Clinical Efficacy and Safety of Oral Apremilast: Treatment Analysis for Chronic Plaque Psoriasis

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Original Research Article

ABSTRACT

Background: Apremilast is an oral, selective phosphodiesterase-4 (PDE-4) enzyme inhibitor, approved by the US-FDA for management of moderate to severe plaque psoriasis. Apremilast belongs to class of drug that function by modulating pro-inflammatory cytokines and have a low molecular weight (<1 kD), identified as small molecules. Due to its convenience in administration via oral or topical route, adequate efficacy, great safety profile and low cost they are emerging as treatment choices in inflammatory dermatosis and other systemic inflammatory disorders.
Material and Methods: A hospital based, prospective, interventional, cohort study was conducted on 78 patients with Chronic plaque psoriasis. Efficacy of Apremilast was studied in 38 patients receiving oral Apremilast with topical steroids in comparison to 36 patients who were given only topical steroids for 16 weeks. Patients were evaluated pre-treatment and then every 4 weeks for a period of 16 weeks and followed up to the 28th week for any adverse effects associated with apremilast therapy. Outcome was assessed on the basis of PASI score and clinical photographs. Side effects in both groups were recorded.
Results: Primary endpoint (PASI75 and above) was achieved in 68.42% patients in group A. Among this patient's PASI 90 was achieved in 13.16% (n=5) and PASI 100 was obtained in 13.16% (n=5). In Group B, none of the patients achieved PASI 75. Most common side effects observed in group A were GI disturbances. No significant adverse effect was noted in group B.
Conclusion: Apremilast has good efficacy and safety in patients with chronic plaque psoriasis. and is generally well tolerated which makes it possible to keep other immunosuppressants to be kept in reserve for more severe stages of disease. Our study supports the favorable benefit:risk profile of oral apremilast.

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1. INTRODUCTION

Psoriasis, a chronic inflammatory systemic disease that affects 2%-5% of the world population,is characterized by erythematous, scaly patches or plaques over the skin [1,2], Psoriasis is predominantly a T-cell mediated disorder. Various genetic and environmental factors play a role in its pathogenesis. Psoriasis has a significant impact on patient's Quality of Life due to it's chronicity, unsightly lesions on skin and frequent remissions and relapses [3]. Apremilast is an oral selective phosphodiesterase-4 (PDE-4) inhibitor which works intracellularly to regulate inflammatory mediators, including pathways relevant to the pathogenesis of psoriasis [4]. PDE4 inhibition elevates intracellular cyclic adenosine monophosphate (C-AMP), which in turn down-regulates the pro-inflammatory mediators, such as tumor necrosis factor (TNF-α), interleukin (IL)-23, and interferon γ and lead to increase in anti-inflammatory mediators, such as IL-10 [4-6]. This study was done to evaluate the safety and efficacy of oral apremilast – PDE-4 inhibitor in the management of Indian patients with chronic plaque psoriasis.

1.1 Aim and Objectives

To evaluate the efficacy and safety of oral apremilast in patients with chronic plaque psoriasis in comparison to patients receiving only topical steroids.

To observe adverse effects of apremilast if any.
To evaluate clinical improvement based on PASI score and clinical photographs.

1.2 Primary Objective

To assess the proportion of patients achieving at least 75% improvement in psoriasis area and severity index score (PASI 75) at week 16 in both groups.

1.3 Secondary Objective

To assess the number of patients achieving PASI 90 and PASI 100 at week 16 in both groups.

To assess the mean decrease in PASI from baseline at 16 week.

To evaluate the safety profile of apremilast upto 28 weeks.

2. MATERIALS AND METHODS

After approval of the institutional ethics committee, prospective cohort study on psoriasis patients was carried out at the Department of Dermatology, tertiary health care hospital, western India from November 2017 to July 2019. 78 histopathologically diagnosed cases of chronic plaque psoriasis were enrolled in the study.

