ORIGINAL RESEARCH

Comparative assessment of the efficacy of methotrexate with apremilast to methotrexate alone in moderate to severe cases of chronic plaque psoriasis

[1]Dr. Rakesh Kumar Meena, [2]Dr. Somya Singhal, [3]Dr. Sreya Todi, [4]Dr. Purnima Raj

[1]Associate Professor, Department of Dermatology, Venereology and Leprosy, Dr. Laxminarayan Pandey Government Autonomous Medical College, Ratlam, Madhya Pradesh, India
[2]AssociatePprofessor, Lala Lajpat Rai Medical College, Meerut, Uttar Pradesh, India
[3]Associate Professor, Department of Pharmacology, Chhattisgarh Institute of Medical Sciences, Bilaspur, Chhattisgarh, India
[4]Professor, Department of Pharmacology, Chandulal Chandrakar Memorial Medical College Durg, Chhattisgarh, India

Corresponding author
Dr. Purnima Raj
Professor, Department of Pharmacology, Chandulal Chandrakar Memorial Medical College Durg, Chhattisgarh, India
Email: purnimarj@yahoo.co.in

Received: 26 September, 2023 Accepted: 29 October, 2023

ABSTRACT

Background: Psoriasis is a chronic inflammatory systemic condition depicting a high relapse rate. The mainstream drugs for treating psoriasis in current times are phosphodiesterase type 4 inhibitor and- Apremilast and a dihydrofolate reductase inhibitor namely methotrexate. **Aim:** The present study was done to comparatively assess the efficacy of methotrexate with apremilast to methotrexate alone in moderate to severe cases of chronic plaque psoriasis. **Methods:** The present prospective comparative evaluation included 80 adult subjects with confirmed diagnosis of chronic plaque psoriasis. A comprehensive clinical and demographic evaluation was done in all subjects with performed structured proforma. Total study subjects were divided into 2 groups of 40 subjects each where Group I subjects were treated using combined oral methotrexate and Apremilast and Group II using Oral Apremilast only and were assessed at 4 and 12 weeks after investigations when required. **Results:** In the present study, 55% (n=44) of subjects were from the age range of 31-50 years and comorbidities including hypertension, diabetes, and others were reported in 27.5% (n=22) subjects. The PASI scores from Group I were lower compared to Group II at all first, second, and third follow-ups. A significantly higher reduction in mean PASI scores was seen in Group I at the follow-ups with 89% improvement at 12 weeks follow-up. **Conclusions:** The present study concludes that multidrug therapy with combined Apremilast and Methotrexate has better efficacy in treating chronic plaque psoriasis in comparison to methotrexate alone.

Keywords: Apremilast, chronic plaque psoriasis, methotrexate, psoriasis

INTRODUCTION

Psoriasis is a chronic inflammatory systemic disease that has characteristic features of erythematous plaques that are chronic presenting micaceous scales on the skin of the affected subjects that are attributed to hyperproliferation of the epidermal keratinocytes. Psoriasis has a prevalence of nearly 1% to 3% globally. A vital role is played by various environmental factors in the development of psoriasis including seasonal variations, trauma, infection, drugs, and other factors. Approximately 30% of cases of early-onset psoriasis are seen in subjects with a positive family history of psoriasis seen in the first-degree relatives.[1]

In 1970, the US FDA (United States Food and Drug Administration) first approved the use of methotrexate in clearing psoriatic lesions which is an antimetabolite drug. Methotrexate works by inhibiting the synthesis of DNA by blocking the dihydrofolate reductase which further stops the cellular reproduction in the psoriatic lesions which leads to the hyperproliferation seen in psoriasis.[2] The effect of the drug is usually

seen in 4-8 weeks. Methotrexate has a long half-life and is hence given as either a single weekly dose or as three divided doses given at 24-hour regular intervals. The starting dose of the drug is usually 2.5 mg which is gradually increased to reach a level where therapeutic effects are seen with no toxicity given as minimum and maximum dose of 10-15 mg and 25-30 mg weekly respectively.[3]

