Section: Dermatology

Original Research Article

A HOSPITAL BASED COMPARATIVE STUDY OF THE EFFICACY AND SAFETY OF ORAL APREMILAST VERSUS ORAL METHOTREXATE IN PATIENTS WITH PSORIASIS ARTHRITIS PATIENTS AT TERTIARY CARE CENTER

Kailash Chander Khatri[1], Sawai Singh[2], Surender Kumar[3]

[1]Assistant Professor, Department of Dermatology, Government Medical College & Attached Group of Hospitals, Barmer, Rajasthan, India.
[2,3]Assistant Professor, Department of Orthopaedics, Government Medical College & Attached Group of hospitals, Barmer, Rajasthan, India.

Received *: 22/01/2025*
Received in revised form *: 15/02/2025*
Accepted *: 09/03/2025*

Corresponding Author:
Dr. Kailash Chander Khatri
Assistant Professor, Department of Dermatology, Government Medical College & Attached Group of Hospitals, Barmer, Rajasthan, India.
Email: kkhatri999@gamil.com

DOI: 10.70034/ijmedph.2025.1.278

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2025; 15 (1); 1480-1484

ABSTRACT

Background: Psoriatic arthritis (PsA), a member of the spondyloarthritis (SpA) family is a chronic inflammatory arthritis with heterogeneous presentation. Treatment with NSAIDs, I/A steroid and csDMARDs had been the backbone of management of PsA for many years. The aim of this study to compare the efficacy and safety of oral apremilast versus oral methotrexate in patients with psoriasis arthritis patients at tertiary care center.

Materials and Methods: This was a hospital based prospective comparative study done on 20 diagnosed cases of psoriasis arthritis at Department of Dermatology of Government Medical College, Barmer, Rajasthan, India during one-year period who gave written informed consent for the treatment were enrolled into two groups to receive 16 weeks of treatment with either oral Apremilast or oral Methotrexate. The patients were divided into two groups of 10 each, A and B. Group A was treated with oral methotrexate (15mg per week) and Group B was treated with oral Apremilast (After the patient completed the starter pack, for maintenance 30 mg tablets was given per orally twice daily) and were evaluated every 4 weeks for a period of 16 weeks and the last follow-up was at 24th weeks.

Results: Among the 20 patients, M:F ratio was 1.85: 1, [65% (13) males and 35% (7) females], mean age of onset was 39.56 years and mean duration of disease was 13.4 years. The % of improvement in patients at the end of 16 weeks in the other group was 60% such that a difference noticed was of around 10%. PDI in group A patients treated with oral methotrexate was 36.79±2.79 at the baseline while in group B it was 38.36±2.12 out of total score of 45. At the end of treatment that is after 16 weeks, the PDI became 17.52±3.26 in group A was statistically significant ($p<0.05$) as compared to patients in group B which was 20.15±2.83.

Conclusion: On comparing the two drugs, methotrexate was comparatively better tolerated and had better efficacy and safety. More studies are required to further prove the efficacy of Apremilast in treatment of this disorder.

Keywords: Apremilast, Methotrexate, Psoriasis arthritis, PDI, PASI.

INTRODUCTION

Psoriatic arthritis (PsA), a member of the spondyloarthritis (SpA) family is a chronic inflammatory arthritis with heterogeneous presentation. It may present as progressive arthritis, skin psoriasis, nail changes, sacroiliitis, spondylitis, enthesitis, dactylitis or uveitis. Prevalence varies from 0.3%-1%.[1] Among patients with psoriasis, 7% to 42% develop arthritis, and plaque psoriasis is the most common phenotype.[2]

Treatment with NSAIDs, I/A steroid and csDMARDs had been the backbone of management of PsA for many years. Improvement in our understanding of immunopathogenesis of PsA, including Th17-Th22 IL-23 axis in mouse models of both psoriasis and PsA,[3] and elevated TNF levels in psoriatic skin, synovium, and joint fluid,[4] has led to new immunomodulatory therapies. Synovial explant tissues obtained from psoriatic arthritis joints have shown to produce higher levels of the Th1 cytokines, IL 2 and IFN-amma.[5] Other innate cytokines, such as IL 18 and IL 15 are also present in psoriatic arthritis synovial tissue. Increase in circulating Th17 and an increase in IL 17 has been found in skin, and synovial tissue and fluid of psoriatic arthritis patients.[6]

