Research Article

INTERNATIONAL RESEARCH JOURNAL OF PHARMACY

www.irjponline.com

ISSN 2230-8407 [LINKING]

EVALUATION AND EFFICACY OF METHOTREXATE IN MODERATE TO SEVERE CASES OF CHRONIC PLAQUE VS METHOTREXATE ALONE- COMPARATIVE CLINICAL TRIAL

Dr. Satish Adulkar

Assistant Professor, Department of Dermatology, Venereology & Leprosy, Santosh Medical College, Ghaziabad, Uttar Pradesh

Address for correspondence

Email id: dr.satish.adulkar@gmail.com

How To Cite: Adulkar S. Evaluation And Efficacy of Methotrexate In Moderate to Severe Cases of Chronic Plaque Vs Methotrexate Alone- Comparative Clinical Trial. International Research Journal Of Pharmacy 2020,11:12:56-60.

DOI: 10.7897/2230-8407.1112109

==========

ABSTRACT

Background: A systemic inflammatory chronic disease with a high recurrence rate is psoriasis. Nowadays, phosphodiesterase type 4 inhibitors like Apremilast and methotrexate, which is a dihydrofolate reductase inhibitor, are the most often used medications to treat psoriasis.

Aim: The purpose of this research was to evaluate, in moderate to severe instances of chronic plaque psoriasis, the relative effectiveness of methotrexate with apremilast against methotrexate alone.

Methods: Eighty adult patients with a verified diagnosis of chronic plaque psoriasis were included in the current prospective comparative investigation. Each patient had a thorough clinical and demographic assessment using 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: Of the patients in this study, 55% (n=44) were between the ages of 31 and 50, and 27.5% (n=22) reported having comorbid conditions such diabetes, hypertension, and other conditions. At all first, second, and third follow-ups, Group I's PASI scores were lower than Group II's. Group I saw an 89% improvement in mean PASI scores during the 12-week follow-up, a much larger drop in scores.

Conclusions: Compared to methotrexate alone, the current study's multimodal treatment combining apremilast and methotrexate is more effective in treating persistent plaque psoriasis.

Keywords: Apremilast, chronic plaque psoriasis, methotrexate, psoriasis

INTRODUCTION

Psoriasis is a chronic inflammatory systemic illness characterised by micaceous scales on the skin of affected individuals and persistent erythematous plaques that are thought to be caused by hyperproliferation of epidermal keratinocytes. Worldwide, the prevalence of psoriasis ranges from 1% to 3%. Many environmental variables, including as seasonal fluctuations, trauma, infection, medicines, and other factors, are important in the development of psoriasis. People having a positive family history of psoriasis in first-degree relatives account for around 30% of instances of early-onset psoriasis.[1]

The US Food and Drug Administration (US FDA) originally authorised the use of methotrexate, an antimetabolite medication, in 1970 for the treatment of psoriatic lesions. Methotrexate functions by preventing dihydrofolate

reductase from doing its job, which further prevents cellular reproduction in psoriatic lesions and ultimately results in the hyperproliferation associated with psoriasis.[2] The medication normally takes 4 to 8 weeks to start working. Due of its extended half-life, methotrexate is usually administered as three separate doses spaced out at regular 24-hour intervals or as a single weekly dosage. The drug's initial dose is typically 2.5 mg, and it is progressively raised to a minimum and maximum dose of 10-15 mg and 25-30 mg weekly, respectively, until therapeutic results are observed without causing toxicity.[3]

Apremilast, the first oral medication authorised by the FDA in 1196 for the treatment of psoriasis, is another innovative medication used to treat psoriatic arthritis and psoriasis. PDE4 (phosphodiesterase type 4) inhibitors, such as apremilast, are oral medications that work intracellularly to promote the synthesis of anti-inflammatory mediators while inhibiting the development of pro-inflammatory mediators.[4] Inhibiting PDE4 raises intracellular cyclic adenosine monophosphate levels, which in turn causes a rise in anti-inflammatory mediator synthesis and a decrease in pro-inflammatory mediator generation. When treating psoriasis and psoriatic arthritis in adults, 30 mg of alevemilast used twice day is advised. 10 mg is the starting dose, and it is raised to the recommended level. This is done in an effort to reduce the potential side effects of Apremilast on the gastrointestinal tract. Apremilast is sold in tablets of 10, 20, and 30 mg in India.[5]

Both psoriasis and psoriatic arthritis are chronic conditions that require ongoing care and frequently recur. For those with moderate to severe chronic plaque psoriasis and psoriasis that significantly impairs quality of life, systemic treatment is advised.[6] Psoriasis is classified as moderate or severe in patients whose afflicted body surface area is between 3 and 10% and more than 10%, respectively. Because of its affordability, convenience of use, and oral mode of administration, methotrexate is typically regarded as a first line of therapy for patients with persistent plaque psoriasis. Furthermore, methotrexate is less expensive than biologics and systemic therapy.[7]

