Abstract

Introduction: Apremilast is the new oral drug in the management of moderate-to-severe plaque psoriasis with well-established effectiveness and safety in long-term clinical trials and a few real-world studies. However, its effectiveness and safety in Indian setup have not been reported yet. **Materials and Methods:** This was retrospective, single-center, longitudinal, observational cohort study where the total study period was 24 weeks. Effectiveness parameters were the proportion of patients achieving psoriasis area and severity index (PASI) 50, 75, 90, and 100 response at week 16 and 24. Safety was measured as the proportion of patients reporting ≥ 1 adverse event (AE) during the study period. **Results:** Data of a total of 70 patients were included in our study. At week 16, 76.92%, 41.53%, 15.38%, and 6.15% patients achieved PASI 50, 75, 90, and 100, respectively. At week 24, 81.53%, 58.46%, 29.23%, and 10.76% patients achieved PASI 50, 75, 90, and 100, respectively. Mean percentage reduction in PASI was 67% at week 24 and DLQI score was reduced significantly to 3.4 from mean baseline DLQI score of 10.8 ($P < 0.001$). 40% of patients reported ≥ 1 AE during the study period. 5 out of 70 patients discontinued apremilast due to AE. Nausea was most common AE reported by 21.4% patients followed by diarrhea (18.57%), headache (17.4%), vomiting (8%), weight loss (7.69%), myalgia (6.15%), and gastritis (6.15%). Most of the AEs were of mild-to-moderate severity. **Conclusion:** The results of this study support the long-term use of apremilast monotherapy as an efficacious and safe treatment option for the management of moderate-to-severe plaque psoriasis.

Keywords: Apremilast, efficacy, psoriasis, real-world, safety

Introduction

Psoriasis is a chronic, auto-inflammatory skin condition with prevalence ranging from 0.9% to 8.5%.^[1,2] It is characterized by increased proliferation of keratinocytes, an increase in cutaneous blood flow, and leukocytic infiltration of the papillary dermis and the epidermis. Psoriasis is not only associated with disfiguring lesions, but patients may also experience distressing psychological sequelae and disability.^[3] Psoriasis is also associated with other systemic diseases such as cardiovascular disease and psoriatic arthritis (PsA), which further impacts the quality of life of patients with psoriasis.^[4,5]

Conventionally, systemic agents are used in the management of moderate-to-severe psoriasis. Although treatment options for moderate-to-severe psoriasis have expanded in recent years, these therapies have

shortcomings that limit patient treatment options.^[6-8] Approved conventional systemic therapies such as methotrexate, acitretin, and cyclosporine are associated with severe adverse events (AEs), such as hepatotoxicity, nephrotoxicity, and leukocytopenia.^[9-11] Although biological agents are very efficacious in the management of psoriasis, almost half of the patients on biologicals discontinue therapy due to overwhelming monitoring regimens, fear of injections, inability to tolerate their medications, and mainly because of cost of therapy.^[12-15]

Apremilast is a novel oral agent that was approved in India in 2017 for the treatment of moderate-to-severe plaque psoriasis. It is a phosphodiesterase 4 (PDE4) inhibitor that modulates inflammatory signaling pathways and plays a central role in the pathogenesis of psoriasis.^[16] In two pivotal phase III clinical trials, ESTEEM 1 and ESTEEM 2, apremilast was associated

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with acceptable safety profile and statistically significant improvement in the severity of the disease compared to placebo for management of moderate-to-severe plaque psoriasis.^[17,18] Additionally, multiple real-world studies have also demonstrated the effectiveness and safety of apremilast in the management of moderate-to-severe plaque psoriasis.^[19-25]

However, experience with apremilast in the real-world setting for moderate-to-severe plaque psoriasis is lacking in the Indian setup. Hence, we conducted this study with the aim to determine the real-life outcomes of apremilast use in patients with psoriasis in a busy dermatological practice.