Methotrexate is an antimetabolite drug which was initially used for treatment of cancer. In the 1950s it was found to be also effective in clearing psoriasis and was thereby approved for its use by the FDA in 1970s. It mainly acts as an inhibitor of DNA synthesis by blocking dihydrofolic reductase enzyme so that it helps to prevent reproduction of the cells in the lesions and thus the function of the skin returns back to normal.[7] It has a very long half-life and thus drug is given as an weekly administration and is efficacious at this dosage. Usually 4–8 weeks are required for the therapeutic effects of the drug to become evident. It is taken once in a week, orally. Either in a single dose or in three doses taken at an interval of 12-hour over a period of 24 hours. It is started with a test dose of 2.5 mg and then gradually increase dose until a therapeutic level is achieved (average range, 10–15 mg weekly; maximum, 25–30 mg weekly).[8] It is associated with various side effects which includes Hepatotoxicity, chronic use of the drug may lead to hepatic fibrosis, fetal abnormalities or death, myelosuppression therefore drug is contraindicated during pregnancy. Therefore, baseline complete blood count (CBC) and liver function tests (LFT) have to monitored weekly until target dose is achieved, then every 4–8 weeks.[9]

Apremilast is a new drug which is taken orally for treatment of conditions like psoriasis and psoriatic arthritis. This oral drug selectively targets the molecules which are inside the immune cells of the body. It acts by adjusting the complicated processes of inflammation within the cell, thereby correcting the overactive immune response that causes inflammation in people with psoriatic disease, leading to improvement in flaking and scaling as well as joint tenderness and swelling. Apremilast is an oral phosphodiesterase type 4 inhibitor (PDE4) which works intracellularly and helps to regulate various inflammatory mediators, including pathways which are relevant for the pathogenesis of psoriasis.[10] Inhibition of this PDE4 inhibition elevates intracellular cyclic adenosine monophosphate, which in turn down regulates the inflammatory responses and modulates production of anti-inflammatory cytokines. Apremilast was approved by the US Food and Drug Administration (FDA) in 2014 and by the European Commission in 2015 for treatment of psoriasis and psoriatic arthritis.[11,12] It is the first oral drug to receive FDA approval for psoriasis since 1996.[13-16] It is available as a 30-mg tablet which has to be taken by mouth. Its dosing begins as a five-day medication that is a start pack, where the dosage has to gradually increased until the recommended dose of 30 mg twice daily is reached. This drug is designed to be taken continuously to maintain improvement.[17] In patients with severe renal impairment, the area under the plasma drug concentration-time curve (AUC) of apremilast increased by approximately 88% while clearance diminished by approximately 47%, thereby warranting dosage reductions.[18,19]

The aim of this study to compare the efficacy and safety of oral apremilast versus oral methotrexate in patients with psoriasis arthritis patients at tertiary care center.

MATERIALS AND METHODS

This was a hospital based prospective comparative study done on 20 diagnosed cases of psoriasis arthritis at Department of Dermatology of Government Medical College, Barmer, Rajasthan, India during one-year period who gave written informed consent for the treatment were enrolled into two groups to receive 16 weeks of treatment with either oral Apremilast or oral Methotrexate.

The Inclusion criteria were patients aged 18 years or older; psoriasis arthritis patients with any one of the criteria's A) Psoriasis Area and Severity Index (PASI) score of 12 or higher, B) body surface area involvement 10% or more; patients willing for treatment.

Exclusion criteria were patients with clinically significant or major uncontrolled disease; patients on biologics within the past 12 to 24 weeks; patients on active topical agents for psoriasis within the past 2 weeks; patients with liver or renal impairment; patients with insulin-dependent diabetes mellitus, uncontrolled hypertension; patients with Hepatitis B or HIV infection; pregnant, breast-feeding patients.

