Original article

Comparison of Effectiveness of Apremilast versus Methotrexate and Apremilast in Patients with Chronic Plaque Psoriasis

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ABSTRACT

Background: Chronic plaque psoriasis is a prevalent, immune-mediated skin disorder characterized by erythematous plaques with silvery scales. The condition significantly impacts patients' quality of life, necessitating effective treatment strategies.

Objective: To compare the efficacy of apremilast versus methotrexate plus apremilast in patients with chronic plaque psoriasis.

Methods: This prospective observational study was conducted at the Outpatient Department of Dermatology Services Hospital, Lahore. After getting approval from Ethical Review Committee, sixty patients of plaque psoriasis were observed in two groups of thirty patients each, depending on which treatment they were taking. Group A patients received apremilast, while Group B received oral methotrexate combined with apremilast. The primary outcome was the achievement of PASI 75 (75% reduction in Psoriasis Area and Severity Index) after three months of treatment. Patients were followed up after 3 months for calculation of PASI.

Results: The study included 34 males (56.7%) and 26 females (43.3%), with a mean age of 42.80 ± 10.68 years. The baseline PASI score significantly reduced from 28.25 ± 5.86 to 7.09 ± 2.18 after three months. The mean percentage reduction in PASI score was 69.89 ± 11.22% in Group A and 76.76 ± 9.80% in Group B. Efficacy was observed in 42.9% of patients in Group A and 57.1% in Group B, which was statistically significant (p value =0.014).

Conclusion: The combination of methotrexate and apremilast was more effective than apremilast alone in treating chronic plaque psoriasis.

Keywords:
Chronic plaque psoriasis, Apremilast, Methotrexate, PASI score, Efficacy.

INTRODUCTION

Psoriasis is a chronic, immune-mediated, inflammatory skin disorder characterized by recurrent papulosquamous lesions, predominantly affecting the extensor surfaces. The severity of the disease can vary widely, from a few localized plaques to full-body involvement. In Europe and the United States, the prevalence of psoriasis is approximately 2 to 3%, while an Asian study reported a prevalence of 0.47%.[1]

ARTICLE INFO

Article History
Received: 01.10.2024 | Accepted: 03.06.2025
Conflict of Interest: The authors declare no conflict of interest exist.
Funding: None.

Citation: Zafar M, Tariq H, Amin U, Abbass A, Batool S, Asad F. Comparison of effectiveness of apremilast versus methotrexate and apremilast in patients with chronic plaque psoriasis J Fatima Jinnah Med Univ. 2025; 19(2): 95-99.

DOI: https://doi.org/10.37018/PEGI3677

The exact pathogenesis remains unclear, but environmental and genetic factors are known to contribute.[2] Emotional and psychological stress are recognized as significant triggers for both the onset and exacerbation of psoriasis. Relief of stress and anxiety reduces the severity of psoriasis.[3]

The disease's inflammatory process involves several cytokines, including interleukin (IL)-17, which promotes inflammation and leads to the hyperproliferation of epidermal keratinocytes—histologically characteristic of plaque psoriasis.[4] One of the inflammatory pathways implicated involves cyclic adenosine monophosphate (cAMP), a second messenger protein essential for modulating inflammation.[5]

Apremilast, an oral phosphodiesterase-4 (PDE4) inhibitor, functions by elevating cAMP levels, thereby regulating the immune response linked to psoriasis. Methotrexate, on the other hand, inhibits DNA synthesis by competitively inhibiting dihydrofolate reductase, an enzyme crucial for cell division, thus exerting an anti-mitotic effect on psoriatic skin.[6]

Among the various treatment options, this study primarily focuses on methotrexate and apremilast. Methotrexate reduces the overgrowth of skin cells,

thereby diminishing scale formation, while apremilast modulates immune responses to reduce inflammation.[7]