Materials and Methods

Study design

The present study was retrospective cohort study, wherein review of medical records of patients of psoriasis was conducted at a tertiary care center in Ahmedabad, who were prescribed apremilast in a community dermatology practice during January 2018 to September 2018. Data were collected in a structured manner which was specific for the management of psoriatic patients.

Inclusion criteria

Data from both male and female patients ≥ 18 years of age, with moderate-to-severe plaque psoriasis, on apremilast 30 mg twice daily, who were systemic treatment naive or who failed on at least one systemic therapy or relapsed immediately after achieving significant improvement or had contraindication for standard systemic therapies were included in the study. For effectiveness analysis data from only those patients who have completed 24 weeks of therapy were considered while for safety analysis data from all the patients who have taken at least one dose of apremilast for the treatment of plaque psoriasis were considered. The severity of psoriasis was measured based on PASI/DLQI. Those patients having PASI ≥ 10 or DLQI ≥ 10 were classified as having moderate-to-severe plaque psoriasis.^[26,27]

Effectiveness assessment

For effectiveness assessment data from all the patients were analyzed based on the following parameters

Primary efficacy endpoint

1. Proportion of patients achieving at least 75% improvement in psoriasis area and severity index score (PASI 75) at week 16 and week 24.

Secondary efficacy endpoints

1. Percentage of patients achieving PASI 50, 90, and 100 response at week 16 and 24
2. Improvement in mean PASI score from baseline at week 24

3. Improvement in mean DLQI score from baseline at week 24.

Safety assessment

Safety assessment was done by analyzing all the AEs reported by the patients during treatment. The primary safety endpoint was the percentage of patients experiencing ≥ 1 AEs during 24 weeks of treatment. The secondary endpoints were the percentage of patients who discontinued apremilast therapy before 24 weeks.

Data analysis

Descriptive statistics were used to summarize effectiveness and safety endpoints using Graphpad Prism version 8. Quantitative variables were analyzed using means and standard deviations, and categorical variables were analyzed using frequencies and percentages. P values ≤ 0.05 were considered statistically significant.

Results

Data of a total of 90 patients with psoriasis who visited for dermatological consultation during the study period were screened. Of the 90 patients screened, data from 70 patients who fulfilled the inclusion criteria were included in the study. Apremilast 30 mg twice daily was prescribed to all the patients after initial titration to minimize the gastrointestinal side effects.^[28] Of the 70 patients, data from 65 patients were considered for final analysis. Five patients discontinued apremilast therapy because of AEs before 24 weeks and hence data of these patients were not considered for efficacy analysis [Figures 1-4].

The average age of the patients was 41.37 ± 15.2 years. Out of 70 patients, 51 were male (72.8%) while 19 were female (27.2%). The mean disease duration was 9.11 ± 9.02 years. Twenty percent ($n = 14$) patients were having other comorbidities such as hypertension and diabetes mellitus. Out of 70 patients 55.71% ($n = 39$) patients were previously treated with methotrexate, 31.42% ($n = 22$) were systemic treatment naive, 11.42% ($n = 8$) patients were on biologicals while 10% ($n = 7$) patients were previously on cyclosporine [Table 1].

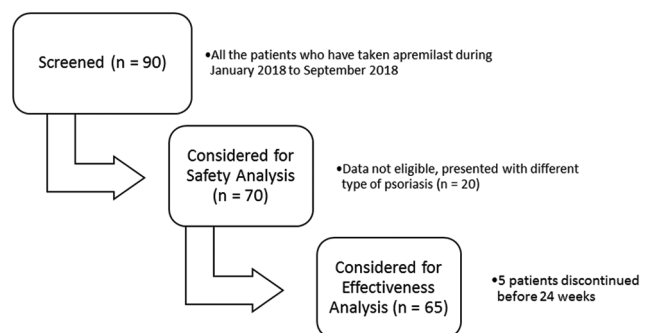


Figure 1: Patients selection criteria

Effectiveness evaluation

Of the 65 patients analyzed, 41.53% ($n = 27$) patients achieved the primary endpoint of PASI 75 response at the end of 16 weeks [Figures 5-8]. After continuing monotherapy with apremilast for 24 weeks, there was further improvement in the severity of psoriasis with 58.46% ($n = 38$) patients achieving PASI 75.

