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Original Research Article

An open label randomized placebo-controlled study of apremilast in common immune mediated papulosquamous hair and pigmentary dermatoses

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ABSTRACT

Background: Apremilast is a novel PDE4 inhibitor which interferes with several key processes of inflammation. The objective of this study was to determine the efficacy and safety profile of apremilast in common immune mediated papulosquamous, hair and pigmentary dermatoses.
Methods: It was a prospective, open labelled, randomised, placebo-controlled study done over a period of 18 months. A total number of 100 patients were enrolled in which 50 were cases and 50 were controls. Psoriasis, lichen planus, alopecia areata and vitiligo cases were randomly enrolled at our OPD. Apremilast starter pack was given initially for 1 week followed by 30 mg twice daily for four months. All patients were followed up every 4 weeks for 16 weeks. Photographic documentation, assessment of PASI, LPSI, SALT, VASI and adverse effects were noted at baseline and at each visit. Patients were followed up for 6 months after the treatment for any recurrences.
Results: Mean percentage improvement of PASI score in psoriasis group, LPSI score in LP group, SALT score in alopecia areata group and VASI score in vitiligo group was 62%, 71%, 24.4% and 15% respectively. Apremilast was more effective in psoriasis and lichen planus groups.
Conclusions: Apremilast is an effective treatment option for mild to moderate psoriasis and lichen planus but was found to be less efficacious in alopecia areata and vitiligo, according to our study. Apremilast was well tolerated with minimal side effects which were manageable with symptomatic treatment.

Keywords: Apremilast, Papulosquamous, Alopecia, Pigmentary dermatoses

INTRODUCTION

An immune-mediated inflammatory disease is any group of diseases that lack a definitive etiology but are characterized by common pathways leading to inflammation which may be triggered by dysregulation of the normal immune response.[1] Most common immune mediate dermatoses include psoriasis, atopic dermatitis, lichen planus, atopic dermatitis, alopecia areata, pemphigus, vitiligo, bullous pemphigoid and dermatomyositis.[2] Papulosquamous disorders are a heterogeneous group of disorders whose etiology primarily is unknown. These disorders nosology is based on a descriptive morphology of clinical lesions characterized by scaly papules and plaques. The major types in this group include psoriasis and lichen planus. Psoriasis is a chronic, systemic, immune-mediated inflammatory disorder, characterized by multiple remissions and relapses.[3] Up to 30% of patients with skin disease develop psoriatic arthritis. The most common form of psoriasis is plaque psoriasis (80% to 90% of patients) well-demarcated erythematous patches, papules, and

plaques covered by silvery-white scales.[3] Lichen planus is an inflammatory disease with idiopathic etiology that affects the skin, mucous membranes, and appendages. It presents extremely pruritic, flat-topped, polygonal, violaceous papules, and plaques.[4] It also belongs to an autoimmune disease category vitiligo is a common pigment disorder characterized by acquired loss of function or absence of melanocytes, leading to distinct depigmentation areas.[5]

Vitiligo is a pigment disorder characterized by the acquired development of white macules on the skin due to the functional loss of melanocytes in the skin, the hair, or both. The standard systemic drugs used in treating common immune-mediated papulo-squamous, hair, and pigmentary dermatoses are methotrexate, oral corticosteroids, phototherapy, biologicals, and various treatment modalities with which we encounter different systemic side effects like hepatic, renal, pulmonary involvement etc.[6] Major systemic side effects are one of the main reasons for limiting the use of standard systemic drugs like methotrexate.

Apremilast is a novel, orally available inhibitor of type-4 cyclic nucleotide Phosphodiesterase (PDE-4). By inhibiting PDE-4.[6] It increases intracellular levels of cAMP and thereby inhibits the production of multiple pro-inflammatory mediators including PDE-4, TNF-ALPHA, Interlukin-2 (IL-2), interferon gamma, leukotrienes, and nitric oxide synthase.[7] PDE-4 inhibition may restore the homeostatic balance between pro- and anti-inflammatory signalling. There are few studies showing efficacy of apremilast in psoriasis and few case studies showing its efficacy in other dermatoses like lichen planus, alopecia areata, vitiligo, Bechet's disease etc. The aim of the study was to assess the efficacy and safety profile of Apremilast in common immune-mediated dermatoses in a single platform.