2.1 Inclusion Criteria

The inclusion criteria consisted of male and female patients aged 18 years or older, suffering from chronic plaque psoriasis of more than > 6 month of disease duration. Any other systemic drugs taken by patients were withdrawn at least 6 weeks before inclusion in study.

2.2 Exclusion Criteria

Exclusion criteria were weight less than 50kg, variants other than chronic plaque psoriasis, pregnant and lactating women, female patient planning pregnancy in near time or not ready to use contraception, any other form of treatment or concomitant drugs for psoriasis, any general debilitating condition, active infection, immune-compromised patients, cardiac, renal and hepatic impairment, psychiatric disorders and patients not willing to give written informed consent.

2.3 Randomization

Total 78 patients were enrolled in our study. Patients were randomized by computer randomization in two groups. Group A included 42 patients treated with oral apremilast 30 mg twice daily with topical corticosteroid therapy and group B included 36 patients treated with only topical corticosteroid therapy for a total of 16 weeks. Apremilast dose was titrated from 10mg on day 1 and gradually increased to 30mg twice daily from day 6 onwards and continued for a total 16 weeks.

Both the groups of patients applied betamethasone valerate 0.1% cream for skin and betamethasone dipropionate 0.05% lotion for scalp lesions once a day and petroleum jelly twice a day. Other concomitant drugs allowed were oral cetirizine 10mg, paracetamol 500mg as and when required and daily supplements of folic acid 5 mg, calcium and vitamin D3 (500mg/250IU).

2.4 Pre Medication Workup

In both groups, all routine hematological investigations (complete blood count, fasting and postprandial blood sugar, renal and liver function test), routine urine examination, serology for HIV, Syphilis, Hepatitis B, C, Mantoux test, echocardiogram (ECG) and X-ray chest were done at baseline. Hematological investigations were repeated at 8 weeks and 16 weeks (+/- 5days). Other investigations including abdominal sonography and urine, stool examination were done as and when required during the study period. Urine pregnancy test was done in all female patients at baseline, 8 weeks and 16 weeks in group A.

2.5 Outcome Measures

Outcome was assessed on the basis of PASI score and clinical photographs; evaluated at baseline and then every 4 week for a period of 16 weeks. All patients were advised to continue topical therapy after week 16. Adverse effects if any were recorded at each visit upto 28th week. The parameters studied were efficacy analyzed by PASI score calculation and drug safety by the proportion of adverse events (AEs). In the event of intolerable and severe adverse events, patients were excluded from the efficacy study but were included in safety study.

2.6 Statistical Analysis

The normality of the data was checked by the shapiro wilk test. As our data did not follow a normal distribution, Mann-Whitney U test was used to calculate the significance difference in the outcome between the two groups. Mean and standard deviation were used for continuous variables and P value of <0.05 was considered being statistically significant.

3. RESULTS

Total 78 patients (58 male and 20 female) with chronic plaque psoriasis of more than 6 months duration were included in the study.The baseline demographic data of all patients are shown in Table 1.

Group A had 35 male and 7 female patients with mean age (SD) of 43 (15.1) years while Group B had 23 male and 13 female patients with mean age (SD) of 43.3(11.4) years.

In group A, out of the 42 patients, 38 (90.48%) patients completed 16 weeks treatment. 4 patients (9.52%) were withdrawn from the study before 8 weeks.

All patients in group B completed the study.

Comparison between mean PASI and PASI Improvement at 4 weeks interval upto 16th week is shown in Table 2.

In Group A; mean PASI score (SD) at week 0 =15.6 (10.9), at week 4=10.0 (7.7), at week 8 =7.2 (6.30), at week 12=5.0 (4.6) and at week 16=3.4 (4.1).We achieved our primary objective (PASI75 and above) in 68.42% (n=26) patients.

In Group B, mean PASI score (SD) at week 0 =13.2 (3.9), at week 4=12.0 (3.5), at week 8=11.3 (3.6), at week 12=10.3 (3.4) and at week 16 = 9.6 (3.4). None of the patients in group B achieved PASI 75 and above. 8.33%(n=3) patients achieved PASI 50 .