Psoriasis can be effectively treated using biologic medicines, which are more recent forms of therapy. Nevertheless, their high cost and mode of administration are drawbacks. Apremilast is regarded as a safe, oral, first-line therapy in cases of early methotrexate tapering because it is inexpensive, has a superior safety profile, and is effective. According to these results, using methotrexate and retinoids together may be a more effective way to treat psoriasis.8 Therefore, in moderate to severe instances of persistent plaque psoriasis, the purpose of the current study was to compare the effectiveness of methotrexate with apremilast vs methotrexate alone.

MATERIALS AND METHODS

The current prospective clinical trial aims to evaluate, in moderate to severe instances of chronic plaque psoriasis, the relative effectiveness of methotrexate with apremilast against methotrexate alone.

The Institutional Ethical Committee approved the study before it could be completed. Before beginning the study, all participants gave their verbal and written informed permission.

Eighty volunteers, all female, who had been diagnosed with psoriasis and were at least eighteen years old, were evaluated for the research. Following the study participants' final inclusion, a thorough history was taken and a clinical examination was conducted using a pre-made structured proforma. This proforma included information about the disease history in first-degree relatives, joint pain history, involvement of the scalp or nails, reliving and aggravating factors, length of the current episode, duration of the disease, and age at which the disease first appeared. A history of drug and alcohol use, smoking, and nutrition was also documented. A thorough systemic and general physical examination, as well as a skin examination that included morphologic psoriasis type identification, came next.

The gold standard scoring methodology used for psoriasis grading is composed on PASI, or psoriasis and area severity index scores. PASI scores were utilised in the current investigation to evaluate the response to therapy as well as the severity of the condition. Laboratory investigations were performed on subjects when indicated. These investigations included skin biopsy, HIV testing in at-risk subjects, serological testing for Hepatitis B and C in subjects with abnormal liver function tests, chest X-ray, random blood sugar, urine microscopy, renal function tests, liver function tests, and complete blood count.

Eighty patients with moderate to severe psoriasis were randomly assigned to two groups for the current investigation. Group I subjects received Apremilast with oral methotrexate in a dose of 7.5 mg once a week, along with 5 mg of folic acid on the days when methotrexate was not administered as a therapy. Day 1–4 saw the administration of a 10 mg dose once daily, Day 5–9 saw the administration of a 20 mg dose once daily, and Day 9 saw the administration of a 30 mg dose once daily. Group II administered 7.5 mg of oral methotrexate once a week and gave all individuals a 5 mg folic acid pill on days when methotrexate was not administered. 12 weeks of treatment were spent in this manner.

At the four, eight, and twelve-week marks, the patients were brought back for a follow-up visit during which a clinical examination and history taking were conducted, along with any necessary investigations, PASI scores, and a weight assessment. Based on the necessity, the necessary adjustments to the therapy were made.

Friedman's ANOVA test and SPSS software version 21.0 (IBM Corp., NY, USA) were used to statistically analyse the collected data. The means and standard deviations of the data were reported. A p-value of less than 0.05 was considered statistically significant.

RESULTS

In moderate to severe instances of chronic plaque psoriasis, the purpose of the current prospective clinical trial was to compare the effectiveness of methotrexate with apremilast vs methotrexate alone.

For the study, eighty psoriasis patients—female and male—were assessed and divided into two groups. On the days when methotrexate was not given as treatment, Group I got 5 mg of folic acid in addition to 7.5 mg of oral methotrexate once a week. A dose of 10 mg was administered once day on Days 1-4, a dose of 20 mg once daily on Days 5-8, and a dose of thirty mg once daily on Day 9. On days when methotrexate was not given, Group II provided each person a 5 mg folic acid tablet in addition to 7.5 mg of oral methotrexate once a week. This was the way the therapy was conducted for 12 weeks.

Group I's mean age was 39.32±13.24 years, whereas Group II's mean age was 42.52±14.21 years. In Groups I and II, the age of onset was 32.82±15.06 and 32.52±12.75 years, respectively. For Group I and II, the duration of psoriasis was 6.93±6.62 and 10.11±8.21 years, respectively. As indicated in Table 1, the mean length of the current episode was 1.64±1.64 years for Group I and 2.36±1.76 years for Group II.

A non-significant difference (p=0.11) was seen between the two groups of research individuals who received methotrexate and combination treatment when comparing their mean PASI scores. In the fourth week, methotrexate alone showed a non-significantly higher mean (p=0.13) than combination treatment.

