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Original Article

Comparison of efficacy of apremilast versus methotrexate in patients with moderate to severe chronic plaque psoriasis

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Abstract

Objective To compare the efficacy of apremilast versus methotrexate in patients with moderate to severe chronic plaque psoriasis.

Methods Comparative Experimental Study, which was conducted in Department of Dermatology, Mayo Hospital Lahore. Total 112 patients enrolled after informed consent and divided into two groups. Group A received apremilast 30mg twice daily from day 6 onwards (titrating the dose in the first five days) and Group B given methotrexate 0.3-0.5mg/kg orally. Efficacy assessed by reduction in PASI score comparing baseline with score at end of 12 weeks.

Results Reduction in PASI score from baseline 24.58±5.17 to 9.90±4.18 at the end of 12 weeks (efficacy 47.3%) observed in Group A, while in Group B, PASI score reduced from 25.38±8.41 to 12.94±4.95 (efficacy 21.80%). Adverse effects for both groups were minimal.

Conclusion Both apremilast and methotrexate are good treatment options and highly effective in treating chronic plaque psoriasis. However, apremilast showed greater efficacy and reduction in PASI score as compared to methotrexate.

Key words
Efficacy; Apremilast; Methotrexate; Chronic plaque psoriasis.

Introduction

Psoriasis is a chronic, papulosquamous, inflammatory and proliferative skin disorder that is immune mediated and mostly involves extensor surfaces and scalp. Its severity ranges from few scattered plaques to the involvement of the whole-body surface. In Europe and US prevalence of psoriasis is 2 to 3% while a study done in Asia shows a prevalence of 0.47%.[1-2] Pathogenesis is not fully known but it includes environmental and hereditary factors.[3] Psoriasis not only affects skin and joints but it is associated with malignancies, gastrointestinal, cardiac and hepatobiliary diseases.[4] Emotional and psychological stress leads to onset of psoriasis and its exacerbation.[4] Various topical treatments used for psoriasis include corticosteroids, vitamin D and it analogues, salicylic acids, dithranol and phototherapy while the systemic therapies include methotrexate, retinoids, cyclosporine and biologicals.[5]

Apremilast, a novel agent, is an inhibitor of the enzyme phosphodiesterase 4 (PDE4), leading to elevation of cAMP levels thus results in alteration of inflammatory response liable for psoriasis. This drug received US Food and Drug Administration (FDA) approval in 2014 for management of moderate-to-severe chronic

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plaque psoriasis in adults who are suitable candidates for systemic therapy and phototherapy.[6] Methotrexate is an effective antipsoriatic agent and is given for moderate to severe plaque, acute pustular and erythrodermic psoriasis. This drug is also helpful in psoriatic arthropathy. It was approved by FDA in 1970s. It causes the competitive inhibition of enzyme dihydrofolate reductase (an enzyme involved in cell division) thus inhibiting DNA synthesis and leading to decrease cell turnover in psoriasis patients.[7]

Among the extensive range of medications available for the treatment of psoriasis we are principally focusing on Methotrexate and Apremilast. Methotrexate, an anti-mitotic drug decreases turnover of skin cells and thus decreases the scale formation while Apremilast modulates the immune system to control the inflammatory reactions.[8-9]

In one study, 75% or greater reduction from baseline Psoriasis Area and Severity Index score (PASI-75) was observed in 43.3% patients on apremilast.[10] In another study, 81% patients treated with apremilast achieved 75% or greater reduction from baseline Psoriasis Area and Severity Index score (PASI-75).[11] In another study, the baseline PASI scores in apremilast and methotrexate groups were 11.9±2.8 and 6.9±4.8 respectively. In the follow-up (3 months), PASI score in apremilast group reduced to 7.9±3.4 while in the methotrexate group it reduced to 0.8±0.4. Reduction of ≥75% from baseline (PASI-75) was observed in 28.5% of the patients treated with apremilast and 85.9% of the patients who received methotrexate.[12] In another study, no statistically significant difference was observed between apremilast and methotrexate in PASI 75 (13.1% vs. 28.0%; p=0.09).[13]

Psoriasis significantly impacts the quality of life. Early diagnosis and treatment reduces the functional disability. Although different studies have been done worldwide with variability in results there had been no such study in our setup, untill now. So, the current study has been planned to assess the therapeutic effects of apremilast and comparison of its efficacy with methotrexate in the patients of psoriasis. It will open a window for modern research protocols thus helping to set priorities for the patient's treatment.