Table 1. Baseline demographic data in group A and group B

	Group A				Group B				
	N	Mean	SD	95% CI	N	Mean	SD	95% CI	P Value
age	42	43.0	15.1	38.303 to 47.697	36	43.3	11.4	39.461 to 47.150	0.922
bmi	42	26.5	6.4	24.503 to 28.521	36	27.2	5.6	25.281 to 29.040	0.53
duration	42	7.8	5.5	6.099 to 9.532	36	5.8	4.1	4.425 to 7.214	0.076
ht	42	1.6	0.1	1.619 to 1.679	36	1.6	0.1	1.583 to 1.644	< 0.0001
wt	42	71.4	14.4	66.862 to 75.852	36	70.2	12.7	65.873 to 74.460	0.7

Table 2. Mean PASI AND PASI reduction comparison between Group A and Group B

|	Group A				Group B				P Value
	N	Mean	SD	95% CI	N	Mean	SD	95% CI	
1st PASI (week 0)	38	15.6	10.9	12.018 to 19.203	36	13.2	3.9	11.903 to 14.558	0.22
2nd PASI(week 4)	38	10.0	7.7	7.422 to 12.494	36	12.0	3.5	10.795 to 13.161	0.158
3rd PASI(week 8)	38	7.2	6.3	5.162 to 9.286	36	11.3	3.6	10.079 to 12.516	0.0011
4th PASI(week 12)	38	5.0	4.6	3.424 to 6.476	36	10.3	3.4	9.188 to 11.506	< 0.0001
5th PASI(16 week)	38	3.4	4.1	2.003 to 4.724	36	9.6	3.4	8.432 to 10.724	< 0.0001
PASI_REDUCTION_AT_4_WK	38	38.1	17.7	32.239 to 43.863	36	9.2	10.4	5.706 to 12.769	< 0.0001
PASI_reduction_at_8__week	38	50.3	25.0	42.022 to 58.486	36	14.7	13.3	10.216 to 19.246	< 0.0001
PASI_REDUCTION_AT_12WK	38	64.0	24.8	55.808 to 72.128	36	22.0	13.3	17.462 to 26.455	< 0.0001
PASI_reduction_at_16_week	38	74.0	28.4	64.693 to 83.361	36	27.5	16.7	21.862 to 33.183	< 0.0001

Primary endpoint achievement in Patients
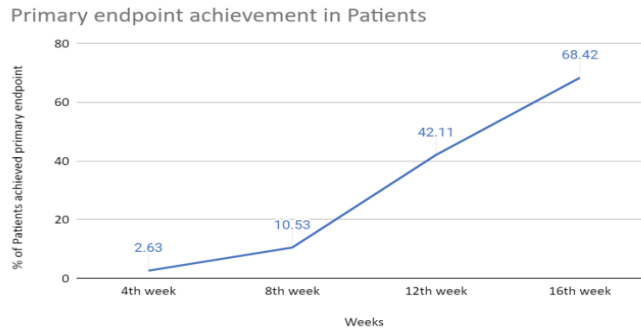
Fig. 1. % of patients achieving primary endpoints at 4th,8th,12th and 16th week of study

In Group A, mean PASI reduction from baseline was 74.0 ± 28.4 while in Group B it was 27.5 ± 16.7 at the end of 16 weeks. Average PASI score reduction from baseline to week 16 in group A was significant as compared to group B (P < 0.0001).

Primary endpoint of PASI 75 (Fig. 1) was achieved by 1 patient (2.63%) at the end of 4th week, 4 patients (10.53%) by the end of 8th week, 16 patients (42.11%) by the end of 12th week and 26 patients (68.42%) by the end of the 16th week in group A.

Among patients achieving PASI 75 and above, PASI 75 was achieved in 61.54% (n=16), PASI 90 was achieved in 19.23% (n=5) and PASI 100 was obtained in 19.23% (n=5).

