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ORIGINAL ARTICLE

Efficacy and safety of apremilast in patients with moderate to severe chronic plaque psoriasis.

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ABSTRACT… Objective: To measure efficacy and safety of apremilast in patients with moderate to severe chronic plaque psoriasis. **Study Design:** Non Randomised Clinical Trial. **Setting:** Department of Dermatology Lahore Medical and Dental College / Ghurki Trust and Teaching Hospital, Lahore and Services Institute of Medical Sciences, Lahore. **Period:** 6th April 2022 to 31st July 2023. **Methods:** It was a non-randomized single group clinical trial in which patients were enrolled according to inclusion criteria for 6 months duration. This study was conducted at LMDC/ Ghurki Trust and Teaching Hospital, Lahore and Services Institute of Medical Sciences, Lahore with ethical letter no LM&DC/ 4961-62. Apremilast was given in 30mg twice daily dosage for 16 weeks and follow up was done after a treatment gap of 8 weeks. PASI score and body surface area was calculated before and after treatment. Data was analysed by SPSS version 22.0. **Results:** 30 patients were enrolled for the trial. Out of them, 12 patients achieved PASI 90, 5 patients achieved PASI 75, 8 patients achieved PASI 50, 7 patients had less than 50% reduction in PASI at the end of 16 weeks. After a treatment gap of 8 weeks 100% patients returned with relapse of psoriasis, with average PASI score of 6.04. Reported side effects included nausea, vomiting, abdominal pain and mild weight loss. Five patients left treatment due to severe nausea, vomiting and abdominal pain. **Conclusion:** Apremilast significantly reduces signs and symptoms of psoriasis with a good safety profile.

Key words: Apremilast, Phosphodiesterase 4 Inhibitor, Psoriasis.

INTRODUCTION

Psoriasis is a long standing inflammatory, autoimmune disease linked with many co-morbidities inclusive of dysmetabolic syndrome, mental illness and circulatory diseases which place negative effect on patients' health, comfort and happiness.[1] It influences both genders equally.[2] Psoriasis is caused by several factors including genetic, environmental, immunological factors and some drugs.[3] Prevalence of psoriasis is affected by climate, sun exposure, and ethnicity.[2] Approximately 2- 3% of the population is affected by psoriasis.[4] It presents with various symptoms including scaling, itching and burning.[5] It is clinically identified by erythematous and scaly plaques.[6] It is a multisystem disease and skin involvement is the most common presentation of the disease.[7] Psoriasis demands long lasting management with drugs which should be effective as well as safe.[5,8]

Patients who have moderate to severe chronic plaque psoriasis can be managed with topical as well as systemic medications.[9] Topically applied drugs have some side effects, for example, corticosteroids cause immunosuppression, retinoids are teratogenic, tar-based treatments cause staining and malodor, dithranol causes skin irritation and discoloration.[10] Due to these effects such treatments may not be preferred for some patients.[9] Patients un-responsive to topical treatments or have tolerability issues may get benefit from systemic treatments, thus avoiding significant quality-of-life (QOL) impairment.[9] Systemic agents include methotrexate or biological agents but they may become unsuitable due to their side effects or cost, thus we require further oral therapeutic agents that offer acceptable safety profile for psoriasis.[5]

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Systemic treatments are generally prescribed to patients who have moderate psoriasis affecting 3%- 10% of body surface area (BSA), or severe psoriasis involving > 10% BSA and in those patients who face remarkable changes in their quality- of- life.[4]

Apremilast got FDA approval in 2014 and European commission in 2015 as management option for moderate to severe chronic plaque psoriasis and joints involvement due to psoriasis. Apremilast is the latest oral drug approved by FDA after 1996, for treatment of psoriasis.[11] It is an efficacious drug in patients of psoriasis of specific areas including nail, scalp and palmoplantar psoriasis which are sometimes difficult to treat.[1]

Apremilast is used in many diseases which are inflammatory in nature including psoriasis, atopic dermatitis, inflammatory bowel disease and psoriatic arthritis.[4] Apremilast, a phosphodiesterase inhibitor, targets PDE4 enzyme specifically. Through this target inhibition it increases intracellular cyclic adenosine monophosphate (cAMP) levels and stops the production of many factors which cause inflammation like TNFα, Interleukin 12 and 13, interferon gamma and nitric oxide synthase and increases level of many factors which prevent inflammation e.g., IL 10 and causes inhibition of keratinocyte response.[4,12] Hence it changes many factors which are involved in causing inflammation in psoriasis and psoriatic arthritis.[13]