A study reported that 28.5% of patients treated with apremilast achieved PASI-75, while 85.9% of those treated with methotrexate achieved the same level of reduction.[8] Furthermore, a significantly higher proportion of patients in a combined methotrexate-apremilast group achieved a Modified Palmoplantar Psoriasis Area and Severity Index-75 at week 16, compared to those treated with apremilast alone (43% vs. 30%, respectively).[9] However, this study was done on palmoplantar psoriasis, not in generalized psoriasis which is the most prevalent type.[1]

Although few studies worldwide have reported varying results of efficacy of individual drugs,[5-9] there is a notable lack of research focusing on comparison of apremilast versus its combination with methotrexate in local population since no study has been done on the comparison of apremilast versus combination of apremilast and methotrexate. Since ethnicity plays an important role in pathogenesis as well as response to treatment,[1] this study aimed to observe the therapeutic effects of apremilast alone in comparison to its combination with methotrexate in treating psoriasis patients in Pakistan. The findings will provide valuable insights for future research and inform treatment priorities for psoriasis, ultimately benefiting patient outcomes and guiding clinical practices.

PATIENTS AND METHODS

This observational study was conducted in the Outpatient Department of Dermatology at Services Hospital, Lahore, from December 16, 2023, to June 15, 2024. After obtaining approval from the ethical review committee, Patients of both genders, aged between 18 and 60 years, with clinically diagnosed psoriasis, who were to be treated with apremilast alone or in combination with methotrexate were observed after providing written informed consent. Participants were selected through non-purposive consecutive sampling. Exclusion criteria included patients who had received any other anti-psoriatic treatment in the last thirty days.

Detailed history and thorough physical and cutaneous examination of all patients was done. Pre-treatment Psoriasis Area and Severity Index (PASI) scores were calculated. Relevant serological tests including renal and liver function tests and fasting lipid profiles were carried out to follow up for side effects and to rule out any contraindications to the therapeutic agents.

A sample size of 60 patients was calculated by 95% confidence level with 80% power of test and 5% level of significance and taking expected percentage as 28.5% patients taking apremilast only and 85.9% patients taking methotrexate and Apremilast according to the reference study.[8] The patients were observed in two treatment groups as follows: Group A was being treated with apremilast 30 mg twice daily from day 6 to 12 weeks after the recommended initial dosage titration from 10mg per day on day 1 to 50mg per day on day 5 (with 10mg increments per day), while patients of group-B were given oral methotrexate (0.3 mg per kg per week in three divided doses with a l2-hour interval between doses and tab folic acid on 2 methotrexate free days) and apremilast 30 mg twice daily from day 6 till the end of 12 weeks after the recommended initial dosage titration from day 1 to day 5. PASI scores were assessed by the researcher at follow up visit on pre-designed proforma. Patients were followed up for calculation of PASI and observation of any side effects (nausea, nightmares, hepato- or nephrotoxicity) every four weeks till 12 weeks. Efficacy was considered as ≥75% reduction in PASI score after 12 weeks from baseline i.e. achievement of PASI 75.[5] This is calculated as follows:

$$\text{Percentage reduction in PASI score} = \frac{\text{Baseline score} - \text{Posttreatment score}}{\text{Baseline score}} \text{x } 100$$

Data were entered and analysed using SPSS V25.0. Quantitative variables like age, duration of disease and PASI score at each visit were expressed by mean ± S.D. Qualitative variables like gender and efficacy were represented in frequency or percentages. Effectiveness was compared between groups by applying Chi-square test. Data were stratified for age, gender and duration of disease to deal with effect modifiers. Post-stratification, Chi-square test was applied, taking p-value ≤ 0.05 as significant.

RESULTS

The study included a total of 60 participants. Demographic details of patients in both groups like age and gender distribution, duration of disease, are given in Table 1.

Comparison of the two treatment groups and achievement of effectiveness are detailed in Tables 2 and 3. Although both the treatments were effective in reducing the PASI score from baseline, the difference in effectiveness between the two treatment groups was statistically significant (p = 0.014) (Table 2). Effectiveness was observed in 42.9% of patients in Group A and 57.1% in Group B, which was statistically significant (p-value =0.014). Regarding confounding factors, none was statistically significant association to achievement of efficacy (p-value < 0.05) as depicted in Table 3.