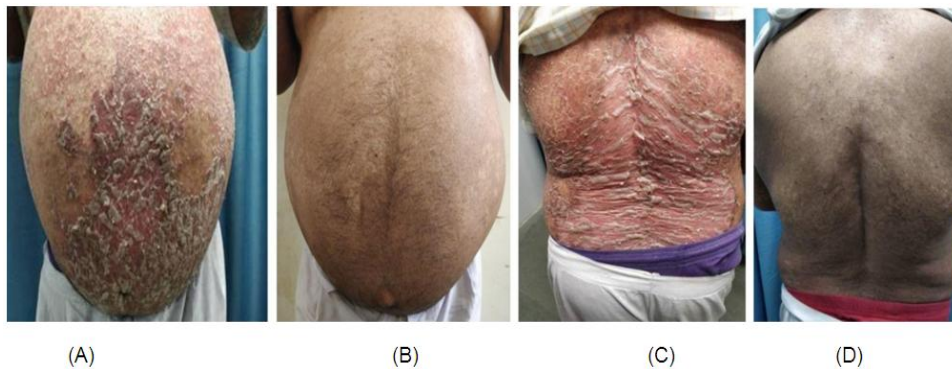(A) (B) (C) (D)

Fig. 2. Pre and Post photographs showing PASI 100 improvement (Patient A)

(A) (B) (C) (D)

Fig. 3. Pre and Post photographs showing PASI 100 improvement at 16th week (Patient B)
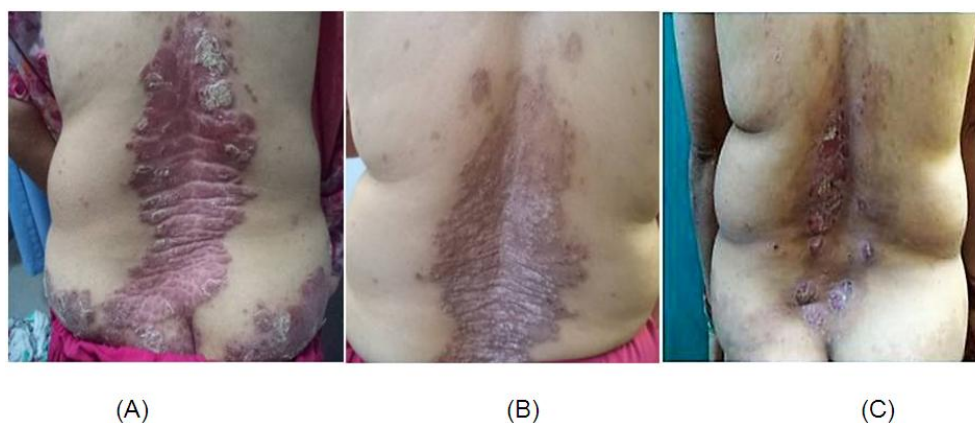
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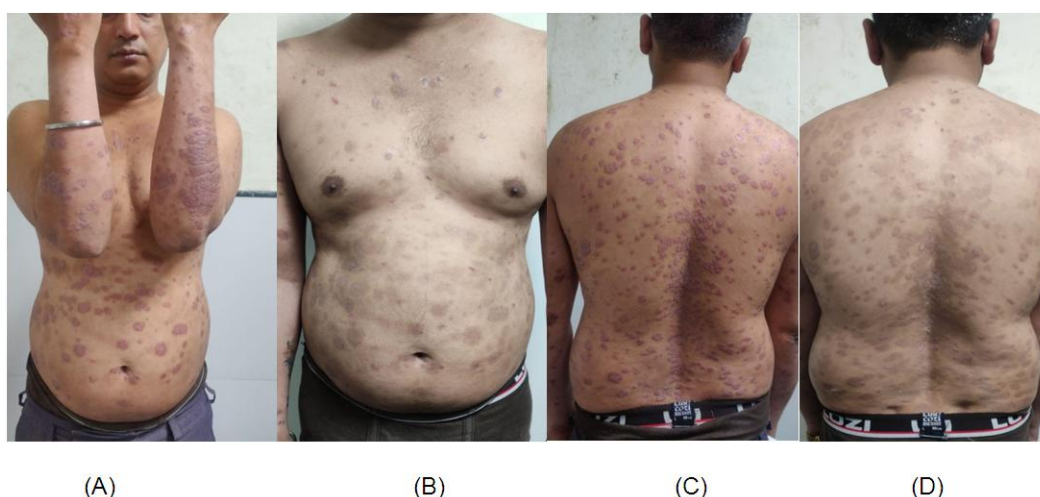**Fig. 4. Pre and Post photographs showing PASI 75 improvement**