METHODS

A prospective, hospital based, open labelled, randomised, placebo controlled observational study was conducted with a sample size of 100 patients aged 18 years and above, diagnosed clinically and confirmed histo-pathologically as psoriasis, lichen planus, alopecia areata and vitiligo attending DVL outpatient department of Maharajah's Institute of Medical Sciences, Vizianagaram from a period of January 2019 to June 2020 were enrolled in the study, after obtaining voluntary informed consent.

They were further divided into 50 cases and 50 controls, the cases being patients treated with the drug apremilast. Pregnant and lactating women, patients who were in Paediatric age group, patients with gastrointestinal abnormalities, respiratory disorders, migraine and nutritional disorders, history of psychiatric disorders were excluded from the study. After obtaining approval from institutional ethics committee, investigations like complete blood count, liver function tests, renal function tests were done wherever necessary including skin biopsy for Histopathological examination (HPE).

Disease severity score noted before the study wherever applicable (for psoriasis- Psoriasis area severity index (PASI score), Lichen planus severity index (LPSI score) for lichen planus, for vitiligo- Vitiligo area severity index (VASI score), for alopecia areata- Severity of alopecia tool score (SALT score).[3]

Patients in apremilast group were prescribed apremilast starter pack for one week, after one week, patients were prescribed a fixed dose of 30 mg BD for 4 months, and in few patients, the dose was titrated depending upon the tolerance of the patient. After every 4 weeks, patients were followed up to know the response to treatment and adverse effects. After 4 months of treatment, patients were followed up for another 6 months at an interval of 2 months to know any recurrences. Pre-treatment and post-treatment with apremilast photographs were taken. Response was graded according to percentage of BSA improvement as mild (0-25%), moderate (25%-50%), good (50%-75%), excellent (>75%) and reduction in disease specific scores.

Statistical analysis

Data was collected, tabulated, and all statistical analysis was done by using SPSS trial version 25 and in MS excel 2007. Quantitative variables are all mean±SD. Qualitative variables were expressed as frequency and percentage. Chi square test was used for expressing the categorical data. Repeated measures ANOVA t-test was used for comparison of means. All subjective analysis $p<0.05$ were considered as statistically significant.

RESULTS

In the present study of 100 patients, 48 patients were included in the psoriasis group (24 cases, 24 controls), 22 patients in the lichen planus group (11 cases, 11 controls), 18 patients in the alopecia areata group (9 cases, 9 controls) and 12 patients in vitiligo group (6 cases, 6 controls). In the total study population of 100 patients, 64% were males, and 36% were females with a male-female ratio of 1.78 (Table 1).

Mean percentage Improvement of PASI score in the Apremilast group was 70.2% and, in the placebo, group was 33.6% (Table 3). Mean percentage improvement of LPSI score in the lichen planus patients on apremilast was 67.1% and in the placebo, group was 24.8% (Table 4). The alopecia areata patients, mean percentage improvement of the SALT score in the apremilast group was 31.37% and, in the placebo, group was 9% (Table 5).

In vitiligo patients, mean percentage improvement of VASI score in the apremilast group was 27.5% and, in the placebo, group was 11.01% (Table 6).

Table 1: Age-wise distribution of study participants

Age group (years)	Psoriasis group (N=48)		Lichen planus group (N=22)		Alopecia areata group (N=18)		Vitiligo group (N=12)	
	N	%	N	%	N	%	N	%
18-30	12	25	3	13.6	11	61.1	4	33.3
31-40	20	41.7	7	31.8	4	22.2	4	33.3
41-50	5	10.4	7	31.8	3	13.6	3	25
5-60	8	16.7	4	18.3	0	0	1	8.4
>60	3	6.2	1	4.5	0	0	0	0

Table 2: Disease wise distribution into groups.

