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Original Article

Effect of apremilast on cardiovascular risk in psoriasis patients in comparison with methotrexate

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ABSTRACT

Objectives: To compare the change in cardiovascular risk factors who are taking apremilast and methotrexate.

Materials and Methods: This hospital-based prospective cohort study included 40 newly diagnosed cases of psoriasis who were divided into two groups – group A (receiving methotrexate) and group B (receiving apremilast) and were assessed at baseline and after 12 weeks. The outcome was assessed on the basis of psoriasis area and severity index score and the biochemical parameters.

Results: A total of 50 patients diagnosed with chronic plaque psoriasis were enrolled in the study, out of which 40 completed the study. At the end of 12 weeks, patients treated with apremilast showed a 49.39% reduction in mean PASI score, while those on methotrexate showed a 46.19% reduction. Significant elevation of alanine transaminase was seen only in the methotrexate group with $P < 0.05$. No significant change was observed in blood glucose levels in both groups. hs-CRP levels in the methotrexate group showed a significant decrease as compared to apremilast ($P < 0.05$).

Limitations: Absence of blinding, psoriasis patients not stratified according to severity, and a small sample size were the major limitations.

Conclusion: On comparing the two drugs, methotrexate is considered to have more cardioprotective action.

Keywords: Apremilast, Methotrexate, Psoriasis

INTRODUCTION

Psoriasis is a chronically relapsing inflammatory disorder with cutaneous and rheumatologic manifestations characterized by increased cardiovascular diseases. Chronic inflammation in psoriatic patients predisposes them to diseases with inflammatory components, mostly cardiovascular morbidity. This study was done to compare the change in cardiovascular risk factors who are taking apremilast and methotrexate.

Several meta-analyses[1,2] showed that the spectrum of inflammation is systemic with an elevation of interleukin (IL)-6, tumor necrosis factor (TNF)-alpha, C-reactive protein (CRP), E-selectin, and intercellular adhesion molecule-1 which are predictors of cardiovascular mortality.[3]

CRP, an acute-phase protein, is an emerging marker of cardiovascular inflammation leading to atherosclerosis. It has been shown that high-sensitivity CRP (hs-CRP) predicts cardiovascular risk when traditional risk factors are normal.[4,5]

Studies have shown that hs-CRP did not correlate with cardiovascular risk and was found to be an independent predictor of recurrent cardiovascular events in the Asian population.[6,7] Another study from South India showed that CRP is a sensitive risk factor for cardiovascular disease in psoriasis patients.[8]

ThromboxaneA2 produced by activated platelets is unstable and hydrolyzed within about 30 s to the inactive thromboxaneB2, which is completely excreted by the urine. Hence, thromboxane B2 urinary assay is a non-invasive test to measure platelet activation. It has been shown that urinary thromboxane B2 measurement is a useful indicator of major adverse cardiovascular events.

Apremilast is a Food and Drug Administration-approved medication for the treatment of moderate to severe psoriasis and psoriatic arthritis. It selectively inhibits phosphodiesterase (PDE)-4, which reduces inflammation, leading to a reduction of TNF-alpha, IL-23, and an increase of IL-10.[9]

A large number of epidemiological studies performed in various countries have demonstrated that psoriasis is associated with an increased prevalence of cardiovascular diseases. However, there is a gap in understanding the effect of methotrexate and apremilast on cardiovascular risk, and hence, more studies are needed to establish such a link.[10]

Aims and objectives

The aims of this study were as follows:

1. To evaluate the effect on biochemical parameters pertaining to cardiovascular risk in psoriasis patients after 12 weeks of treatment with apremilast in comparison with methotrexate
2. To compare the efficacy of methotrexate with apremilast in treating chronic plaque psoriasis.

MATERIAL AND METHODS

This is a prospective cohort study conducted in a tertiary care center after getting clearance from the Ethical Committee. All consecutive new patients who attended the dermatology department with chronic plaque psoriasis diagnosed clinically in the period between February 1, 2021, and August 1, 2021, were enrolled in the study. The participant will be informed about the study, and written consent was obtained. A total of 50 patients were enrolled in the study. Sample size calculation was done by independent *t*-test.