Another novel drug used for the treatment of psoriatic arthritis and psoriasis is Apremilast which is also the first oral drug approved by the FDA for the treatment of psoriasis in 1196. Apremilast is an oral drug belonging to PDE4 (phosphodiesterase type 4) inhibitors and acts intracellularly to increase the production of anti-inflammatory mediators and decrease the formation of pro-inflammatory mediators.[4] PDE4 inhibition increases the level of intracellular cyclic adenosine monophosphate which increases the production of anti-inflammatory mediators and decrease the formation of pro-inflammatory mediators. The recommended adult dose of Apremilast in psoriasis and psoriatic arthritis is 30 mg given twice daily. The initial dose given is 10 mg which is increased to reach the recommended dose. It is done to minimize the gastrointestinal adverse effects associated with Apremilast. In India, Apremilast is marketed in 10, 20, and 30 mg tablet forms.[5]

Psoriatic arthritis and psoriasis are chronic disease that needs long-term treatment and shows frequent relapse. Systemic therapy for psoriasis is recommended in subjects with significant psoriasis-related impact on quality of life and moderate to severe chronic plaque psoriasis.[6] In subjects where 3-10% and >10% of the body surface area is affected with psoriasis, psoriasis is considered moderate and severe respectively. Methotrexate is usually considered a line of treatment in chronic plaque psoriasis cases owing to its oral route of administration, ease of use, and lower cost. Also, Methotrexate is comparatively economical compared to systemic therapies and biologic treatments.[7]

Biologic treatments are highly effective and newer therapies for treating psoriasis. However, they have disadvantages concerning their route of administration and high cost. In early tapering cases of Methotrexate, Apremilast is considered a safe, oral, and first-line treatment as it has a better safety profile, and efficacy, and is low cost. These reports depict that the combined use of Apremilast and Methotrexate can be a better treatment strategy for controlling psoriasis.[8]

Hence, the present study aimed to comparatively assess the efficacy of methotrexate with apremilast to methotrexate alone in moderate to severe cases of chronic plaque psoriasis.

MATERIALS AND METHODS

The present prospective clinical study was aimed to comparatively assess the efficacy of methotrexate with apremilast to methotrexate alone in moderate to severe cases of chronic plaque psoriasis. The study was done after the approval was given by the Institutional Ethical Committee. An informed consent was taken from all participants in verbal and written form before study participation.

The study assessed 80 subjects from both genders with confirmed diagnoses of psoriasis and was of age 18 years or more. After the final inclusion of the study participants, a detailed history was recorded followed by clinical examination on a preformed structured proforma including the disease history in first-degree relatives, scalp or nail involvement, joint pain history, reliving and aggravating factors, current episode duration, disease duration, and age of disease onset. The history concerning drug intake, alcohol intake, smoking, and diet were also recorded. This was followed by skin examination including morphologic psoriasis type and comprehensive systemic and general physical examination.

PASI or psoriasis and area severity index scores form a gold standard scoring criteria used for psoriasis grading. In the present study, PASI scores were used to assess disease severity and to assess the response to treatment. In subjects where indicated, laboratory investigations were done including the skin biopsy, HIV in subjects at risk, Hepatitis B and C serological tests in subjects with deranged Liver function tests, Chest X-ray, random blood sugar, urine microscopy, renal function tests, liver function tests, and complete blood count.

The 80 subjects included in the present study with moderate to severe psoriasis were randomly divided into two groups where Group I subjects were managed with Apremilast with oral Methotrexate in 7.5 mg dose once a week along with folic acid 5mg folic acid on the days when methotrexate was not given as a therapy where on days 1-4 10 mg dose was given once daily, days 5-8 a dose of 20 mg once daily, and from day 9: 30 mg once daily dose was given. In Group II, 7.5 mg Oral methotrexate was given once a week and 5 mg folic acid tablet to all the subjects on days when methotrexate was not given. The therapy was followed for 12 weeks.