Disease groups (N=100)	Apremilast group (N=50)	Placebo group (N=50)
Psoriasis group (N=48)	24	24
Lichen planus group (N=22)	11	11
Alopecia areata group (N=18)	9	9
Vitiligo group (N=12)	6	6

Table 3: Percentage reduction of PASI score in apremilast group and placebo group.

Group (N=48)	Mean PASI at baseline	Mean PASI at 4 weeks	Mean PASI at 8 weeks	Mean PASI at 12 weeks	Mean PASI at 16 weeks	Percent reduction of PASI	P value
Apremilast group (N=24)	13.91±8.43	9.26±6.91	7.63±5.58	5.46±4.9	4.15±5.42	70.2	0.001**
Placebo group (N=24)	7.3±3.29	6.4±2.94	5.56±2.1	5.11±2.12	4.85±2.11	33.6	0.01**

Note: PASI: Psoriasis area severity index, *p<0.05, **p<0.01.

Table 4: Percentage reduction of LPSI score in apremilast group and placebo group.

Group (N=22)	Mean LPSI at baseline	Mean LPSI at 4 weeks	Mean LPSI at 8 weeks	Mean LPSI at 12 weeks	Mean LPSI at 16 weeks	Percent reduction of LPSI	P value
Apremilast group (N=11)	22.36±14.8	17.18±11.5	12.36±8.7	9.27±8.2	7.36±8.2	67.1	0.032*
Placebo group (N=11)	16.5± 9.14	16.18±8.89	15.18±9.4	14.45±8.9	12.4±7.87	24.8	0.02*

Note: LPSI- Lichen planus severity index, *p<0.05, **p<0.01.

Table 5: Percentage reduction of SALT scores in apremilast group and placebo group.

Group (N=18)	Mean SALT at baseline	Mean SALT at 4 weeks	Mean SALT at 8 weeks	Mean SALT at 12 weeks	Mean SALT at 16 weeks	Percent reduction of SALT	P value
Apremilast group (N=9)	26.78±8.2	26.56±8.1	24.55±6.96	21.5±7.25	18.38±6.14	31.37	0.001*
Placebo group (N=9)	26.22±7.01	26±6.91	24.43±6.93	24.14±7.22	23.86±7.36	9	0.479

Note: SALT-Severity of alopecia tool score, *p<0.05, **p<0.01.

Table 6: Percentage reduction of VASI score in apremilast group and placebo group.

Group (N=12)	Mean VASI at baseline	Mean VASI at 4 weeks	Mean VASI at 8 weeks	Mean VASI at 12 weeks	Mean VASI at 16 weeks	Percent reduction of VASI	P value
Apr-emil-ast group (N=6)	23.17±8.54	23.17±8.54	23.17±8.54	18.6±6.42	16.8±4.76	27.5	0.16

Continued.

Group (N=12)	Mean VASI at baseline	Mean VASI at 4 weeks	Mean VASI at 8 weeks	Mean VASI at 12 weeks	Mean VASI at 16 weeks	Percent reduction of VASI	P value
Place-bo group (N=6)	29.5±11.31	29.0±11.31	26.25±12.12	26.25±12.12	26.25±12.12	11.01	0.78

Note: VASI-Vitiligo area severity index, *p<0.05,**p<0.01.

DISCUSSION

Apremilast is a PDE4 inhibitor which is the key enzyme in the degradation of CAMP thereby inhibiting the synthesis of several pro-inflammatory cytokines and chemokines, such as tumor necrosis factor-alpha, interleukin 23, CXCL9, and CXCL10 in multiple cell types.[7]

As this novel PDE4 inhibitor interferes with several key processes of inflammation, it may emerge as a promising new drug for the treatment of chronic inflammatory diseases such as those of the skin and the joints.