A similar trend was seen with other secondary endpoints. At week 16, 76.92% ($n = 50$), 15.38% ($n = 10$), and 6.15% ($n = 4$) of patients achieved PASI 50, 90, and 100 response, respectively. After the continuation of apremilast monotherapy for 24 weeks, further improvement in PASI was seen with 81.53% ($n = 53$), 29.23% ($n = 19$), and 10.76% ($n = 7$) patients achieved PASI 50, 90, and 100 response at the end of 24 weeks [Figure 2].

After 24 weeks of therapy with apremilast, the mean percentage reduction in PASI score from baseline was 67.8%. Mean PASI score at baseline was 17.11 ± 9.06 which was significantly reduced to 5.51 ± 7.05 after 24 weeks of apremilast therapy ($P < 0.001$). Similarly, after 24 weeks mean DLQI score was significantly reduced to 3.4 from mean baseline DLQI score of 10.8 ($P < 0.001$). 55% ($n = 36$) patients reported a DLQI score of < 5 after 24 weeks of therapy [Figure 3].

24.61% ($n = 16$) patients failed to achieve clinical improvement ($< 50\%$ improvement in PASI) with apremilast monotherapy after 16 weeks while 18.46% ($n = 12$) of patients failed to show clinical improvement after 24 weeks of therapy.

Table 1: Baseline Demographic Details ($n=70$)

Variable	Value
Sex No. (%)	
Male	51 (72.8%)
Female	19 (27.2%)
Age mean \pm SD, y	41.37 \pm 15.2 years.
Disease duration, mean \pm SD, y	9.11 \pm 9.02 years
Baseline PASI score, mean \pm SD	17.11 \pm 9.06
Baseline DLQI score	10.8
Comorbidities, No. (%)	14 (20%)
Hypertension	6 (8.6%)
Diabetes mellitus	6 (8.6%)
IHD	2 (2.9%)
Dyslipidemia	2 (2.9%)
Alcoholic liver disease	1 (1.4%)
H/o previous therapies prior to apremilast	
No. (%)	
Methotrexate	39 (55.71%)
Systemic treatment naive	22 (31.42%)
Biologics	8 (11.42%)
Cyclosporine	7 (10%)

Safety evaluation

Out of 70 patients who were considered for safety evaluation, 28 (40%) patients reported ≥ 1 drug-related AEs. Nausea was one of the most common side-effect reported by 21.4% ($n = 15$); followed by diarrhea (18.57%, $n = 13$); headache (17.4%, $n = 11$); vomiting (8%, $n = 6$); weight loss $> 10\%$ loss of body weight (7.69%, $n = 5$); myalgia (6.15%, $n = 4$); and gastritis (6.15%, $n = 4$). Most of the side-effects were reported within the first 4 weeks. They were tolerable, temporary, and usually resolved within 2–4 weeks [Figure 4].

Five patients discontinued apremilast therapy within the first 2 weeks because of AEs. Three patients discontinued because of diarrhea; 1 patient because of nausea; and 1 patient discontinued apremilast because of severe headache. None of the patients experienced mood disturbance or depression or suicidal ideation.