Fig. 5. Pre and Post photographs showing PASI 90 improvement

[Fig. 2] and [Fig. 3] shows pre and post clinical photographs of patients with PASI 100 improvement at the end of 16th week.

[Fig. 4] shows pre and post clinical photographs of patient with improvement of PASI 75 at the end of 16th week.

[Fig. 5] shows pre and post clinical photographs of patient with improvement of PASI 90 at the end of 16th week.

3.1 Safety Evaluation

For safety evaluation in group A, all 42 patients were considered and evaluated upto 28 weeks, 22 (52.38%) patients reported ≥1 drug-related AEs. The most common adverse events in group A were gastrointestinal (GI) disturbances, respiratory infection, headache, weight loss, joint pain [Table 3]. Total adverse events reported in apremilast group were 33 out of which majority of the (36.36%) adverse events were mild GI disturbances during the initial period of treatment and resolved even on continuation of medicine. Most of the adverse effects were mild which were resolved with continued therapy, with conservative management. Highest frequency of adverse effects were observed during the first 2 weeks of dosing and decreased thereafter. Two patients experienced side effects after 16 weeks. One patient developed colitis 4 weeks after completion of treatment and One patient had significant weight loss (>10%) which was observed during the post treatment phase (16th-28th week) with no identifiable cause for the weight loss. None of the patients in group B had any significant side-effects during the study period.

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Table 3. Adverse events in group A (oral apremilast)

Serial number	Adverse effects	Adverse events N, (n%), (m%)
1)	Gastrointestinal Problems (Diarrhea, Nausea & Vomiting, Dyspepsia, Acidity)	12(28.57%),(36.36%)
2)	Weight Loss	6(14.28%),(18.18%)
3)	Severe increase in disease activity	2(4.76%),(6.06%)
3)	Joint Pain, Calf Pain	3(7.14%),(9.09%)
4)	Upper Respiratory tract Infection, Bronchitis	2(4.76%),(6.06%)
5)	Headache	2(4.76%),(6.06%)
6)	Chest Pain	2(4.76%),(6.06%)
7)	Depression And Insomnia	1(2.38%),(3.03%)
8)	Urinary tract infection	1(2.38%),(3.03%)
9)	Ghabharaman	1(2.38%),(3.03%)
10)	colitis	1(2.38%),(3.03%)
11)	Hypersensitivity	0(0%)
	Total adverse events reported	33

N= No. of patients who reported the following adverse event
n%= % of patients of the total group population(42) reported adverse events.
m%= % of adverse events encountered of the total adverse events (33) reported

Four patients from group A were excluded from study due to intolerable adverse events or exacerbation of disease. One patient had a urinary tract infection due to E.coli and another had uneasiness ('*Gabhraman*'). Both of them improved after omitting apremilast. Laboratory parameters and ECG were normal in patients who experienced uneasiness due to drugs. Patients with UTI also had other parameters within reference range except pus cells and presence of E.coli in urine. Two patients who had exacerbation of disease between 2nd to 4th week of study in group A decided to discontinue apremilast therapy and to switch over to other systemic therapy and were followed up for any delayed side-effects related to study drug. As the patients decided to discontinue the study during the initial phase of treatment only and did not complete the 4 month study , patients were not included in the efficacy analysis of the drug.