No patient was lost to follow up. All patients were compliant to both therapies and no side effect was reported to require stopping the therapy or switching treatment groups.

Table 1: Distribution of Study Participants by Treatment Group

Variable		Apremilast Frequency (%)	Methotrexate plus Apremilast Frequency (%)	p-value
Gender	Male	19 (55.9%)	15 (44.1%)	0.297
	Female	11 (42.3%)	15 (57.7%)	
Age Group	18 to 30 years	7 (63.6%)	4 (36.4%)	0.168
	31 to 45 years	8 (34.8%)	15 (65.2%)	
	46 to 60 years	15 (57.7%)	11 (42.3%)	
Duration of Disease	6 months to 3 years	12 (41.4%)	17 (58.6%)	0.196
	> 3 years	18 (58.1%)	13 (41.9%)	

Table 2: Comparison of Quantitative Variables Between Apremilast and Methotrexate Plus Apremilast

Variable	Apremilast (Mean ± SD)	Methotrexate plus Apremilast (Mean ± SD)	p-value
Age (years)	43.27 ± 11.46	42.33 ± 10.01	0.738
Duration of Disease (years)	2.86 ± 0.98	3.19 ± 0.90	0.171
PASI Score at Baseline	28.02 ± 5.48	30.47 ± 5.44	0.339
PASI Score after 3 months	9.36 ± 1.74	6.81 ± 2.55	0.190
Improvement in PASI Score (%)	67.89 ± 11.22	76.76 ± 9.80	0.014*

* Significant p-value < 0.05

Table 3: Effectiveness Of Treatment Groups By Demographics

Age Group (years)	Efficacy	Apremilast (Frequency, %)	Methotrexate plus Apremilast (Frequency, %)	p-value
18 to 30	Yes	1 (25.0%)	3 (75.0%)	0.440
	No	6 (85.7%)	1 (14.3%)	
31 to 45	Yes	5 (31.3%)	11 (68.8%)	0.591
	No	3 (42.9%)	4 (57.1%)	
46 to 60	Yes	9 (60.0%)	6 (40.0%)	0.781
	No	6 (54.5%)	5 (45.5%)	
Male	Yes	6 (37.5%)	10 (62.5%)	
	No	13 (72.2%)	5 (27.8%)	0.420
Female	Yes	9 (47.4%)	10 (52.6%)	
	No	2 (28.6%)	5 (71.4%)	0.390
(Disease duration) 6 months to 3 years	Yes	5 (27.8%)	13 (72.2%)	
	No	7 (63.6%)	4 (36.4%)	0.057
> 3 years	Yes	10 (58.8%)	7 (41.2%)	
	No	8 (57.1%)	6 (42.9%)	0.925

Significant p-value < 0.05

DISCUSSION

This study highlighted the superior effectiveness of combination of apremilast and methotrexate versus apremilast alone. Although no study is reported in literature focussing on this comparison, few studies have been done comparing the individual drugs. Kumar et al.[10] compared the efficacy of methotrexate with apremilast to methotrexate alone in psoriasis in Indian population. They noted an 89% reduction in PASI score with highly significant (p<0.001) superiority of multi-drug therapy over methotrexate alone. These observations were comparable to current study's results probably because of similar ethnicity and demographics of the two study populations. Khan and colleagues[11] conducted a retrospective study in Karachi involving 51 patients and found that 72.5% achieved a PASI reduction of ≥75% on apremilast alone. Their study indicated significant improvements in PASI scores over 16 weeks, similar to findings of this study. However, this study showed a slightly lower effectiveness rate of 57.1% compared to 72.5%. Additionally, adverse effects led to treatment discontinuation in 25.4% of patients in their study, while current study did not observe any adverse effects.

