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CLINICAL EFFECTIVENESS OF APREMILAST IN PATIENTS OF PSORIASIS IN A INDIAN TERITIARY CARE CENTRE

Dermatology

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ABSTRACT

Apremilast is an oral phosphodiesterase 4 inhibitor approved for the treatment of Plaque Psoriasis. Many studies have demonstrated its short and long term efficacy but there is a dearth of real life data especially in the Indian Population.The aim of this study is to report the effectiveness of Apremilast in clinical practice in Patients of Psoriasis in a tertiary care hospital in India. **Methodology** : A prospective, single centred, observational study conducted in Gandhi medical College, Bhopal for 1 year (June2021-May2022). Effectiveness Parameters were proportion of patients achieving Psoriasis Area Severity Index (PASI) 50, 75, 90, 100 response at week 16 and 24. **Results:** Data of a total 61 patients were included. At week16, 52.8 %, 32%, 15.1% patients achieved PASI 50, 75, 90 respectively. At week 24, 9.8%, 37.3%, 41.2% ,11.8% patients achieved PASI 50, 75, 90, 100 respectively. Mean percentage reduction in PASI was 9.6% at week 24. **Conclusion:** Apremilast showed 50% improvement in PASI score which showed high efficacy in clinical practice among the Indian patients with psoriasis in terms of therapeutic response. This study supports that apremilast is one of the safer options in the management of moderate to severe Plaque psoriasis.

KEYWORDS

Apremilast, Psoriasis, Efficacy, PASI score

INTRODUCTION

Psoriasis is one of the most recurrent, common, chronic, immune mediated disorder affecting approximately 1-8 % population of the world.[1] In India the prevalence ranges from 0.44 and 2.2 % with overall incidence of 1.02%. [2] It not only physically affects the patients but also negatively impacts their quality of life as it is associated with a number of systemic diseases such as cardiovascular diseases and psoriatic arthritis.[3] The lesions range from small reddish papules to large scaly plaques. The aetiology of the disease is not clearly understood but genetic predisposition and role of immune system in the pathology of the disease have identified development of treatment which targets specific immunological aspect of the disease.

Conventionally, systemic agents used to treat moderate to severe plaque psoriasis such as methotrexate, acitretin, cyclosporin etc are associated with severe adverse effects such as hepatotoxicity, leukocytopenia and nephrotoxicity. Biologicals agents are also used but require routine monitoring and are subjected painful injections and adverse reactions. With emerging innovative research, a novel small molecule, Apremilast has been approved for treatment to moderate to severe plaque psoriasis in India in 2017.[4] Apremilast is an oral phosphodiesterase 4 inhibitor with a remarkable efficacy profile. Many clinical trials and real world studies Apremilast has been associated with significant improvement of severity of the disease. However, there is limited data among the Indian population especially in the central India regarding the real life outcome of Apremilast in the dermatological practice in the treatment of plaque psoriasis.[5-10] The objective of this study was to evaluate the efficacy of Apremilast 30 mg twice daily in patients with moderate to severe plaque psoriasis.

MATERIALS AND METHODS

Study Design

The present study was initiated after obtaining approval from institutional ethics committee Gandhi Medical College,Bhopal, Madhya Pradesh. (Date 25/8/2021,no. 27099/MC/IEC/2021). It was a prospective observational study with multiple follow up, conducted in the the department of dermatology, Gandhi medical college, Bhopal for the period of 1 year duration from June 2021 to May 2022. Data was collected in a structured manner after obtaining due consent from the patients.

Inclusion Criteria

Data was collected from both male and female patients ≥ 18 years of age, diagnosed with moderate to severe plaque psoriasis, on apremilast 30 mg twice daily , who were naive to systemic therapy or relapsed immediately after achieving significant improvement or who failed at least one systemic therapy or had contraindication for standard systemic therapy. For effectiveness analysis data was considered only from patients who completed 24 weeks of treatment. The severity of psoriasis was measured based on the psoriasis area severity index score (PASI). Where a PASI score of ≥ 10 were classified as having moderate to severe disease. The patients excluded from the study were those who diagnosed with psoriasis but treated with other medications along with apremilast. Those allergic to drug studied, pregnant and lactating women. Patients with comorbidities like Migraine, Depression , GERD who are undergoing treatment for the same.