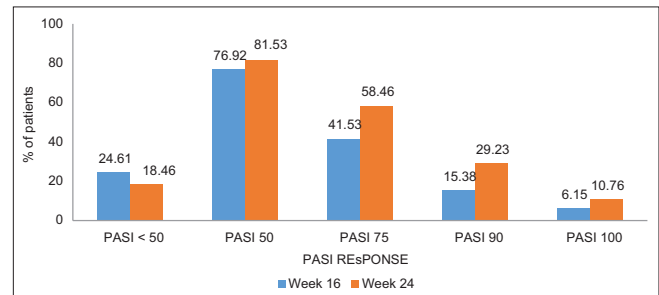


Figure 2: Proportion of patients achieving PASI response at week 16 and week 24

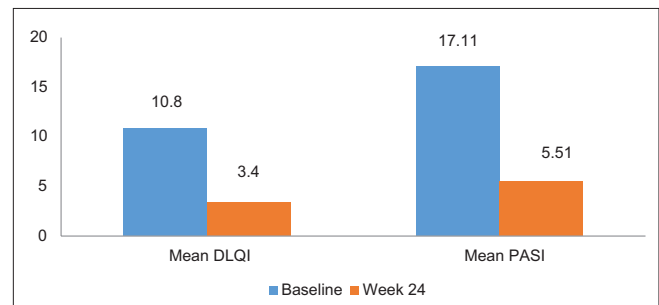


Figure 3: Change in mean DLQI and mean PASI score at week 24

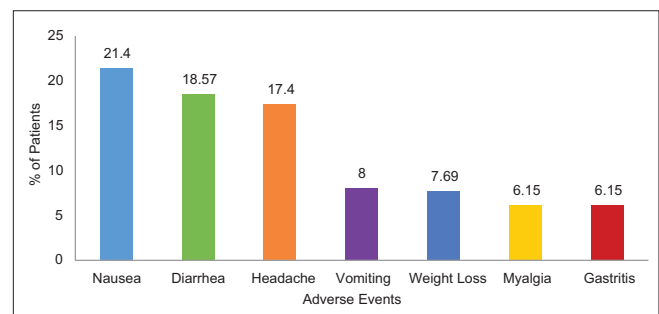


Figure 4: Proportion of patients showing ≥ 1 AE with apremilast

Discussion

Apremilast has been evaluated in multiple randomized controlled trials (ESTEEM 1^[17] and 2,^[18] LIBERATE^[27]) with acceptable effectiveness and safety profile. Previously, Papadavid *et al.*,^[20] Vujic *et al.*,^[21] Ighani *et al.*,^[19,24] Ohata *et al.*,^[25] and Wong *et al.*^[22] reported a real-world experience of apremilast in the management of moderate-to-severe psoriasis [Table 2]. However, experience with apremilast in real-world setup, where multiple other factors affect the treatment outcome, is lacking in India.

The demographic characteristics of our patients were in-between compared to those reported in ESTEEM trials and real-world studies. Regarding the average age (41.37 years) at baseline, patients in our study were of similar age than those in ESTEEM 1, 2 and LIBERATE studies^[17,18,29] and were much younger compared to patients included in real-world studies.^[19-25] Mean baseline PASI was slightly higher in ESTEEM 1, 2 and LIBERATE studies and much lesser in other studies as compared to our study. The use of prior systemic and biologic therapies in our study varied greatly compared to the clinical trials. More patients in our study had previous experience of conventional systemic therapy compared to ESTEEM studies (65.71% vs. 37.7% to 38.7%).^[17,18] Conversely, our study included less number of patients who failed previous biological therapy compared to ESTEEM trials (11.42 vs. 28.8% to 33.6%).^[17,18]

Primary effectiveness endpoint

In our study, 41.53% ($n = 27$) patients achieved primary endpoint of PASI 75 response at the end of 16 weeks, these results are in accordance with the results reported by LIBERATE trial (39.8%),^[29] Ighani *et al.* (39.9%),^[24] and Wong *et al.* (47%).^[22]

Our efficacy results are slightly better than those achieved in ESTEEM trials (ESTEEM I and II).^[17,18] In ESTEEM 1, 33.1% of patients achieved PASI 75 response at week 16 while in ESTEEM 2, 28.8% of patients achieved PASI 75 at week 16. This could be attributed to the fact that the majority of our patients were having less severe disease compared to patients in ESTEEM trials. Similarly, difference in baseline PASI can explain the differing results in our study and those reported by Papadavid *et al.*^[20] and Ighani *et al.*^[19] in their real-world studies [Table 2].