4. DISCUSSION

As the first PDE4 inhibitor approved for use in chronic plaque psoriasis, Apremilast provides clinicians with a new arsenal for fighting psoriasis with good efficacy, acceptable safety profile and relatively low cost. One of the major breakthroughs was when it was studied as a treatment for chronic plaque psoriasis under the ESTEEM 1[5] and ESTEEM 2[7] studies where a total of 562 and 274 patients were included respectively. Since then Apremilast has been evaluated in multiple randomized controlled trials like Agarwal S et al [2], De A et al [8], Papadavid et al.[9] Ighani et al[10],Vujic et al [11], Wong et al [12], LIBERATE [13] , Shah et al [14] etc. with acceptable effectiveness and safety profile [Table 4].

The demographic characteristics of our patients were in-between compared to those reported in ESTEEM trials and real-world studies. The average age of patients in our study was 43 years which was comparable to ESTEEM I [5] & II [7] and LIBERATE [13] studies.

The mean PASI at baseline in our study being 15.6 was similar to that of WONG et al [12] (16.1) studies and a little lower than that of ESTEEM I [5] and ESTEEM II [7] studies where mean baseline was PASI 19.4 and 18.9 respectively.

In our study, Out of the 38 Patients, 68.42% (n=26) in group A achieved the primary endpoint of PASI 75 (Fig. 2) response at the end of 16 weeks, these results are in accordance with the results reported by, LIBERATE trial [14] (39.8%), Ighani et al [10]. (39.9%), and Wong et al [12]. (47%). In a study by Agrawal S et al [2] PASI 75 was achieved in 26% of patients. Our efficacy results are slightly better than those achieved in ESTEEM trials (ESTEEM I [5] and II [7]). In ESTEEM I [5], 33.1% of patients achieved PASI 75 response at week 16 while in ESTEEM II [7], 28.8% of patients achieved PASI 75 at week 16.

Table 4. Demographic data of patients, treatment effectiveness and safety evaluation of apremilast in different previous studies

	Our Study	Agarwal s et al(8 weeks)[2]	De A et al[8]	Papadavid et al[9]	Ighani et al[10]	Vujic, I et al[11]	WONG ET AL[12]	ESTEEM 1[5]	ESTEEM 2[7]	LIBERATE (52 week)[13]	Shah et al(24 week)[14]
Mean Age	43.0(15.1)	-	-	55	54.1	51	50	45.8 (13.1)	45.3(13.1)	46.0 (13.6)	41.37±15.2
No.of patients	42	73	39	50	148	48	59	562	274	83	70
M/F	35/7	-	-	35/15	85/63	33/15	26/33	379/183	176/98	49/34	51/19
Mean PASI at baseline	15.6(10.9)	-	13.6	10.8	12.2	10.7	16.1	19.4	18.9	19.4	17.11±9.06
Mean PASI at end of study	3.4(4.1)	-	4	4.3	5.3	-	5.6	-	-	-	5.51 ± 7.05
<PASI 50(%)	15.79%	39.72%	8%	-	-	-	-	-	-	-	
PASI 50(%)	15.79%	28.76%	38%	92.60%	-	41.80%	-	58.70%	55.50%	62.70%	76.92%
PASI 75(%)	68.42%	31.50%	48%	58.60%	39.90%	18.80%	47%	33.10%	28.80%	39.80%	41.53%
PASI 90(%)	26.32%	-	2.70%	28.60%	-	6.30%	10%	9.80%	8.80%	14.50%	15.38%
PASI 100(%)	13.16%	-	2.70%	17.90%	-	-	15%	-	-	-	6.15%
>=1 adverse events(% of pts)	52.38%	-	46%	30%	62.20%	64.60%	45.80%	69.30%	68%	71.10%	40%
Most common adverse event	GI disturbance	nausea and vomiting	Diarrhea	GI disturbance	-	Diarrhea	-	Diarrhea	nausea and diarrhea	nausea and diarrhea	Nausea and diarrhea

Out of the 38 patients in our study, 13.16% (n=5) achieved PASI 90 (Fig. 3) which is comparable with LIBERATE [13] trial where after 16 weeks of therapy 14.5% of patients achieved PASI 90.