Effectiveness Assessment

For effectiveness assessment data from the all the patients meeting inclusion criteria were assessed 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 Endpoint

1. Percentage of patients achieving PASI 50, 90 and 100 response at week 8,12,16 and 24
2. Improvement in mean PASI score from baseline at week 24.

Data Analysis

Statistical analysis was done using SPSS version 23.0. Continuous and categorical data was expressed in terms of mean and percentage respectively. The collected data was analysed statistically using proportions ,chi-square test, Multivariate Anova Test (MANOVA). A P-value of less than 0.005 was considered to be statistically significant.

RESULTS

A total of 95 patients diagnosed with psoriasis who visited dermatological OPD of Gandhi Medical College and associated Hamidia hospital during the study period were screened. Of the 95 patients screened, 61 patients who fulfilled the inclusion criteria were included in the study. All the patients were prescribed apremilast 30 mg twice daily after the initial titration to minimise the gastrointestinal side effects.[94] Of the 61 patients, 53 patients were considered for final analysis. 3 patients discontinued apremilast because of AEs and 5 patients were lost to follow up before 24 weeks and hence data of these patients were not considered for efficacy analysis.

The average age of the patients were 39.4 ±9.7 years. Out of 61 patients, 47 (77%) were males and 14 (23%) females. The mean duration of disease was 8.5 ± 5.9 years. Among the patients included in the study 5% were having associated comorbid conditions such as

diabetes, varicose veins and hypertension. Out of 61 patients, 52 (85.3%) patients were treated with methotrexate and steroids, while only 4 (6.6%) patients were systemically naive to treatment. The mean baseline PASI in our study was 26.7 ±9.72.

Table 1. Baseline demographic and disease characteristics

Characteristics	Apremilast (n=61)
Age, mean (SD), years	39.4 ± 9.7
Sex (Male/Female), n%	47/17
BMI, Mean (SD), kg/m2	25.09 ± 4.2
Weight, mean (SD), kg	62.7 ± 11.2
Duration of psoriasis, mean (SD), years	8.5 ± 5.9
Baseline PASI Score	26.7 ± 9.72
Prior use of psoriasis medication	
Totally naive to systemics Methotrexate Methotrexate and Steroids Methotrexate, steroids, Antihistamines Methotrexate, steroids, azithromycin and zinc	4(6.6) 3(5) 52(85.3) 1(1.7) 1(1.7)
Type of psoriasis	
Chronic plaque psoriasis PalmoPlantar Psoriasis Erythrodermic psoriasis Others	51(83.7) 6(9.9) 3(5) 1(1.7)

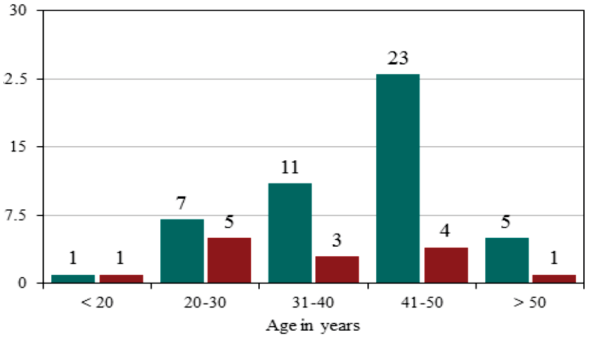

Figure 1- shows Age wise sex distribution of patients with psoriasis.