Secondary effectiveness endpoints

In our study after 16 weeks of therapy, 76.92% of patients achieved PASI 50 vs. 58.7% in ESTEEM I and 55.5% in ESTEEM II; 15.38% of patients achieved PASI 90 vs. 9.8% in ESTEEM I and 8.8% in ESTEEM II; and 6.15% of patients achieved PASI 100 (not reported in the ESTEEM trials).^[17,18] Inclusion of less severe psoriasis patients compared to ESTEEM trials, where the population had more severe psoriasis, can explain the difference in results. The same reason can explain the difference between our results and those reported by Papadavid *et al.* where the majority of patients were of moderate severity.^[20] In their study, 92.6% of patients achieved PASI 50; 28.6% of patients achieved PASI 90; PASI 100 was achieved by 17.9% of patients.^[20] Regarding PASI 90, our results are in accordance with LIBERATE trial where after 16 weeks of therapy 14.5% of patients achieved PASI 90.^[29]

In our study, there was a significant improvement in the proportion of patients achieving PASI 50, 75, 90, and 100 responses after continuing therapy with apremilast. After 24 weeks of monotherapy with apremilast, 58.46% of patients achieved PASI 75 response; 81.53% of patients

Table 2: Demographic characteristics of patients, safety outcomes and treatment effectiveness of apremilast

Parameter	Our study	Papadavid <i>et al.</i> ^[20] ($n=50$)	Vujic <i>et al.</i> ^[21] ($n=48$)	Ighani <i>et al.</i> ^[24] ($n=148$)	Ighani <i>et al.</i> ^[19] ($n=34$)	Ohata <i>et al.</i> ^[25] ($n=50$)	Wong <i>et al.</i> ^[22] ($n=59$)	Esteem 1 ^[17] ($n=562$) ^a	Esteem 2 ^[18] ($n=274$) ^a	Liberate ^[27] ($n=83$) ^a
Age (mean) yrs.	41.37±15.2 years	55	51	54.1	53.5	58.6	50	45.8	45.3	46.0
Sex (male/female)	51/19	35/15	33/15	85/63	20/14	30/20	26/33	379/183	176/98	49/34
PASI 50* (% of pts.)	76.92	92.6	41.8	-	-	35.7	-	58.7	55.5	62.7
PASI 75* (% of pts.)	41.53	58.6	18.8	39.9	55.9	19	47	33.1	28.8	39.8
PASI 90* (% of pts.)	15.38	28.6	6.3	-	-	14.3	10	9.8	8.8	14.5
PASI 100* (% of pts.)	6.15	17.9	-	-	-	-	15	-	-	-
Mean DLQI Baseline	10.8	11.1	-	-	-	-	16	12.1	-	11.4
Mean DLQI wk. 16	3.4	3.9	-	-	-	-	7	-	-	-
Mean PASI Baseline	17.11	10.8	10.7	12.2	13.1	10.1	16.1	19.4	18.9	19.4
Mean PASI wk. 16	5.51	4.3	-	5.3	3.9	5.3	5.6	-	-	-
≥1 adverse events (% of pts.)	40	30	64.6	62.2	67.6	76	45.8	69.3	68	71.1
Discontinuation due to adverse event (% of pts.)	7.14	12	4.2	-	14.7	18.8	5.1	5.2	5.5	3.6

a: No. of patients on apremilast; *: % of pts. at week 16

achieved PASI 50 response; 29.23% of patients achieved PASI 90 response while 10.76% of patients achieved PASI 100 response. None of the published studies has reported the efficacy evaluation at week 24, however, a similar trend was reported by ESTEEM 1, 2, and LIBERATE trials wherein continuation of apremilast therapy beyond 16 weeks was associated with an increase in the proportion of patients showing improvement in the severity of psoriasis.^[17,18,29] This highlights the fact that continuous therapy with apremilast is beneficial in patients with moderate-to-severe psoriasis.