Methods

This comparative experimental study was conducted in the Dermatology Department, Mayo Hospital, Lahore. In total 112 patients, of only gender or age ranging from 18-60 years, having chronic plaque psoriasis, of any duration with PASI ≥10 were enrolled through non probability convenient two groups of 56 patients each.

Psoriasis Patients having characteristic erythematous, scaly, indurated lesions over extensor surfaces of the skin, with PASI ≥10.

Patients suffering comorbidities like eczema, lichen planus, systemic illnesses like chronic liver disease, lung disease, anemia, alcoholics, drug allergy, BMI <18, pustular, erythrodemric, psoriatic arthritis, using any topical treatment within 2 weeks, systemic therapy before 4 weeks, phototherapy within 30 days of study, pregnant or lactating female or suffering from Hepatitis B/ Hepatitis C/ HIV were excluded. Distributed group A and B using lottery method.

Methotrexate An antimetabolite, administered to group B in the form of a tablet 0.3-0.5mg/kg, orally once a week for 12 weeks. Tablet folic acid 5mg once daily was given to patients to minimize systemic side effects. ***Apremilast*** A phosphodiesterase 4 inhibitor, administered to

group A, as a tablet 30mg twice daily from day 6 onwards for 12 weeks. ***Efficacy*** assessed as a reduction in PASI score, calculated at baseline and on completion of 12 weeks. Drug considered efficacious if the reduction in PASI from baseline will be ≥75%.

Efficacy assessed at baseline and after 12 weeks. Information regarding demographic data and outcome variables recorded in a predesigned proforma. SPSS version v25 was used for data analysis. Quantitative variables like duration of disease and age assessed as mean±standard deviation. Chi-square test used for the comparison between groups. Qualitative variables like gender and efficacy, presented as frequency and percentages. Effect modifiers such as gender, age and disease duration were controlled by stratification. Post stratification chi-square test was applied for the comparison between two groups. P-value of ≤0.05 was taken as statistically significant.

Results

A total of 112 patients enrolled and 110 patients completed the study. Among patients from Group A, the mean age was 40.22±11.81 years, whereas in Group B it was 41.04±11.17 years. The number of male patients in study was 47 (42.72%) while 63 (57.27%) patients were females. Mean duration of disease of the patients in Group A was 3.1±1.1 years and Group B was 3.3±1.5 years. In Group A, the mean PASI score at baseline 24.58±5.17 which reduced to mean PASI value of 9.90±4.18 at the end of 12 weeks with a mean percentage reduction of 63.51±19.26%. In group B, mean PASI at baseline 25.38±8.41 which reduced at 12th week follow up to the mean PASI score of 12.50±6.48 with mean percentage reduction of 50.88±18.71% **(Table 1)**. In the apremilast group the efficacy achieved in 26 (47.3%) patients. Among methotrexate group the efficacy was achieved in 12 (21.8%) patients.

Table 1 Summary Statistics of PASI score at Baseline & 12 weeks along with percentage reduction between Study Groups

PASI	*Study Group*	
	Apremilast (n=55)	*Methotrexate (n=55)*
Baseline	24.58±5.17	25.38±8.41
12^{the} week	9.90 ± 4.18	12.94±4.95
Mean Percentage reduction	63.51%	50.88%

Table 2 Distribution of efficacy between study groups.