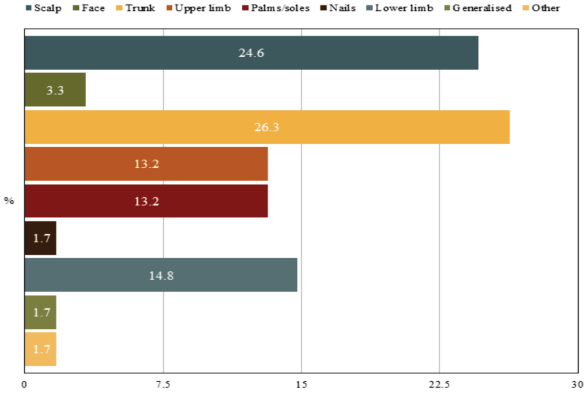

Figure 2- shows distribution of patients based on site of leision.

Table 2- shows clinical response to Apremilast.

	4 weeks (n=61)	8 weeks (n=56)	12 weeks (n=54)	16 weeks (n=53)	24 weeks (n=53)
PASI 50	3 (4.9%)	15 (26.8%)	34 (63%)	28 (52.8%)	5 (9.4%)
PASI 75	0	1 (1.6 %)	6 (11.1%)	17 (32%)	19 (35.8%)
PASI 90	0	0	1 (1.8%)	8 (15.1%)	21(39.6%)
PASI 100	0	0	0	0	8(15.1%)
Total	3	16	41	53	53

Above table shows 26.8% patients achieved PASI 50 at week 8 followed by 63% at week 12 and 52.8% at 16 weeks. Proportion of patients achieving PASI 75 increased at week 12 from 11.1% to 35.8% at week 24. 39.6% achieved PASI 90 and 15.1 % achieved PASI 100 at week 24.

Effectiveness Evaluation

Of the 53 patients considered for effectiveness evaluation 32% (n=17) of patients achieved primary endpoint of PASI 75 response at the end of 16 weeks. After continuing monotherapy with apremilast for 24 weeks, there was further improvement in the severity of psoriasis with 35.8 % (n=19) patients achieving PASI 75.

A similar trend was seen with other secondary endpoints. At 8 week follow up the primary efficacy endpoint of consistent improvement, quantified as at least 50% reduction in baseline signs and symptoms (PASI 50), was achieved by 26.8% (n=15) of patients, 1.6% (n=1) of whom achieved PASI 75. At 12 weeks 63% (n=34),11.1% (n=6),1.8% (n=1) of patients achieving PASI 50, 75, 90 respectively. At 16 weeks this number rose significantly to 52.8% (n=28), 15.1% (n=8) of patients achieving PASI 50 and PASI 75 response respectively. After continuation of Monotherapy with apremilast for 24 weeks , further improvement in PASI was seen with 9.4% (n=5), 39.6% (n=21), 15.1% (n=8) patients achieving PASI 50, 90 and 100 respectively.

After 24 weeks of treatment with apremilast, the mean PASI score at baseline was 26.7 ±9.72, which was significantly reduced to 3.3 ± 3.1 (F value = 8.51, significance 0.00)

DISCUSSION

Apremilast has been evaluated in multiple randomised controlled trials and real world studies with acceptable effectiveness profile in the management of moderate to severe psoriasis. However, there is limited experience of apremilast in the Indian setup especially in the central Indian population.

Majority of the patients included in the study belonged to the age group 41-50 years (44.3%) followed by 31-40 years (23%) (Fig5.1) The average age of the patients was 39.4 ± 9.7 years.(Table 5.1) Regarding the mean age at baseline, patients in our study were younger than those included in **ESTEEM 1,2 & LIBERATE studies** and also the real world studies.[3,5,6,7,9,10,11,12,13,14,15] Out of 61 patients, 77% were males and 23% females (Table2). This is similar to the previous studies done by **Papadavid et al.**(70% male and 30% female)[11], **Vujic et al.** (68.8% male and 31.3% female),[13] **Ighani et al.** (57.4% males , 42.6% females),[9] and differs from the study by **Wong et al.** (44% male, and 55.9% female).[12] Most patients in our study had previous experience of conventional systemic therapy compared to ESTEEM studies (93.7% vs 37.7% and 38.7%)[5,6] and only 6.3% patients were naive to systemic therapy.