The patients were explained regarding the objectives as well as the method of study. A complete history was taken, clinical examination and biopsy was done wherever it was necessary. Patients underwent the necessary investigations monthly until week 16. If relevant abnormality in any of the laboratory values was noted during treatment or during an event of any serious and intolerable side effects the patients were discontinued from the present study and relevant anti-psoriatic treatment was started for the patients.

The patients were divided into two groups of 10 each, A and B. Group A was treated with oral methotrexate (15mg per week) and Group B was treated with oral Apremilast (After the patient completed the starter pack, for maintenance 30 mg

tablets was given per orally twice daily) and were evaluated every 4 weeks for a period of 16 weeks and the last follow-up was at 24th weeks.

Clinical evaluation of joint disease was done by a rheumatologist, while clinical evaluation of cutaneous manifestations was performed by a dermatologist at baseline and at each follow up. Follow-up schedule was maintained regularly, and every call of the patient was attended by the investigator group. Patients who developed serious adverse effect like life threatening infection with organ involvement or requiring hospital admission were withdrawn from the therapy. Statistical analysis was done using chi-square test, Fisher's exact test, paired sample t-test and independent sample t-test.

RESULTS

Among the 20 patients, M:F ratio was 1.85: 1, [65% (13) males and 35% (7) females], mean age of onset was 39.56 years and mean duration of disease was 13.4 years. [Table 1]

The rate of response to the medications was evaluated based on PASI score which was evaluated and tested at the baseline, every 4 weeks for a period of 16 weeks and the last follow-up was at 24 weeks.

On accessing the results in group-A patients after 16 weeks of treatment, patients showed around 70% of improvement which on comparing with patients with oral Apremilast was relatively more. The % of improvement in PASI score in methotrexate group at the end of 16 weeks was statistically significant ($p<0.05$) as compared to that of group B. The % of improvement in patients at the end of 16 weeks in the other group was 60% such that a difference noticed was of around 10%. On follow-up at 24th week patients in group A showed sustained results as compared to that of patients in group B (table 1).

PDI score was used and was assessed at the baseline and then at the end of 16 weeks and the time of follow-up at 24 weeks. PDI in group A patients treated with oral methotrexate was 36.79±2.79 at the baseline while in group B it was 38.36±2.12 out of total score of 45. At the end of treatment that is after 16 weeks, the PDI became 17.52±3.26 in group A was statistically significant ($p<0.05$) as compared to patients in group B which was 20.15±2.83 (table 1).

Side effects observed were less in patients treated with methotrexate as compared to that of patients treated with tab Apremilast. [Table 2]

Table 1: The comparison of demographic & Clinical data in between groups

Variables	Group A (oral methotrexate) N=10	Group B (oral Apremilast) N=10	P-value
Age (in years) (Mean ± SD)	40.13±2.56	39.68±2.92	>0.05
Male: female ratio	6:4	7:3	1.00
Duration of psoriasis (in years) (Mean ± SD)	14±1.75	13±3.63	>0.05
	PASI Score		
At baseline	18.92±2.27	18.63±3.08	Intra group comparison P<0.0001**
At 8 weeks	9.26±1.85	9.98±0.84	
At 16 weeks	4.72±1.38	5.26±1.03	
	PDI (Mean ± SD)		
At baseline	36.79±2.79	38.36±2.12	<0.05*
At 16 weeks	17.52±3.26	20.15±2.83	<0.05*
TJC	24.60± 15.27	18.58 ± 11.8	<0.05*
SJC	17.62 ± 12.64	13.19 ± 9.82	<0.05*
VAS for pain	7.46 ±2.12	7.86 ± 1.63	>0.05

Table 2: Side effects

Side effects	Group A (oral methotrexate) N=10	Group B (oral Apremilast) N=10
Diarrhoea	1	3
Nausea and vomiting	1	4
Upper respiratory tract	0	3
Infections	1	1
Git intolerance	1	3
Headache	0	4
Mood disorders	0	2
Abdominal pain	0	0