Pharmacokinetic studies show that it is a rapidly absorbed drug, having Tmax value of 2 hours.[14] It has a moderately long half-life of 8.2 hours.[15] Apremilast is a maximally absorbed drug and only 4 % is excreted in unchanged form in feces. Elimination t1⁄2 is 7 –16 hours.[13] Range of absorption of apremilast is not changed if it is given along with food.[16] Plasma clearance in healthy individuals is t10L/hours and final elimination t1⁄2 is 6-9 hours.[15]

Apremilast is a safe drug and causes no harm to hematological, renal or hepatic system and does not affect the immunological system like other drugs which are used for psoriasis Apremilast. needs no daily testing and its safety data is available for up to 5 years.[12] Apremilast is a novel management option for people who have moderate to severe chronic plaque psoriasis.[1] It can also be used in psoriatic arthritis patients as a DMARD and for patients having metabolic syndrome because it also reduces weight.[1,6]

Thomas et al in their study on efficacy of apremilast in psoriasis noted that 40.0% of patients achieved 75% or more PASI reduction, 50.0% patients attain ≥ 50% reduction of PASI score after 12 weeks, 10.0% patient did not show any significant PASI reduction.[12] Vujic et al in their study included forty-eight patients between April 2015 and January 2017, 6.3% reached PASI 90, 18.8% reached PASI 75 and 16.7% attained 50% reduction in PASI score. Weight of the patients was indirectly linked with 50% reduction in PASI response in 37 patients ($p < 0.05$). 64.6% patients presented with side effects, mostly diarrhea in 21 patients (43.8%), 7 patients reported with headache (14.6%) and pain in joints reported in 5 patients (10.4%).[17]

Currently no study has been done on the use of Apremilast in Pakistan as it has recently become available. Keeping in view all the benefits of this drug we planned this pilot study project to check the effectiveness and safety of Apremilast 30mg twice daily, in patients with moderate to severe chronic plaque psoriasis, based on Psoriasis area and severity index (PASI) and Body surface area (BSA) assessments in our population (NCT06032858).

METHODS

The research was conducted in out-patient department of Dermatology unit of Ghurki Trust and Teaching Hospital, Lahore and Services Institute of Medical Sciences, Lahore with ethical letter no LM&DC/ 4961-62. The study duration was 6th April 2022 to 31st July 2023. Non-Probability Purposive sampling was used. It was a Non -randomized Clinical trial Study. Inclusion criteria were, patients ages between 18-59 years, both genders, diagnosed patient of chronic plaque psoriasis, patients eligible for oral or parenteral treatments, patients not responding to topical

treatments. Exclusion criteria were patients who show hypersensitive reactions to apremilast or to any of its inactive component, pregnancy, lactation, infections like viral hepatitis, active or history of incompletely treated Tuberculosis, use of other systemic therapies in last 4 weeks. By using 95% level of confidence and 10% Margin of error researcher had taken 30 patients from OPD department of Dermatology unit of Lahore Medical and Dental College /Ghurki Trust and Teaching Hospital, Lahore and Services Institute of Medical Sciences, Lahore. After taking permission from Institutional Ethical Committee (Ref: No. LMDC /4961-62). A total of 30 patients fulfilling the requirement were enrolled for the study. Each patient was counselled, gave a written consent, a written detailed proforma was filled in. Diseased areas were photographed and assessed for PASI Score and BSA score. Efficacy was measured by 50% reduction in Psoriasis area and severity index (PASI) score from initial score and by Body surface area (BSA) calculations on zero, eight and sixteen weeks and at 24 weeks to see relapse of disease and adverse events. A dose of apremilast 30 mg twice daily was given to the patients and was adjusted as follows:

Day	Morning	Evening
DAY 1	10mg	-
DAY 2	10mg	10mg
DAY 3	10mg	20mg
DAY 4	20mg	20mg
DAY 5	20mg	30mg
DAY 6 and ongoing	30mg	30mg

Patients were followed at 0, 8 and 16 weeks of treatment and for relapse at 24 weeks. On every visit PASI and BSA were measured. Data was collected using standard format with details like age, gender and duration of disease etc. Data was entered and analyzed through SPSS version 22.0. Frequencies and percentages were calculated for qualitative parameters like gender. Means & standard deviations were presented for quantitative parameters (age, duration of disease, PASI score and BSA score). Comparison of demographic profile of patients with efficacy and safety was done using t-test considering p-value ≤ 0.05 as significant.

RESULTS

The study included 30 patients with chronic plaque psoriasis, 5 patients left treatment due to side effects and these are results of 25 patients. The majority of participants were males 84% and (92.0%) were married. The average age was 43 years (range: 23-69). The average weight and waist circumference were 72.03 kg (range: 35-110) and 36.55 cm (range: 30-47), respectively. The duration of the disease varied, with 50% having psoriasis for more than 10 years. Most patients (66.7%) had prior treatment experience.