This study was designed to evaluate the efficacy of apremilast in patients of psoriasis.The patients were compared for mean reduction in PASI from baseline to week 24. The treatment was effective as there was a reduction in PASI score over the course of the study. The mean baseline PASI in our study was 26.7 ±9.72 which was higher as compared to **ESTEEM 1,2 LIBERATE and other real world studies**.[5,6,7]

Primary Effectiveness Endpoint

The primary endpoint in this study was met, with a significant proportion of patients treated with apremilast achieving a PASI-75 response at week 16. In our study , during the 8 week follow up, the primary efficacy endpoint of consistent improvement, quantified as at least 50% reduction in baseline signs and symptoms (PASI 50), was achieved by 26.8% of patients which was similar to the results in the study by **Melis D et al.** [16] who found 58.3% patients had achieved PASI 50 and 18.7% achieved PASI 75 after 8 weeks of treatment. This study also reported that in the other real world studies that investigated the profile of apremilast there have been no reports of efficacy after 8 weeks of treatment. [16] By 16 weeks, the number of patients achieving PASI 50 increased to 52.8% with 32% patients achieving PASI-75 and 15.1% achieving PASI 90. These results are in accordance with the results reported by ESTEEM trial (58.7 % in ESTEEM 1 and 55.5% in ESTEEM 2); 15.1% achieved PASI 90 vs 9.8 % in ESTEEM 1 and 8.8 % ESTEEM 2.[5,6] The similarities can be attributed to the fact that the patients included in our studies were having moderate to severe disease similar to those included in the trials.[5,6,7] The difference in the results with the real world studies done by Ighani et al.(39.9%)[9] and Wong et al.[12] can be due to the differences in the baseline PASI. Regarding PASI 90, our results are in accordance with LIBERATE trial where after 16 weeks of therapy 14.5% of patients achieved PASI 90.[7]

Secondary Effectiveness Endpoints

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

apremilast, 39.6 % of patients achieved PASI 90 response; 35.8 % of patients achieved PASI 75 response, 9.4 % achieved PASI 50 response and 15.1 % of patients achieved PASI 100 response. A similar trend was reported by Shah BJ et al.[3] and ESTEEM 1,2, LIBERATE trials [5,6,7] wherein continuation of apremilast therapy beyond 16 weeks was associated with increase in proportion of patients showing improvement in the severity of psoriasis. [5,6,7] This highlights the fact that continuous therapy with apremilast is beneficial in patients with moderate to severe psoriasis.

The present study had certain limitations. Firstly, it was an open lable study. No comparsion was made with existing conventional and commonly used treatment arms such as Psoralens, methotrexate, acitretin etc. Secondly, data reported were limited to 24 weeks and this does not provide longer term efficacy and relapse related information of the disease. Thirdly, the results in this study population may not be generalisable as the sample size was small, and the study did not include those with comorbidities or medical history.

The results reported across studies suggest that apremilast presents an alternative new therapeutic option for physicians and patients who require systematic therapy but prefer an oral option. In three recent major surveys, it was reported that both patients and physicians have acknowledged unmet treatment needs for chronic plaque psoriasis, including safety and tolerability concerns with current therapies and concerns of some patients regarding the use of injectable therapies. Moreover, the findings from these surveys indicates that large number of patients are dissatisfied with and discontinue the current psoriasis therapies. The benefit risk profile of Apremilast which shows, moderate efficacy, but is devoid of significant organ toxicity, may help to address these unmet needs.

CONCLUSION

The present study designed to evaluate the efficacy of apremilast in patients of psoriasis verified the results of previous clinical trials and real world studies. The present study demonstrated apremilast significantly reduced the severity of moderate to severe plaque psoriasis over 16 weeks. Improvements were generally sustained through 24 weeks in patients who continued apremilast beyond 16 weeks. Apremilast has moderate efficacy in chronic plaque psoriasis, with improvement of lesions at special sites like scalp, palms and soles.

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