Efficacy	*Study Group*		*Total*
	Apremilast	*Methotrexate*	
Yes	26 (47.3%)	12 (21.8%)	38 (34.5%)
No	29 (52.7%)	43 (78.2%)	72 (65.5%)
Total	55 (100%)	55 (100%)	110 (100%)
p-value: 0.005			

Statistically both groups showed insignificant difference i.e. p value <0.005 **(Table 2).** The study results showed that in patients with duration of disease ≤2 years, in apremilast group the efficacy was achieved in 11 (52.4%) patients, whereas in the methotrexate group, the efficacy was achieved in 5 (21.7%) patients (p-value=0.035). Similarly in patients with duration of disease >2 years, in apremilast group the efficacy was achieved in 15 (44.1%) patients, and among methotrexate group the efficacy was achieved in 7 (21.9%) patients (p-value=0.045) **(Table 3)**. Patients on apremilast varyingly experienced diarrhea, headache, nausea managed with medications, and one patient discontinued treatment due to infection. Methotrexate group suffered from nausea, stomatitis and one patient discontinued treatment due to deranged liver function tests **(Table 4)**.

Discussion

Psoriasis is a not a rare disease. It is genetically determined, chronic disease with remissions and relapses. The disease significantly affects the quality of life because of morbidity associated with it. Every new treatment modality is a blessing for the patients of psoriasis. Different

Table 3 Distribution of efficacy between study groups according to duration of disease.

Efficacy		*Study Group*		*Total*	*P value*
		Apremilast	*Methotrexate*		
≤2 years	Yes	11 (52.4%)	5 (21.7%)	16 (36.4%)	0.035
	No	10 (47.6%)	18 (78.3%)	28 (63.6%)	
>2 years	Yes	15 (44.1%)	7 (21.9%)	22 (33.3%)	0.045
	No	19 (55.9%)	25 (78.1%)	44 (66.7%)	

Table 4 Safety profile.

Side effects	*Apremilast (Group A)*	*Methotrexate (Group B)*
Diarrhea	4 (7.2%)	-
Nausea	1 (1.8%)	3 (5.4%)
Headache	1 (1.8%)	-
Stomatitis	-	1 (1.8%)
Infection	1 (1.8%)	-
Deranged LFTs	-	1 (1.8%)

treatment options are available like topical treatment for mild disease and systemic treatment for moderate to severe disease like methotrexate, acitretin, cyclosporine, apremilast biologic therapies (e.g. etanercept, infliximab, and secukinumab) and phototherapy. Combination drug therapy is also used depending upon short and long-term considerations, disease severity, efficacy side effect profile of available treatment options, quality of life of the patient and affordability.[14]

Our study results showed that both apremilast and methotrexate were effective as evident by the decreasing scores for psoriasis area severity index, once treatment started. But after 12 weeks of treatment, apremilast was found to be the better option, with a greater number of patients achieving efficacy.

In our study, mean age in group A was 40.22 and 41.04 in group B, with minimum and maximum age of 18 and 60 years. Study conducted by Lomholt showed the average age of 12 years.[15] Study conducted in large US surveys, reported 28 years, as average age of onset of disease.[16] While study results from UK revealed the mean age of onset as 33 years depicting that 75% patients suffered from psoriasis before 46 years of age.[17] A German study showed bimodal age distribution with early age of onset of 16-22 years and later 57-60 years.[18]

Our study population consisted of 47 (42.72%) males and 63 (52.27%) female patients. The greater percentage of females reported is perhaps due to greater feelings of stigmatization related to disease and being more strongly impacted psychologically. Women suffer more with psoriasis; feeling unhappy (women: 18.5%; men: 11.3% stressed (women: >60%; men: 42%), socially isolated (women: 25-28%; men: 19-24%), stigmatized (Feelings of Stigmatization Questionnaire score; women: 93.2; men: 78.0), and reduced libido (women: 33%; men: 19%).[19] That is why more women chose to seek treatment for their psoriasis in our study. In another study by Gawlik *et al.* 16 out of a total of 130 patients, 56.92% (70) were female.[20] The gender distribution in this study is closer to our own. While some other studies indicated males to be affected more in Germany[21] (0.76% vs. 0.66%), and in United States[22] [2.5% vs. 1.9% with an odds ratio=1.37 (95% CI: 1.14–1.64).