Parameter	N	%	Mean±SD (Range)
Gender			
Male	21	84	
Female	4	16	
Age (years)			42.28±11.74 (27-66)
Marital Status			
Married	23	92.0	
Unmarried	2	8.0	
Weight (kg)			71.33±16.63 (35-110)
Waist			36.88±4.71 (30-47)
Duration (years)			
<1	4	16	
1-10	8	32	
>10	13	52	
Prior Treatment			
Yes	18	72.0	
No	7	28.0	

Table-I. Demographic & clinical profile of chronic plaque psoriasis patients (n=25)

At the end of 16 weeks, 6 patients (24%) achieve PASI 50, 8 patients (32%) achieve PASI 75, 5 patients (20%) achieve PASI 90 and 6 patients (24%) achieve PASI 100. The mean PASI score significantly decreased from baseline (19.16 to 9.08) at the end of 16 weeks.

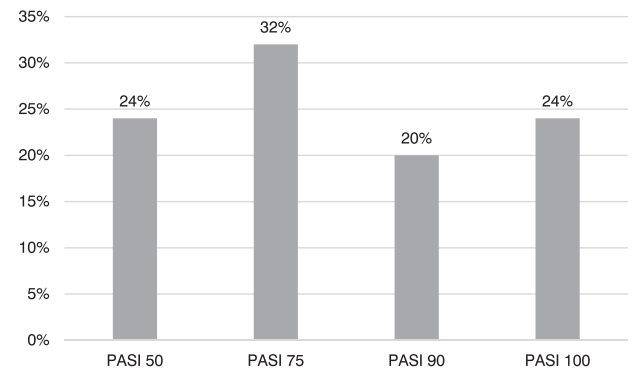
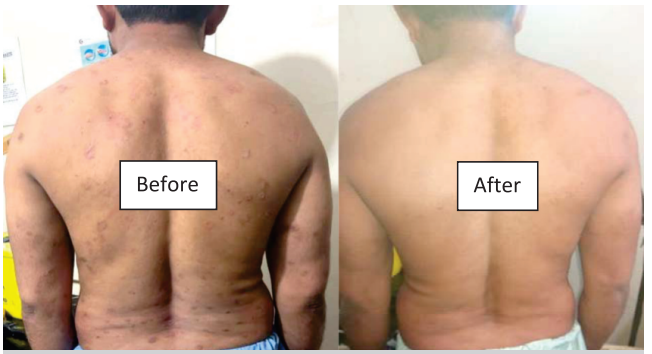
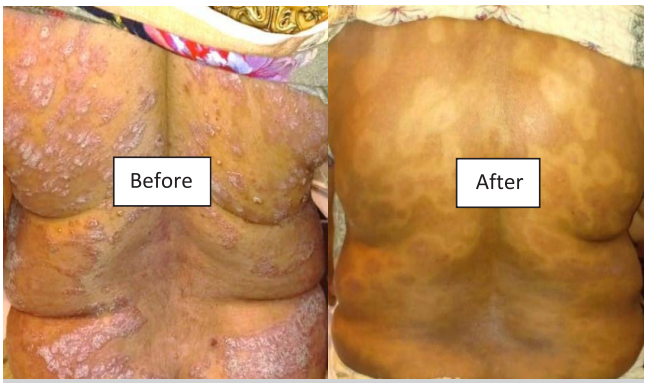


Figure-1. PASI reduction at end of 16 weeks



Picture-1. Clinical images of patient taken before starting treatment and 16 weeks after treatment



Picture-2. Clinical images of patient before starting treatment and after 16 weeks

On completing treatment for 16 weeks, a follow up was done after a treatment gap of 8 weeks. All patients returned with relapse of psoriasis, with average PASI score of 6.04. Body surface area involvement of 19 patients was <10%, and 6 patients with >10%.

16 patients (53%) developed adverse effects after starting the treatment, which were mild, tolerable and spontaneously resolved within few weeks. Most common effects were nausea, diarrhea, abdominal pain. 14 (46.6%) patients did not develop any side effects. 2 patients left treatment due to severe diarrhea, 3 patients left treatment due to sinking of heart, nausea and abdominal pain. Mild weight loss was noted in 5 patients (20%) at end of 16 weeks but they did not leave treatment.

PASI Score	Mean	SD	P-Value
Baseline	19.16	10.74	
At 8 weeks	9.08	7.16	<.001
At 16 weeks	9.21	5.59	
At 24 weeks (relapse)	6.28	5.07	
Body Surface Area			
	<10%	>10%	
Baseline	10	20	
At 8 weeks	17	8	.007
At 16 weeks	19	6	
At 24 weeks (relapse)	19	6	
	Adverse effects		
	Yes	No	
At 4 weeks	16	14	
At 16 weeks	5	20	.011
At 24 weeks	0	25	

Table-II. Improvement in efficacy and safety measures from baseline to 24 weeks (n= 25)

Positive results include a significant drop in PASI score and BSA at end of 16 weeks with tolerable side effects throughout the course of the study. Apremilast was well tolerated with the frequency of side effects being very mild. Apremilast is appropriate for individuals with moderate to severe chronic plaque psoriasis due to its good safety profile and low incidence of side effects.