Similar to other secondary efficacy parameters, there was a significant improvement in baseline PASI score and DLQI of patients in our study ($P < 0.001$). There was a significant increase in the quality of life of patients with more than 50% of patients achieving DLQI of <5 at the end of 24 weeks. These results were in accordance with real-world studies by Papadavid *et al.*,^[20] Wong *et al.*,^[22] Ohata *et al.*,^[25] Vujic *et al.*,^[21] and clinical trials (ESTEEM 1, 2, and LIBERATE).^[17,18,29]

Safety endpoints

In regards to safety, 40% of patients reported ≥ 1 AEs compared to 68.0%–69.3% of patients in the clinical trials



Figure 5: Pre & Post photographs showing PASI 75 response after 16 weeks



Figure 7: Pre & Post photographs showing PASI 100 response after 12 weeks



Figure 6: Pre & Post photographs showing PASI 90 response after 16 weeks



Figure 8: Pre & Post photographs showing PASI 100 response after 20 weeks

and other real-world studies by Ighani *et al.*,^[19,24] Mayba *et al.*,^[23] and Ohata *et al.*^[25] This low incidence of AEs in our study may be attributed to lack of awareness amongst patients regarding reporting of AE which is usually seen in India.

In our study, common AE such as nausea and diarrhea were reported by 21.4% and 18.57% patients, respectively. These results are in accordance with clinical trials ESTEEM 1 (diarrhea, 18.8% and nausea, 15.7%),^[17] ESTEEM 2 (diarrhea, 15.4% and nausea, 18.8%),^[18] and other real-world studies by Papadavid *et al.* (diarrhea and nausea, 20%),^[20] Mayba *et al.* (diarrhea, 37%),^[23] and Ighani *et al.* (diarrhea, 14.7% and nausea, 20.6%).^[19]

A total of 7.69% of patients also reported weight-loss within 24 weeks in our study. Weight-loss is a well-known AE of apremilast in long-term 52-week therapy, but short-term 24-week weight-loss data were not reported in the clinical trials for comparison.

More proportion of patients (17.4%) in our study reported headache compared to ESTEEM 1 and 2 trials where only 5.5%–6.3% of patients reported headaches and 7.3%–7.4% reported tension headaches.^[17,18] One unusual AE reported by patients in our study was generalized myalgia. In our study, 6.15% of patients reported generalized myalgia. No comparison data were reported in clinical trials regarding generalized myalgia, however, Ighani *et al.*^[24] reported an incidence of back pain and leg pain in 1%–2% of patients, similarly in ESTEEM 2, back pain was reported by 2.2% of patients.^[18] The high proportion in real-world practice could be due to patient recall bias and subsequent overreporting. In addition, previous studies were conducted in western countries and a higher incidence of headache and myalgia in our study may be related to racial distinction.

Only 7.14% of patients out of 70 in our study discontinued apremilast due to AEs, similar discontinuation rates were seen in ESTEEM 1, 2 (5.2% and 5.5%, respectively),^[17,18] and LIBERATE (3.6%)^[29] trials, and other real-world studies by Vujic *et al.* (4.2%)^[21] and Wong *et al.* (5.1%).^[22] Similar to other studies, diarrhea was the most common reason followed by nausea for discontinuation of apremilast in our study. None of the patients in our study discontinued apremilast due to lack of efficacy which has been reported in various real-world studies.

Overall, our study is one of the very few study to evaluate the real-world safety and efficacy data of apremilast monotherapy for plaque psoriasis, especially in the Indian setup. The results of this study have been found to be generally consistent with the results of other retrospective real-world studies that evaluated the efficacy and safety of apremilast therapy in the management of moderate-to-severe psoriasis. Many patients in our study had failed previous conventional systemic therapy. Results of our study prove that apremilast is beneficial in such patients.

Limitations of our study include the small population, possible recall bias in reporting of AEs, and the internal shortcomings of retrospective real-world studies (lack of external validity and reproducibility).

In conclusion, the results of this study verify those of previous clinical trials and real-world studies. They support apremilast monotherapy as an efficacious and safe treatment option for the management of moderate-to-severe plaque psoriasis. It has also been seen that continuation of apremilast therapy is associated with further improvement in the severity of psoriasis with favorable safety profile which merits long-term use of apremilast.

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Conflicts of interest

There are no conflicts of interest.

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