The sample size was calculated by independent *t*-test.

Based on the mean and standard deviation of psoriasis area and severity index (PASI) score observed in an earlier publication[11] with a 95% confidence level and 90% power minimum sample size comes to 20 in each group, expecting 20% loss for follow-up, we have taken 25 in each group. Since we got only 25 in each group, our sample size was 50.

The patients who received antipsoriatic treatment with methotrexate and apremilast were followed up.

Group A-Oral methotrexate 7.5 mg once per week was given.

Group B-A starter pack of apremilast was given in the following regime: Days 1–4: 10 mg once daily; Days 5–8: 20 mg once daily; and Day 9 onward: 30 mg daily.

Clinical (PASI score) and biochemical (Fasting blood glucose, lipid profile blood counts, liver enzymes, high-sensitivity C-reactive protein [hsCRP], and urinary thromboxane B2) assessments were done at baseline and after 12 weeks, and the results were compared between two groups.

The data were analyzed by the Statistical Package for the Social Sciences version 25. The chi-square test was used to describe a statistically significant correlation with the severity of skin involvement. An Independent *t*-test was used to analyze the cardiovascular risk improvement with treatments. $P < 0.05$ was considered significant.

Inclusion criteria

The following criteria were included in the study:

1. Patients with chronic plaque psoriasis
2. Patients above 18-years.

Exclusion criteria

Pregnant and lactating patients, those with a history of cardiovascular diseases, on aspirin, statins, and other cardiovascular drugs were excluded from the study.

RESULTS

A total of 50 patients diagnosed with chronic plaque psoriasis were enrolled in the study, out of which 40 completed the study [Figure 1]. Patients who received methotrexate and apremilast were followed up. (In the methotrexate group, five patients were lost to follow-up due to unknown reasons during the 1st month itself, four in the apremilast group stopped the drug due to abdominal pain, and one in the apremilast group had the serious adverse effect – an episode of myocardial infarction after 1 month of treatment). The baseline data are given in Table 1. Figure 1 shows a flowchart representation of the study.

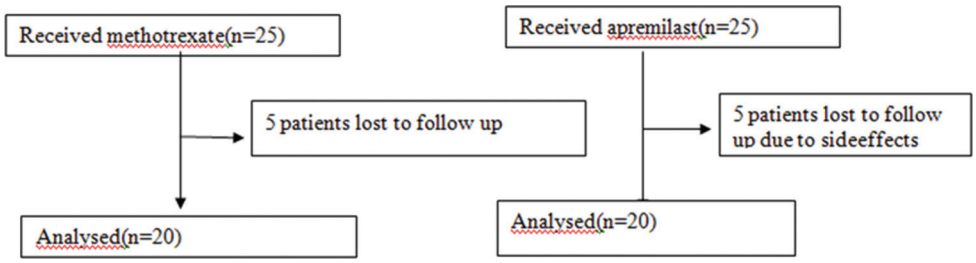

Figure 1: Schematic figure showing the number patients included in the study and followed up.

Table 1: Baseline demography and PASI score at baseline and after 12 weeks.

	Apremilast	Methotrexate	*P*-value
Age in years*	44.4±15.4	43.4±11.1	0.815
Male: Female ratio	14:6	15:5	0.723
Duration in years*	4.2±2.4	6.8±3.9	0.016
PASI baseline	13.26±2.6	16.05±4.5	0.001
PASI at 12 weeks	6.71±2.8	8.6375±4.2	0.001

*Mean±Standard deviation. PASI: Psoriasis area and severity index

PASI score

At the end of 12 weeks, patients treated with apremilast showed a 49.39% reduction in mean PASI score, while those on methotrexate showed a 46.19% reduction. The change in PASI score did not differ significantly between the two groups [Table 2].

Lipid profile

There was a statistically significant reduction in serum triglycerides and low-density lipoprotein (LDL) cholesterol in the methotrexate group and a reduction of high-density lipoprotein (HDL) in the apremilast group with $P < 0.05$ [Table 2].