When compared with other treatments like methotrexate, cyclosporine, biologicals, systemic corticosteroids, lesser side effects, and higher safety profile makes apremilast treatment of choice in many autoimmune-mediated disorders like psoriasis, lichen planus, vitiligo, and alopecia areata as they share a common pathogenic pathway.[7]

In the present study, In psoriasis patients, after 16 weeks of treatment with apremilast, PASI 50 was achieved by 54.16% of patients, PASI 75 was achieved in 29.16% of patients and PASI 90 was achieved in 8.33% of the patients (Table 3, Figure 1) which is in concurrence with Kim et al, Paul et al, and Shah et al reported 62.7% and 76.92% of patients in their respective studies achieved PASI 50 at the end of 16 weeks which was comparatively higher than that observed in the present study.[8-10]

However, Vujic et al and Ohata et al, reported PASI 50 at the end of 16 weeks as 41.8% and 35.7% respectively which was lower when compared to the present study.[11,12]

PASI 50 was 12.5% in the placebo group after 16 weeks. 8.33% of patients achieved PASI 100 which was similar to the findings of Shah et al.[10]

The present study indicates that, considering the safety profile of apremilast and lack of any serious adverse effects, apremilast can be preferred over methotrexate and cyclosporine for initial treatment in mild cases of chronic plaque psoriasis. Combination therapy of apremilast with methotrexate may also be utilized for faster attainment of PASI 75 in moderate to severe cases of chronic plaque psoriasis.

In the present study, the severity of lichen planus was assessed by LPSI score (lichen planus severity index) ranging from 0-80.

Out of 11 patients in the apremilast group, 8 patients had LPSI scores between 0-20 whereas 2 patients had LPSI scores between 20-40. After 16 weeks of treatment with apremilast, the mean LPSI score decreased from 22.36±14.8 to 7.36±8.2 with the percentage improvement of 67.1% which was statistically significant (p=0.032) (Table 4, Figure 2). The efficacy of apremilast was found to be statistically significant compared to the placebo group after 16 weeks. The results of the present study opine that apremilast has good efficacy in lichen planus.

In a case series reported by Paul et al 30% of patients attained 2nd grade or more improvement in physician global assessment scale which was used alternate to LPSI score.[13]

In alopecia areata patients, the mean SALT score at baseline was 26.78±8.2 which reduced to 18.38±6.14 with mean percentage of reduction of 31.37%. The improvement of efficacy in the apremilast group was statistically significant (p=0.0001) (Table 5, Figure 3). the present study does not agree with Mikhaylov et al reported that only 8.33% of patients in the apremilast group attained SALT 50 after 25 weeks.[14] Similarly, Liu et al reported poor treatment outcome with apremilast in alopecia areata.[15]

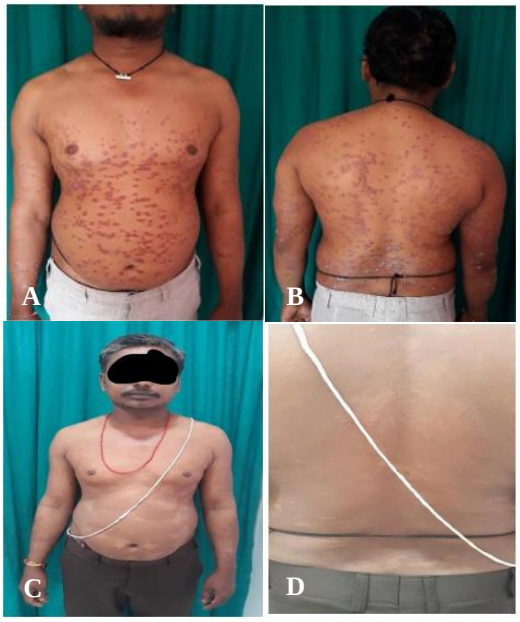

Figure 1: Pre-and post-treatment with apremilast in chronic plaque psoriasis (A, B) at baseline; and (C, D) at 16 weeks.