The subjects were recalled for follow-up at the 4^{th}, 8^{th}, and 12^{th} weeks where history was recorded and clinical examination was performed along with needed investigations as mentioned, PASI scores, and weight assessment. Required changes in treatment were done based on the need.

The data gathered were statistically analyzed using SPSS software version 21.0 (IBM Corp., NY, USA) along with Friedman's ANOVA test. The data were expressed as means and standard deviations. The p-value of <0.05 was taken as statistical significance.

RESULTS

The present prospective clinical study was aimed to comparatively assess the efficacy of methotrexate with apremilast to methotrexate alone in moderate to severe cases of chronic plaque psoriasis. The study

assessed 80 subjects from both genders with psoriasis and divided into two groups where Group I subjects were managed with Apremilast with oral Methotrexate in 7.5 mg dose once a week along with folic acid 5mg folic acid on the days when methotrexate was not given as a therapy where on days 1-4 10 mg dose was given once daily, days 5-8 a dose of 20 mg once daily, and from day 9: 30 mg once daily dose was given. In Group II, 7.5 mg Oral methotrexate was given once a week and 5 mg folic acid tablet to all the subjects on days when methotrexate was not given. The therapy was followed for 12 weeks. The mean age of study subjects in Groups I and II was 39.32±13.24 and 42.52±14.21 years respectively. The age of onset was 32.82±15.06 and 32.52±12.75 years in Groups I and II respectively. The duration of psoriasis was 6.93±6.62 and 10.11±8.21 years respectively in Group I and II. The mean duration of the present episode was 1.64±1.64 and 2.36±1.76 years from Group I and II respectively as shown in Table 1.

Table 1: Comparison of demographics in two groups of study subjects

S. No	Characteristics	Group I (n=40)	Group II (n=40)
1.	**Present episode duration (years)**	1.64±1.64	2.36±1.76
2.	**Disease duration in years**	6.93±6.62	10.11±8.21
3.	**Onset age (years)**	32.82±15.06	32.52±12.75
4.	**Mean age (years)**	39.32±13.24	42.52±14.21

On comparison of mean PASI scores in the two groups of study subjects, a non-significant difference was seen in the two groups with methotrexate and combined therapy with p=0.11. In 4th week, a non-significantly higher mean was seen with methotrexate only compared to combined therapy with p=0.13. In the 8th week, significantly higher PASI scores were seen with methotrexate alone with 9.87±4.02 compared to combined Methotrexate and Apremilast with 4.83±2.43 which was highly significant with p<0.001. At the 12th week, similar significantly higher mean PASI scores were seen in Group II with 6.33±2.92 compared to 2.47±1.64 in Group I. The results were statistically significant with p<0.001 (Table 2). In the present study, scalp and nail involvement was seen in 70% (n=56) and 52.5% (n=42) subjects respectively.

Table 2: Comparison of PASI scores in two groups at different time intervals

S. No	Follow-up time	Group I (n=40)	Group II (n=40)	p-value
1.	**Baseline**	23.45±8.07	18.23±7.43	0.11
2.	**4th week**	10.62±3.77	13.74±5.07	0.13
3.	**8th week**	4.83±2.43	9.87±4.02	**<0.001**
4.	**12th week**	2.47±1.64	6.33±2.92	**<0.001**

Concerning the comparison of the difference in mean PASI scores, it was seen that from baseline to 4th week, mean PASI scores were significantly higher in Group I with 12.81±6.82 compared to Group II with 4.47±2.84with p<0.001. From the 4th week to the 8th week, mean PASI scores were significantly higher in Group I with 5.77±2.65 compared to Group II with 5.77±2.65 with p=0.0003. In the 8th to 12th week, mean PASI scores were higher in Group II at 3.53±1.86 compared to 2.34±1.33 in Group I. The difference was statistically non-significant with p=0.31 as depicted in Table 3.