DISCUSSION

Psoriasis is defined as chronic inflammatory disorder which is genetically determined and leads to hyper- proliferation of the skin. It is a disfiguring condition in which there is alteration in growth and differentiation of the epidermis. Various factors play a major role in its etiology like hormonal, environmental, genetic, drugs, trauma, sunlight. The most common type of psoriasis is chronic plaque psoriasis which is characterized by well- defined red color plaques which are scaly and indurated involving the extensors aspect of the body and also the scalp.[20,21] Psoriasis had a bimodal distribution of age of onset. According to a study done by Lomholt the average age reported was 12 years.[22] According to a study done in large US surveys, average age of onset was reported to be 28 years.[23]

While on the studies done in UK said mean age of onset as 33 years such that around 75% patients had psoriasis before 46 years of age.[24] In our study, patients in both the groups were in the mean age group of 40.13±2.56 and 39.68±2.92 respectively and the mean duration of psoriasis in all the patients was around 13-14 years. In one of the German study, early age of onset was 16 years and 22 years, and the later age involved was 57- 60 years.[26] In our study both males and females were almost equally affected in a ratio of 6:4 in the first group while ratio of 7:3 in group B patients. As per various studies psoriasis affects equally both males and females.[25] One of the studies done in Germany showed the peak age of onset was 22 years in males and 16 years in females.[26]

Methotrexate inhibits DNA synthesis by competitive inhibition of dihydrofolate reductase, and may thus exert an antimitotic action on the epidermis.[25] In our study, the same dosage of methotrexate was started orally for the patients and patients achieved PASI of 4.72±1.38 by the end of 16 weeks reporting an improvement of 70% and the psoriasis disability index showed an reduction from 36.79 to 17.52 (mean). According to various studies, patients usually present with complains of oral ulcers, gastrointestinal discomfort following the intake of tablet due to folic acid deficiency. Only few patients complained of gastrointestinal intolerance as tablet folic acid was prescribed to our patients. One of the retrospective studies have shown if methotrexate is given in low dosage for a longer period of time it has better efficacy and have reduced or minimal side effects.[27]

Apremilast is an oral PDE4 inhibitor which mainly acts over the cyclic adenosine monophosphate and helps in signalling of intracellular functions and reduces the levels of proteins to modulate the immunity and thereby improves the inflammation which is associated with psoriasis.[28]

Clinical parameters, 60/50 joints TJC/SJC and VAS for pain started showing significant improvement in both the groups starting right from base level, which was sustained till 16 weeks of treatment. Target achievement was seen more in patients with significantly lower TJC/ SJC in both the groups. Our result is consistent with previous studies of MTX and Tofacitinib on PsA and RA.[29]

CONCLUSION

Apremilast is a new drug recently approved for management of psoriasis but due to its daily dosing, non- compliance was observed amongst the patients, and it was associated with various side effects. On comparing the two drugs, methotrexate was comparatively better tolerated and had better efficacy and safety. This study has been done and presented as only few comparative studies of these two drugs have been done till now. More studies are required to further prove the efficacy of Apremilast in treatment of this disorder.