Mean duration of disease in patients was 3.1±1.1 years in our study. This was very less in contrast to what was noted by Colombo *et al.*., in Italy where the mean time of disease duration was 18.7 years. This difference can be due to the fact that the study from Italy included psoriasis patients of all severity and there was no minimum body surface area involvement, whereas in our study, a minimum of 10% of BSA (Body Surface Area) involvement was

required for eligibility.[23] It is possible that patients with greater area severity sought treatment earlier in the course of disease.

For those in the methotrexate group in our study, the mean PASI score at baseline was 25.38±8.41, which had dropped to a mean of 12.94±4.95 at the end of week 12. The mean percentage reduction in PASI was 50.88±18.71%. Methotrexate is a competitive inhibitor of enzyme dihydrofolate reductase, thus having an impact on cell cycle, leading to reduced cell turnover in epidermis.[24] This drug is usually given according to body weight 0.3-0.5 mg/ kg, once a week or in divided doses in three parts, 12 hours apart. Dose can be increased by 2.5-5 mg/week.[25]

Severity of psoriasis can be reduced to at least 50% in more than 75% of patients treated with methotrexate.[26] According to the results of various studies, patients on methotrexate usually present with complains of oral ulceration and gastrointestinal disturbance following the intake of tablet due to deficiency of folic acid. We prescribed tablet folic acid on methotrexate free days, so, gastrointestinal intolerance was observed in only few patients. One of the retrospective studies showed that low dosage of methotrexate if given for prolonged duration has better efficacy and minimal side effects.[27]

Regarding PASI score in our study, patients in the apremilast group had a mean PASI of 24.58±5.17. At the end of week 12, the mean PASI score was 9.90±4.18. In this group, the mean PASI reduction from baseline to the end of week 12 was 63.51±19.26%. Apremilast is an oral inhibitor of enzyme phosphodiestrase-4. This enzyme inhibition leads to elevation of cyclic adenosine monophosphate which in turn reduces the level of pro-inflammatory cytokines and elevation of anti-inflammatory cytokines, thereby improves the inflammation which is associated with psoriasis.[28,29] According to phase III double-blind efficacy and safety trial evaluating the effects of apremilast in psoriasis (Esteem) 1 and 2, apremilast was safe and efficacious for moderate to severe plaque psoriasis and in patients with various comorbities.[30] Four phase studies on this drug showed that 30 mg twice daily dosage achieved PASI response ranging from 29 to 41%.[30] In a study, 43.3% patients treated with apremilast achieved 75% or greater reduction from baseline Psoriasis Area and Severity Index score (PASI-75) and 13.7% patients treated with methotrexate achieved 75% or greater reduction from baseline PASI.[10] In another study,75% or greater reduction from baseline Psoriasis Area and Severity Index score (PASI-75) was observed in 81% patients treated with apremilast.[11]

In our study, efficacy was achieved in 47.3% (26) of patients in apremilast group, whereas patients being given methotrexate, 21.8% (12) achieved a 75% or greater reduction in PASI compared to baseline. Statistically both groups showed insignificant difference. i.e. p value <0.05.In another study, the baseline PASI in methotrexate and apremilast were 6.9±4.8 and 11.9±2.8 respectively. In the follow up (3 months), PASI in methotrexate group was 0.8±0.4 and 7.9±3.4 in apremilast group, ≥75% reduction from baseline (PASI-75) was observed in 28.5% patients treated with apremilast and in 85.9% patients on methotrexate.[12] In another study, statistically significant difference was not found between apremilast and methotrexate in PASI 75 (13.1% vs. 28.0%; p=0.09).[13]

Conclusion

Psoriasis is a chronic and recurrent skin disorder and thus has a significant impact on the quality of life. Various therapeutic options are available for the treatment of psoriasis. This study

compared the efficacy of apremilast with methotrexate and found that, apremilast showed comparatively better results in terms of efficacy and safety than methotrexate.

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