In fact, 13.16% (n=5) patients in group A in our study achieved PASI 100 (Figs. 4-6), such results are not reported in the ESTEEM trials. Inclusion of less severe psoriasis patients compared to ESTEEM trials, where the population had more severe psoriasis, can explain the difference in results. Our results were in accordance with those reported by Papadavid et al [9]. where the majority of patients were of moderate severity. 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.

In our study we achieved PASI 75 and more in 68.42% (n=26) of patients which is higher as compared to other studies probably because of concomitant medium potency topical corticosteroids use. Our study was also on a small population of patients as compared to ESTEEM studies.

Another important finding in present study was that many of the patients had taken some form of systemic therapy before apremilast monotherapy. Thus apremilast is effective in both systemic therapy experienced patients and treatment naïve patients.

In regards to safety, 52%(n=22) of patients reported ≥1 AEs compared to 68.0%–69.3% of patients in the clinical trials and other real-world studies by Ighani et al. [10], Mayba et al [15], and Ohata et al [16].

Out of 42 patients 4 patients withdrew due to severe side effects. Most adverse effects in group A were mild or moderate in severity and discontinuation rate because adverse effects were low. Majority patients had side effects of gastrointestinal disturbance.

Changes in laboratory parameters were not clinically significant. No tuberculosis reactivation was observed during our study. The results from our study demonstrated an acceptable safety profile and was generally well tolerated over 16 weeks.

5. CONCLUSION

Traditional agents for psoriasis management like methotrexate, cyclosporine, retinoids etc. have a potential for long-term toxicity and warrant regular monitoring throughout treatment. Phototherapy requires frequent visits to clinic and may not be convenient for the patient [1,2]. Topical steroids though important concomitant medicine; can lead to various visible, cosmetically unacceptable adverse effects, does not give long lasting remission and tachyphylaxis is major issue on long term use. Concomitant use of topical steroids with apremilast also decreases the cumulative requirement of topical steroids thus decreasing the frequency of adverse events associated with its use. Biological therapies, on the other hand, though effective, have their own disadvantages related to parenteral administration, adverse effect profile, cost of the therapy and management requiring a specialist setting. Therefore, there is an ongoing search for an ideal agent for managing psoriasis [1,2,4].

As apremilast does not interfere with the immune system and act by targeting the central inflammatory signaling pathways it is safer than traditional immuno-suppressive agents [6]. Apremilast may be continued in responders for a longer time to get sustained benefits Some researchers have reported of use of drug safely for more than 12 months [5].

Average cost of apremilast therapy in India is around 20$ per month while biologics costs much higher and out of reach of most patients. Apremilast is extremely cost effective in Indian set up, with comparable efficacy and very high safety profile and is generally well tolerated in treatment of psoriasis, which makes it possible to keep other immunosuppressants to be kept in reserve for more severe stages of disease. Our study supports the favorable benefit: risk profile of apremilast. Apremilast provides a safer therapeutic option, ease of oral administration, minimal interaction potential with other drugs, fairly safe AE profile, minimal laboratory monitoring requirement and lack of cumulative, specific organ toxicity making apremilast an attractive option for patients with psoriasis requiring long term systemic therapy.

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. In conclusion apremilast has proved to be beneficial to patients suffering from moderate to severe psoriasis.

6. LIMITATIONS

We have not evaluated the effect of apremilast on nail, palmo-plantar or joint involvement due to psoriasis, there are studies which show improvement in nail lesions and joint symptoms [4,7].

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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