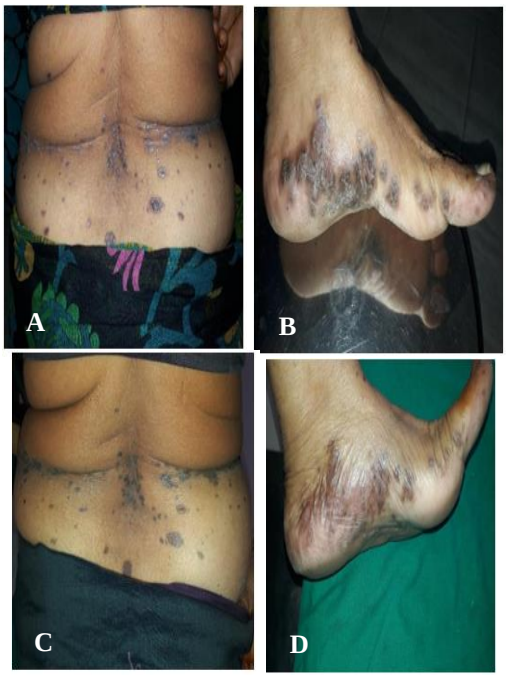

Figure 2: Pre and post treatment of hypertrophic lichen planus with apremilast (A, B) at baseline; and (C, D) at 16 weeks.

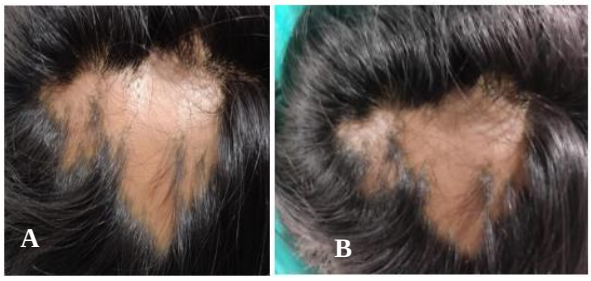

Figure 3: Alopecia areata before and after treatment with apremilast (A) at baseline; and (B) at 16 weeks.

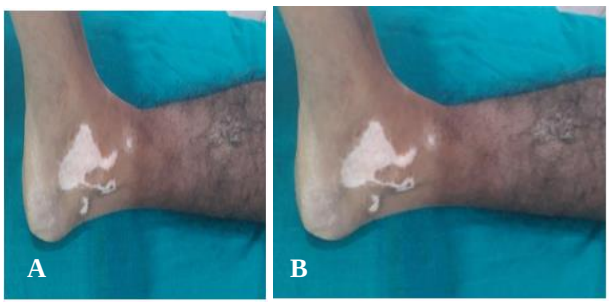

Figure 4: Pre and post treatment of vitiligo with apremilast (A) at baseline; and (B) at 16 weeks.

In vitiligo cases, the efficacy observed in the apremilast group was 23.17±8.54 which reduced very slightly after 16 weeks to 16.8±4.76 with a mean percentage improvement of 27.5% which was not statistically significant (p=0.16) (Table 6, Figure 4). Majid et al studied the role of apremilast in treating vitiligo on 13 patients and found there was control of the progression of vitiligo and also, 8 patients (61.5%) showed some repigmentation.[16] These adverse effects of apremilast were reported by an equal number of patients i.e.; 5 (28%) as nausea, vomitings, and diarrhea in the apremilast group. This was in concordance to Papadavid et al.[17] These adverse effects like nausea, vomiting, headache, arthralgia, and myalgia were manageable with symptomatic treatment and were tolerated by the patients after 2 weeks of treatment.

CONCLUSION

Apremilast is a novel drug, has good long term safety profile, ease of oral administration without the need for screening or ongoing laboratory monitoring makes it sought after drug for localized and mild cases of chronic plaque Psoriasis and generalized as well as hypertrophic Lichen planus. Apremilast in combination with other drugs like methotrexate and cyclosporine may be considered necessary for a better outcome and faster response in moderate to severe chronic plaque psoriasis and lichen planus. Hence it can be considered as a better treatment option for faster response and maintenance therapy. However, since the sample size for the present study is relatively small and drawn from limited geographical area future studies in form of multicentric large scale trials are warranted to extrapolate the results of the present study in larger population.

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Ethical approval: The study was approved by the institutional ethics committee

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