Blood counts

There were no significant reductions in cell counts with both methotrexate and apremilast [Table 2].

Liver enzymes

Among liver enzymes, significant elevation of alanine transaminase was seen only in the methotrexate group with $P < 0.05$ [Table 2].

Fasting blood sugar (FBS)

No significant change was observed in blood glucose levels in both groups [Table 2].

hsCRP

hs-CRP levels in the methotrexate group showed a significant decrease as compared to apremilast with $P < 0.05$ [Table 2].

Thromboxane B2

Only five patients had raised levels of thromboxane b2 levels among 20 patients, and four of these five patients showed decreased levels after 3 months of treatment with methotrexate. Apremilast decreased the thromboxane b2 level of one patient.

DISCUSSION

Psoriasis and cardiovascular disease share similar pathogenic mechanisms, such as vascular endothelial cell dysfunction, oxidative stress, and metabolic syndrome.[12] The mean per cent reduction of PASI score after 12 weeks of treatment was found to be 49.39% for methotrexate and for apremilast 46.19% compared with baseline. Similar studies comparing the relative efficacy of methotrexate and apremilast in chronic plaque psoriasis and psoriatic arthritis found no significant difference in PASI scores between the two groups.[13,14] Similarly, another study comparing the efficacy of both drugs in palmoplantar psoriasis showed that apremilast had a comparable efficacy and safety profile to methotrexate in the management of palmoplantar psoriasis.[15]

In our study, we observed an insignificant rise in the level of total cholesterol (TC) and a modest reduction in triglyceride and LDL after 3 months of treatment with apremilast. However, the level of HDL showed a significant fall. These changes appear contradictory to the previously noted beneficial effect of PDE inhibition on lipid profile. Gualtierotti and De Lucia observed a reduction in TC, TC/HDL ratio after 1 month of treatment with apremilast with further reduction in TC (5%), LDL (25%), and triglyceride (17%) and a 20% increase in HDL after 12 months of treatment.[16]

Gisondi *et al.* showed no significant difference in triglyceride mean levels in psoriasis patients taking methotrexate.[12] Dehpourietal reported a non-significant increase in TC and LDL with a significant increase in HDL in psoriatic arthritis patients receiving methotrexate.[17] In contrast to all this, we observed a significant decrease in LDL triglyceride and a non-significant decrease in TC and HDL in those taking methotrexate.

Table 2: Comparison of biochemical parameters.

	Independent sample t-test			
Group	**Mean**	**Std. Deviation**	***t*-statistic**	***P*-value**
Difference in FBS				
Apremilast	−3.75	30.91223	−1.616	0.114
methotrexate	11	26.67149		
Difference in cholesterol level				
Apremilast	−2.9	31.85312	−1.68	0.101
methotrexate	13.95	31.5836		
Difference in triglyceride				
Apremilast	6.25	26.0038	−1.958	0.058
methotrexate	22.6	26.8022		
Difference in HDL				
Apremilast	3.9	5.27057	1.22	0.23
methotrexate	1.45	7.2727		
Difference in LDL				
Apremilast	4.2815	16.9475	−2.35	0.024*
methotrexate	15.98	14.43109		
Difference in hsCRP				
Apremilast	0.3396	2.57683	−2.31	0.026*
methotrexate	1.774	1.03514		
Difference in PASI				
apremilast	6.5515	3.20077	−0.893	0.378
methotrexate	7.4155	2.9128		
Difference in neutrophil				
apremilast	1.115	7.51204	−0.865	0.392
methotrexate	3.15	7.36475		
Difference in platelet				
apremilast	−9630	90318.6004	−1.569	0.125
methotrexate	26985	52285.99767		
Difference in Hb level				
apremilast	−0.115	1.46225	−0.699	0.489
methotrexate	0.175	1.14012		
Difference in WBC				
apremilast	−94	1329.36629	−1.946	0.059
methotrexate	659	1108.07514		
Difference in ALT				
apremilast	−0.905	7.43048	3.51	0.001*
methotrexate	−15.95	17.67089		
Difference in AST				
apremilast	2.195	7.49544	2.36	0.024*
methotrexate	−6.55	14.78077		
Difference in lymph				
apremilast	−0.31	8.42277	−1.371	0.178
methotrexate	2.65	4.71587		