DISCUSSION

Due to the preselected patient groups in clinical trials, real-life treatment outcomes may differ from trial results. It is decisive to assess efficacy and safety in routine practice as a result. These results can influence our therapeutic regimen and provide us with useful information.[18] In this study, we provide our observations regarding

the effectiveness and adverse events (AEs) of apremilast treatment for moderate to severe chronic plaque psoriasis patients but non-comparative study design, small patient number and short duration of treatment were the obvious limitations of the study.

Papp K et al in their ESTEEM 1 study involving 844 patients demonstrated that PASI 75% reduction was achieved by 33.1 % patients at week 16.[11] Thomas J et al, in their study involving 20 patients demonstrated that PASI 75% and more was achieved by 8 patients, PASI 50% and more by 10 patients, at the end of 12 weeks of treatment.[12] Vujice I. et al in their study involving 48 patients showed that 8 patients (16.7%) had at least a PASI 50, nine (18.8%) a PASI 75 and three (6.3%) a PASI 90.[17]

In comparison to above studies our study is with 30 patients, studied over 16 weeks. 5 patients left treatment due to side effects. From 25 patients 6 patients (24%) achieve PASI 50, 8 patients (32%) achieve PASI 75, 5 patients (20%) achieve PASI 90 and 6 patients (24%) achieve PASI 100. The mean PASI score significantly decreased from baseline (19.16 to 9.08) at the end of 16 weeks. Our study demonstrated relapse of psoriasis after 8 weeks of leaving treatment, with 19 patients (76%) having <10% body surface area involvement and 6 patients (24%) with >10%. This suggests that apremilast should be continued for longer period of time to prevent relapse of disease.

Crowley J et al in their ESTEEM 1 and 2 trials demonstrated that ≥ 1 adverse event was noted in 939 patients (79.3%), the most common being gastrointestinal symptoms, including diarrhea, vomiting, and nausea. Other less frequent side effects noted include headache, upper respiratory tract infections, weight loss, depression and suicidal tendencies. Apremilast did not have any effect on the hematological, hepatic and renal systems.[8] Thomas et al in their study noted that 6 of the 20 patients (30%) developed adverse effects, which were mild, tolerable which resolved spontaneously within the first 2 weeks. Only 1 patient drop out after 3 weeks due to excessive vomiting and diarrhea.[12]

In our study mild side effects were observed in 16 patients (53%) within 4 weeks which settled within a few days without any specific measures. Most common side effects noted were nausea, diarrhea and abdominal pain. Five patients (16.6%) suffered severe nausea, diarrhea, abdominal pain and dropped out of the trial. No effects were noted on hepatic, renal or hematological systems. These adverse effects are most commonly associated with phosphodiesterase inhibitors PDE-4.[19] This inhibition increases intracellular levels of cAMP, which causes chloride ion secretion by activation of chloride channels in small-bowl crypts.[20] PDE4 inhibitors induced nausea and vomiting is believed to arise from central and peripheral mechanisms.[21,22]

In previous studies of ESTEEM 1 and 2 trials mean percentage change from baseline body weight was 1.53. 21.9% of patients lost 5% of their baseline body weight. The proportion of patients reporting weight loss tended to be higher among patients with higher baseline body mass index; this weight loss occurred primarily in the first year of apremilast treatment.[8] In our study we noted minor average weight loss 6.5 % in 5 patients (20%). Patients were obese but they did not leave treatment, rather considered it beneficial.

CONCLUSION

Apremilast clinically and significantly reduces symptoms and signs of chronic plaque psoriasis. It is a safe and inexpensive drug with favorable safety profile and convenient oral administration. It doesn't demand frequent laboratory testing. It is a favorable drug for patients with obesity and associated co- morbidities. It put no effects on hepatic, renal, hematological and on immunological system as compared to other treatment modalities. But relapse of psoriasis after discontinuation of treatment shows that it should be continued for longer period of time. In conclusion apremilast has become a promising, affordable option for psoriasis management in our circumstances.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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1	**Saira Muaaz:** Manuscript writing.
2	**Sumera Hanif:** Data analysis.
3	**Hira Tariq:** Assisted in writing section and provided initial revision.
4	**Talat Masood Akbar:** Gathered literature and contributed to the discussion section.
5	**Faria Asad:** Provided statistical analysis and support for methodology.
6	**Haroon Nabi:** Assisted with formatting and final proof reading.