Papp and coresearchers conducted a phase 2b multicenter study that demonstrated significant efficacy of apremilast over placebo, with PASI-75 achieved by 29% and 41% of patients on 20 mg and 30 mg apremilast, respectively.[12] Current study also observed significant PASI score reductions, with a mean PASI reduction of 73.33 ± 11.01%. The rapid relief from pruritus and sustained efficacy observed in their study is consistent with findings of this study which also showed significant improvement in PASI scores over three months. Papadavid and coworkers found that 59.3% of patients achieved PASI 75 after 16 weeks of apremilast treatment.[13] This result is slightly higher than effectiveness of 58.3% found in the current study.

Malara and colleagues reported a significant monthly reduction in PASI scores, with median PASI scores dropping from 7.0 at baseline to 2.0 at 12

months.[14] This longitudinal analysis aligns with present study, which also observed substantial PASI score reductions over three months. Both studies highlight the long-term effectiveness of apremilast in reducing psoriasis severity.

Ighani and co-researchers conducted a retrospective review and found that 55.9% achieved PASI-75 at week 16 with apremilast.[15] Present study's effectiveness of 58.3% is consistent with their findings. However, the incidence of adverse events in Ighani's study was notable, leading to treatment discontinuation in some cases, which our study did not observe.

Hassanandani and group conducted a comparative study on patients with palmoplantar psoriasis and found that the combination of methotrexate and apremilast significantly reduced m-PPPASI scores at each follow-up.[9] Our study similarly showed significant PASI score reductions in the combination therapy group, with a mean percentage improvement of 76.76 ± 9.80%, indicating the superior efficacy of combination therapy.

Manchanda and coworkers demonstrated significant reduction in PASI scores in both treatment groups, with Group A (apremilast) showing a mean PASI score reduction from 18.21 to 6.35 and Group B (methotrexate) showing a reduction from 23.47 to 2.49.[16] These results are consistent with findings of this study, highlighting the efficacy of both therapies with superiority of methotrexate.

Another study found that methotrexate achieved an 83% reduction in PASI scores, while apremilast achieved 65%.[17] Therefore, where needed efficacy of methotrexate can be improved by adding apremilast to the treatment regimen.

Liu and coworkers conducted a meta-analysis and confirmed the efficacy of apremilast in treating psoriasis, with significant improvements in PASI-75, PASI-50, and PASI-90 scores compared to placebo.[18] These findings are consistent with this study, which demonstrated significant PASI score reductions, supporting the robust efficacy of apremilast in managing moderate to severe psoriasis. Some other recent studies also supported results of this study.[19,20]

The current study is the first study done to observe the difference in efficacy of apremilast versus methotrexate plus apremilast, providing valuable insights into treatment efficacy for chronic plaque psoriasis. The significant reduction in PASI scores across both groups highlights the effectiveness of these therapies. However, limitations like a relatively small sample size and short follow-up period may affect the generalizability of the results. Future studies are needed to include larger, more diverse populations and longer follow-up periods to confirm these findings and assess long-term safety. Further research should also explore the mechanisms behind the observed efficacy differences and evaluate patient-reported outcomes to provide a more comprehensive understanding of treatment impacts on quality of life.

CONCLUSION

This study demonstrated significant efficacy of both apremilast and methotrexate plus apremilast in reducing PASI scores and reducing disease severity in patients with chronic plaque psoriasis, with combination therapy having superior efficacy. Overall effectiveness and safety profiles of apremilast and methotrexate plus apremilast were reaffirmed, highlighting their role in the management of chronic plaque psoriasis.

Author Contributions

Masooma Zafar: Conception and design, analysis and interpretation of data, drafting the article

Hira Tariq: Conception and design, analysis and interpretation of data. drafting the article, critical revision for important intellectual content, final approval.

Uzma Amin: Analysis and interpretation of data, drafting the article.

Alina Abbass: Acquisition of data, conception and design, analysis and interpretation.

Saelah Batool: Analysis and interpretation of data, proofreading.

Faria Asad: Conception and design, analysis and interpretation of data, critical revision for important intellectual content, final approval.

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