Table 3: Mean PASI score difference comparison in two groups at different time intervals

S. No	PASI score difference	Group I (n=40)	Group II (n=40)	p-value
1.	**Baseline- 4th week**	12.81±6.82	4.47±2.84	**<0.001**
2.	**4th week-8th week**	5.77±2.65	3.81±1.95	**0.0003**
3.	**8th week-12th week**	2.34±1.33	3.53±1.86	0.31

DISCUSSION

The study assessed 80 subjects from both genders with psoriasis and divided into two groups where Group I subjects were managed with Apremilast with oral Methotrexate in 7.5 mg dose once a week along with folic acid 5mg folic acid on the days when methotrexate was not given as a therapy where on days 1-4 10 mg dose was given once daily, days 5-8 a dose of 20 mg once daily, and from day 9: 30 mg once daily dose was given. In Group II, 7.5 mg Oral methotrexate was given once a week and 5 mg folic acid tablet to all the subjects on days when methotrexate was not given. The therapy was followed for 12 weeks. The mean age of study subjects in Groups I and II was 39.32±13.24 and 42.52±14.21 years respectively. The age of onset was 32.82±15.06 and 32.52±12.75 years in Groups I and II respectively. The duration of psoriasis was 6.93±6.62 and 10.11±8.21 years respectively in Group I and II. The mean duration of the present episode was 1.64±1.64 and 2.36±1.76 years from Group I and II respectively. These results were consistent with the studies of Yan K et al[9] in 2019 and Shetty VH et al[10] in 2018 where authors reported higher male

preponderance in psoriasis subjects as seen in the present study.

In the present study, comorbidities were seen in 27.5% (n=22) of study subjects including hypertension and diabetes mellitus. Metabolic syndrome is seen in the range of 15% and 35% in developed countries as reported by Ramachandran A et al[11] in 2003 and Gupta A et al[12] in 2003 where authors reported metabolic syndrome in the frequency of 41% and 13% using different criteria for the classification of obesity. The study by Deepa R et al[13] in 2002 reported the frequency of metabolic syndrome to be 11.2%.

In the present study, scalp and nail involvement was seen in 70% (n=56) and 52.5% (n=42) subjects respectively. These results were similar to the study of Chan S et al[14] in 2017 where authors reported 80% scalp involvement in their subjects with psoriasis.

The study results showed that on comparison of mean PASI scores in the two groups of study subjects, a non-significant difference was seen in two groups with methotrexate and combined therapy with p=0.11. In 4th week, a non-significantly higher mean was seen with methotrexate only compared to combined therapy with p=0.13. In the 8th week, significantly higher PASI scores were seen with methotrexate alone with 9.87±4.02 compared to combined Methotrexate and Apremilast with 4.83±2.43 which was highly significant with p<0.001. At the 12th week, similar significantly higher mean PASI scores were seen in Group II with 6.33±2.92 compared to 2.47±1.64 in Group I. The results were statistically significant with p<0.001. These results were in agreement with the results of Haider S et al[15] in 2014 where authors reported mean pre-methotrexate and post-methotrexate PASI were 14.8±4.2 and 4.9±4.3 respectively and with Raza N et al[16] in 2007 where authors reported significant improvement of PASI score from 15.81±5.55 to 8.79±4.19 ($P < 0.01$).

Concerning the comparison of the difference in mean PASI scores, it was seen that from baseline to 4th week, mean PASI scores were significantly higher in Group I with 12.81±6.82 compared to Group II with 4.47±2.84with p<0.001. From the 4th week to the 8th week, mean PASI scores were significantly higher in Group I with 5.77±2.65 compared to Group II with 5.77±2.65 with p=0.0003. In the 8th to 12th week, mean PASI scores were higher in Group II at 3.53±1.86 compared to 2.34±1.33 in Group I. The difference was statistically non-significant with p=0.31. These findings were in line with the study of Hassanandini T et al[17] in 2022 where similar results were reported by authors with the use of Apremilast and methotrexate combination and methotrexate alone as seen in the present study.

CONCLUSIONS

The present study concludes that on comparison of methotrexate alone to combined Apremilast and methotrexate, a higher efficacy is seen with the combined use of Apremilast and Methotrexate. Multidrug treatment has various advantages including early results and better drug toleration which leads to reduced therapy duration. Also, fewer side effects have been associated with the use of combined therapy owing to shorter treatment duration.