During the eighth week, methotrexate by itself showed substantially higher PASI scores (987±4.02) than methotrexate with apremilast (483±2.43), a highly significant difference (p<0.001). Group II had considerably higher mean PASI scores at the 12-week mark, measuring 6.33±2.92, whereas Group I's scores were 2.47±1.64. With p<0.001, the outcomes were statistically significant (Table 2). In the current study, the percentage of individuals with scalp and nail involvement was 70% (n = 56) and 52.5% (n = 42), respectively.

Regarding the comparison of the mean PASI score differences, it was observed that Group I had substantially higher mean PASI scores (12.81±6.82) from baseline to the fourth week than Group II (4.47±2.84 with p<0.001).

Between the fourth and eighth weeks, Group I's mean PASI scores were 5.77±2.65, a significant difference from Group II's 5.77±2.65, with a p-value of 0.0003. Group II's mean PASI scores for the eighth to twelfth week were 3.53±1.86, whereas Group I's were 2.34±1.33. Table 3 shows that the difference was statistically non-significant at p=0.31.

DISCUSSION

The study evaluated 80 psoriasis-affected subjects of both genders and split them into two groups. Group I received Apremilast with oral methotrexate at a dose of 7.5 mg once a week along with 5 mg of folic acid on the days when methotrexate was not given as therapy, and 10 mg of methotrexate once daily on days 1-4, 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. Group I's mean age was 39.32±13.24 years, whereas Group II's mean age was 42.52±14.21 years. In Groups I and II, the age of onset was 32.82±15.06 and 32.52±12.75 years, respectively. For Group I and II, the duration of psoriasis was 6.93±6.62 and 10.11±8.21 years, respectively. The current episode's mean duration was 1.64±1.64 years for Group I and 2.36±1.76 years for Group II, respectively. The present study's results were in line with the findings of Yan K et al.'s 2019 study and Shetty VH et al.'s 2018 study, which indicated a larger male preponderance among psoriasis participants.

In the current study, diabetes mellitus and hypertension were among the comorbidities seen in 27.5% (n=22) of the study participants. According to studies conducted in 2003 by Ramachandran A et al.11 and Gupta A et al.12, who used various criteria for the categorization of obesity, metabolic syndrome is observed in industrialised nations at a frequency of between 15% and 35%. According to a 2002 research by Deepa R et al.13, 11.2% of people had metabolic syndrome.

In the current study, the percentage of individuals with scalp and nail involvement was 70% (n = 56) and 52.5% (n = 42), respectively. These outcomes were comparable to a 2017 research by Chan S et al.14, whose authors reported that 80% of their psoriasis individuals had scalp involvement. The study's findings demonstrated that, when mean PASI scores from the two study subject groups were compared, there was no statistically significant difference between the two groups receiving combination treatment and methotrexate (p=0.11).

In the fourth week, the mean for methotrexate alone was non-significantly greater than the mean for combination treatment (p=0.13). Eighth-week PASI scores showed that methotrexate alone had much higher scores (987±4.02) than the combination of methotrexate and apremilast (483±2.43), a very significant difference (p<0.001). Group II had substantially higher mean PASI scores at the 12-week mark (6.33±2.92) compared to 2.47±1.64 in Group I. With p<0.001, the data demonstrated statistical significance. These findings were consistent with those of Haider S et al. (2015), whose mean PASI scores before and after methotrexate were reported to be 14.8±4.2 and 4.9±4.3, respectively, and Raza N et al. (2016), whose PASI scores significantly improved from 15.81±5.55 to 8.79±4.19 (P < 0.01). Regarding the comparison of the mean PASI score differences, it was observed that Group I had substantially higher mean PASI scores (12.81±6.82) from baseline to the fourth week than Group II (4.47±2.84 with p<0.001). Between the fourth and eighth weeks, Group I's mean PASI scores were 5.77±2.65, a significant difference from Group II's 5.77±2.65, with a p-value of 0.0003.

In the 8^{th} to 12^{th} 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 results were consistent with a research conducted in 2022 by Hassanandini T et al., where authors used methotrexate alone and in conjunction with apremilast to produce comparable outcomes.

CONCLUSION

The current study comes to the conclusion that when methotrexate is used in combination with Apremilast and methotrexate as opposed to methotrexate alone, the latter is more effective. Among the many benefits of multidrug therapy are quicker outcomes and improved medication toleration, which shortens the course of therapy. Because combination therapy involves fewer treatments over a shorter period of time, there have also been reported to be fewer adverse effects.

REFERENCES

1. Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med.* 2009;361:496–509.
2. Chang CA, Gottlieb AB, Lizzul PF. Management of psoriatic arthritis from the view of the dermatologist. *Nat Rev Rheumatol.* 2011;7:588–98.
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.

TABLES

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

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

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**

Table 2: Comparison of PASI scores 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

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