REFERENCES

1. Langley RG, Krueger GG, Griffiths CE. Psoriasis: epidemiology, clinical features, and quality of life. Ann. Rheum. Dis.2005; 64:18-23.
2. Gladman DD, Antoni C, Mease P et al. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann. Rheum. Dis.2005; 64:14-7.
3. Sherlock JP, Joyce-Shaikh B, Turner SP et al. IL-23 induces spondyloarthropathy by acting on ROR-γt+ CD3+ CD4− CD8− entheseal resident T cells. Nat. Med.2012; 18:1069-76.
4. Partsch G, Steiner G, Leeb BF et al. Highly increased levels of tumor necrosis factor-alpha and other proinflammatory cytokines in psoriatic arthritis synovial fluid. J. Rheumatol.1997;24:518-23.
5. Ritchlin C, Haas-Smith SA, Hicks D et al. Patterns of cytokine production in psoriatic synovium. J. Rheumatol.1998;25:1544-52.
6. Jandus C, Bioley G, Rivals JP et al. Increased numbers of circulating polyfunctional Th17 memory cells in patients with seronegative spondylarthritides. Arthritis Rheum.2008;58:2307-17.
7. Weinstein GD. Methotrexate for Psoriasis. JAMA. 1973;225(4):412.
8. 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(5):519-24.
9. Gateva V, Sandling JK, Hom G, Taylor KE, Chung SA, Sun X, et al: A large-scale replication study identifies TNIP1, PRDM1, JAZF1, UHRF1BP1 and IL10 as risk loci for systemic lupus erythematosus. Nat Genet. 2009;41(11):1228-33.
10. Schafer P. Apremilast mechanism of action and application to psoriasis and psoriatic arthritis. Biochem Pharmacol. 2012; 83:1583-90.
11. Otezla. Summit, NJ: Celgene Corporation; 2014. Accessed March 18, 2015. Available at: http://dailymed.nlm.nih.gov/dailymed/ drugInfo.cfm?setid=3acf6751-827d-11e2-9e96 0800200c 9a66.
12. Otezla [summary of product characteristics]. Uxbridge, United Kingdom: Celgene Europe Ltd; 2015. Available at: http://ec.europa.eu/health/ documents/community-register/2015/2015011 5130395/anx_130395_en.pdf. Accessed March 18, 2015
13. Soriatane. Research Triangle Park, NC: Stiefel Laboratories Inc; 2014. Accessed March 18, 2015. Available at: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm ?setid=cec7851f-c7af-4e9ea5e4- a585c70510d2.
14. Neoral. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2013. Available from: http://daily med.nlm.nih.gov/dailymed/drugInfo.cfm?setid=944 61af3-11f1- 4670-95d4-2965b9538ae3. Accessed March 18, 2015.
15. Methotrexate. Fort Lee, NJ: DAVA Pharmaceuticals Inc; 2009. Available from: http://dailymed.nlm.nih. gov/dailymed/drugInfo.cfm?setid=9c4a4784-b063 4c8fb915- aeb18cb149be. Accessed March 18, 2015.
16. Oxsoralen-Ultra. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC; 2015. Accessed March 18, 2015. Available from: http://dailymed.nlm.nih.gov/ dailymed/drugInfo.cfm?setid=ae951dc4- 9031 43bf-943c-cb2366951f23.
17. Available at: https://www.psoriasis.org/about psoriasis/ treatments/ oral-treatments. Accessed March 18, 2015.
18. Otezla (apremilast) prescribing information. Summit, New Jersey: Celgene Corp.; 2014.
19. Food and Drug Administration Center for Drug Evaluation and Research. Nov, 2013. Application number: 205437Orig1s000: clinical pharmacology and biopharmaceutics review, 2013.

20. Rook's Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffi ths. Blackwell Publishing Ltd. 2010.
21. Fry L: An Atlas of Psoriasis. Carnforth, Parthenon Publishing, 1992.
22. Lomholt G. Psoriasis: Prevalence, Spontaneous Course and Genetics. A Census Study on the Prevalence of Skin Diseases on the Faroe Islands. Copenhagen: GEC Gad; 1963: 31–3.
23. Farber EM, Nall ML. The natural history of psoriasis in 5600 patients. Dermatologica 1974; 148:1–18.
24. Nevitt GJ, Hutchinson PE. Psoriasis in the community: prevalence, severity and patients' beliefs and attitudes towards the disease. Br J Dermatol. 1996; 135:533–7.
25. Fry L. Psoriasis. Br J Dermatol 1988;119(4):445-61.
26. Henseler T, Christophers E. Psoriasis of early and late onset: characterization of two types of psoriasis vulgaris. J Am Acad Dermatol. 1985; 13:450-6
27. Haustein UF, Rytter M. Methotrexate in psoriasis: 26 years' experience with low-dose long-term treatment. J Eur Acad Dermatol Venereol 2000; 14:382–8.
28. Gottlieb AB, Strober B, Krueger JG. An open-label, single-arm pilot study in patients with severe plaque-type psoriasis treated with an oral anti- inflammatory agent, apremilast. Curr Med Res Opin. 2008; 24:1529-38.
29. Kingsley GH, Kowalczyk A, Taylor H et al. A randomized placebo-controlled trial of methotrexate in psoriatic arthritis. Rheumatol.2012;51:1368-77.