REFERENCES

1. Chang CA, Gottlieb AB, Lizzul PF. Management of psoriatic arthritis from the view of the dermatologist. *Nat Rev Rheumatol*. 2011;7:588–98.
2. Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med*. 2009;361:496–509.
3. Zerilli T, Ocheretyaner E. Apremilast (otezla): A new oral treatment for adults with psoriasis and psoriatic arthritis. *P T*. 2015;40:495–500.
4. Afra TP, Razmi TM, Dogra S. Apremilast in psoriasis and beyond Big hopes on a small molecule. *Indian Dermatol Online J*. 2019;10:1–12.
5. Schafer P. Apremilast mechanism of action and application to psoriasis and psoriatic arthritis. *Biochem Pharmacol*. 2012;83:1583–90.
6. Tanew A, Radakovic-Fijan S, Schemper M, Hönigsmann H. Narrowband UV-B phototherapy vs photochemotherapy in the treatment of chronic plaque-type psoriasis: A paired comparison study. *Arch Dermatol*. 1999;135:519–24.
7. Naldi L. Epidemiology of psoriasis. *Curr Drug Targets Inflamm Allergy*. 2004;3:121–8.
8. Gottlieb A, Korman NJ, Gordon KB, Feldman SR, Lebwohl M, Koo JYM, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 2. Psoriatic arthritis: Overview and guidelines of care for treatment with an emphasis on the biologics. *J Am Acad Dermatol*. 2008;58:851–64.
9. Yan K, Zhang Y, Han L, Huang Q, Zhang Z, Fang X, et al. Safety and efficacy of methotrexate for Chinese adults with psoriasis with and without psoriatic arthritis.JAMA Dermatol. 2019;155:327–34.
10. Shetty VH, Goel S, Babu AM, Eram H. A comparative study of the efficacy and safety of oral apremilast versus oral methotrexate in patients with moderate to severe chronic plaque psoriasis. *Int J Res Dermatol*. 2018;4:563–9.
11. Ramachandran A, Snehalatha C, Satyavani K, Sivasankari S, Vijay V. Metabolic syndrome in urban Asian Indian adults--a population study using modified ATP III criteria. *Diabetes Res Clin Pract*. 2003;60:199–204.
12. Gupta A, Gupta R, Sarna M, Rastogi S, Gupta VP, Kothari K. Prevalence of diabetes, impaired fasting glucose and insulin resistance syndrome in an urban Indian population. *Diabetes Res Clin Pract*. 2003;61:69–76.
13. Deepa R, Shanthirani CS, Premalatha G, Sastry NG, Mohan V. Prevalence of insulin resistance syndrome in a selected south Indian population--the Chennai urban population study-7 [CUPS-7] *Indian J Med Res*. 2002;115:118–27.
14. Chan CS, Van Voorhees AS, Lebwohl MG, Korman NJ, Young M, Bebo BF, Jr, et al. Treatment of severe scalp psoriasis: From the Medical Board of the National Psoriasis Foundation. *J Am Acad Dermatol*. 2009;60:962–71.

15. Haider S, Wahid Z, Najam-Us-Saher, Riaz F. Efficacy of Methotrexate in patients with plaque-type psoriasis. *Pak J Med Sci Q.* 2014;30:1050–3.
16. Raza N, Usman M, Hameed A. Chronic plaque psoriasis: Streptococcus pyogenes throat carriage rate and therapeutic response to oral antibiotics in comparison with oral methotrexate. *J Coll Physicians Surg Pak.* 2007;17:717–20.
17. Hassanandani T, Panda M, Jena AK, Raj C. Methotrexate monotherapy versus methotrexate and apremilast combination therapy in the treatment of palmoplantar psoriasis: A prospective, randomized, assessor-blinded, comparative study. *Indian J Dermatol Venereol Leprol.* 2022;9:1–8.