*Statistically significant, FBS: Fasting blood sugar, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, WBC: White blood cell, hsCRP: High sensitivity C-reactive protein, Hb: Hemoglobin, ALT: Alanine transaminase, AST: Aspartate transaminase, PASI: Psoriasis area and severity index

We also analyzed the level of urinary thromboxane b2. Still, we observed elevated thromboxane b2 only in five patients, of which four received methotrexate. All of them showed decreased levels after 12 weeks of treatment, and only one received apremilast showed decreased levels after 12 weeks of treatment. Since increased thromboxane levels are associated with vascular inflammation and, hence, adverse cardiovascular outcomes, methotrexate can be considered as cardioprotective.

We observed negligible changes in blood counts. Kolios *et al.* reported lymphopenia following apremilast treatment for 3 months.[18] Studies among animal models showed negligible lymphopenia and neutropenia.

There was no significant change in the level of transaminase in patients treated with apremilast, as observed in our study. This was in accordance with a large scale randomized, controlled trial of apremilast in psoriatic patients where serum enzyme elevation was not different from the placebo group. Salliot and van der Heijde, in 2009, showed that elevated transaminase levels were found in 20% of patients treated with 5 mg methotrexate for 1 year, with levels more than twice the upper limit in 13%.[19] This is in accordance with our findings.

In contrast to previously reported studies where PDE inhibitors exert a beneficial glycemic effect through glucagon-like peptide release, we did not observe any significant change; on the contrary, an insignificant increase in FBS levels was noted among 11 out of 20 patients in the apremilast group. This discrepancy may be due to inherent differences between study populations.

Gisondi *et al*. surveyed psoriasis patients who were newly treated with methotrexate and demonstrated that there was no detected change in FBS levels.[12] Cuchacovich and Espinoza examined 37 patients with rheumatoid arthritis treated with methotrexate for 24 months and found no significant change in FBS.[20] Our study population showed an insignificant decrease in FBS levels after 3 months of treatment with methotrexate.

Since one of the risk factors in cardiovascular risk is systemic inflammation, hsCRP can be used as a tool to identify people at risk.

There was an insignificant decrease in hs-CRP levels following 3 months of apremilast treatment in our study population. In a study by Danese *et al*., apremilast was shown to decrease levels of CRP in ulcerative colitis patients after 12 weeks of treatment.[21]

The previous studies reported decreased hs-CRP after methotrexate treatment for psoriasis.[22] Similar to other investigators, we observed a significant decrease after 3 months of therapy.

Methotrexate's traditional role as a first-line agent for moderate to severe psoriasis is being challenged by the rapid and growing use of biological therapies.

Although many studies point out its unpredictable response and toxicity, it remains admirable in regions with limited resources even after the introduction of newer and more effective biological treatments. It may also, through its antiproliferative, immunosuppressive, and anti-inflammatory effects, improve endothelial function and decrease cardiovascular events.

In a single patient, we observed a positive correlation of hsCRP with disease severity based on PASI score who was admitted following a cardiovascular event after 1 month of treatment with apremilast.

Limitations

The study was carried out in the outpatient clinic of the dermatology department of a tertiary referral center, lack of blinding, psoriasis patients not stratified according to severity, and a small sample size were the major limitations.

CONCLUSION

The results of our study show that methotrexate is superior to apremilast in PASI reduction. In this study, 3-month treatment with methotrexate was found useful in decreasing the risk factors such as LDL, hsCRP, and triglyceride for the development of cardiovascular disease among patients with moderate to severe psoriasis. Apremilast seemed to have a lesser effect on the above risk factors.

Ethical approval

The ethical approval for this study was obtained from the institutional review board. Ethical committee number-17/EC/22/AIMS-78 dated-31-10-2022.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Glenmark Pharmaceuticals sponsored an ELISA kit for urinary thromboxane B2 assay.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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