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A Comparative Study on Efficacy and Safety of Methotrexate Versus Apremilast in the Management of Chronic Plaque Psoriasis: Tertiary Care Center Based Interventional Study

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Abstract

Introduction: Psoriasis is a common skin presentation in dermatology OPD. Methotrexate and apremilast are frequently used for the management of chronic plaque psoriasis.

Objective: To compare the efficacy and safety of methotrexate versus apremilast for the management of chronic plaque psoriasis.

Materials and Methods: This was an interventional study conducted among 41 patients. The patients were divided into 2 groups. Group A received apremilast 10-30mg twice daily, and group B received methotrexate 10-15mg once weekly for 16 weeks. The patients were evaluated at 4, 8 and 16 weeks. PASI score, DLQI score and adverse effects were documented in every follow-up.

Results: The PASI score significantly reduced from 17.22 ± 8.61 (baseline) to 3.90 ± 2.92 (16 weeks) in group A and 18.64 ± 9.02 (baseline) to 5.95 ± 2.89 (16 weeks) in groups B (P = < 0.001). At 16 weeks, the mean PASI score (3.90 ± 2.92) in group A was significantly less than group B (5.95 ± 2.89) (P = 0.02). The percentage reduction of mean PASI from baseline to 16 weeks was 77% in group A and 68.07% in group B. PASI 75 was achieved by 11 patients (52.30 %) in group A and 8 patients (40 %) in group B at 16 weeks. Both groups had a significant decrease in DLQI as compared to baseline at 16 weeks, with insignificant differences between the two groups during each visit. No severe side effects were seen in both groups.

Conclusion: Both treatments can be considered in treating chronic plaque psoriasis. However, apremilast showed more efficacy than methotrexate.

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

Introduction

Chronic plaque psoriasis is the most common type of psoriasis, accounting for 90% of all cases, characterized by red or salmon pink plaque with white or silvery scales occurring predominantly on the extensor aspects of elbows and knees, scalp, lower back, and umbilicus.[1,2] The prevalence of psoriasis varies according to age and geographic region.[3] The worldwide prevalence of psoriasis in adults ranges between 0.27% and 11.4%.[2] The prevalence of the disease in Nepal ranges from 2.9 to 3.6%.[4] This disease has a bimodal distribution and slightly higher male preponderance.[5]

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Methotrexate was approved by the United States Food and Drug Administration (US FDA) in 1972 for the treatment of psoriasis.[5] It inhibits the dihydrofolate reductase enzyme that decreases the synthesis of purines and pyrimidines necessary for DNA synthesis in circulating activated T lymphocytes and monocytes, contributing to the anti-inflammatory and immunosuppressant effects of the drug.[6] Apremilast was approved for the treatment of plaque psoriasis by the US-FDA in 2014.[7] Apremilast is an orally administered PDE4 inhibitor that leads to an increase in cAMP, thereby escalating the levels of anti-inflammatory mediators like IL-10 and decreases the production of pro-inflammatory tumor necrosis factor-alpha, IL-23, and interferon-gamma.[7]

Methotrexate has been used for decades to manage psoriasis, whereas apremilast is a comparatively newer medicine used for the treatment of the same. A handful of studies compare methotrexate and apremilast in chronic plaque psoriasis. Our objective is to evaluate the benefits of methotrexate versus apremilast in managing psoriasis vulgaris.

Methodology

A prospective, randomized, open-level study was conducted on patients with chronic plaque psoriasis presenting at the dermatology department of Nepalgunj Medical College, Banke, Nepal. The study was conducted after obtaining Institutional Ethical Committee clearance (IRC number: 06/080-081). Written informed consent was obtained from all the study participants before their enrolment. The study was conducted from August 2023 to June 2024.

Inclusion criteria

1. Adult patients diagnosed with chronic plaque psoriasis
2. Psoriasis Area and Severity Index (PASI) score from 5 to 72
3. Willing to provide written informed consent for participation

Exclusion criteria

1. Pre-existing blood disorders like anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia
2. History of thromboembolic disorders, recent stroke, myocardial infarction, deep vein thrombosis in last six months
3. Patients under antiplatelet drugs, anticoagulants, or any iron supplementations
4. Patients with elevated serum creatinine
5. Patients with elevated liver enzymes or serum bilirubin levels
6. Patients who were on phototherapy, systemic medicines or biologics for psoriasis in the last six months
7. Patients who were on any topical agents for psoriasis in the last two weeks
8. Pregnant or lactating women

The diagnosis was made clinically based on history, clinical examination, and dermoscopic examination. Biopsy was performed in cases of diagnostic dilemma. A total of 65 patients with chronic plaque psoriasis were evaluated for eligibility. Amongst them, 10 were not eligible, and 7 did not consent to participate in the study. The remaining 48 patients meeting the study criteria were enrolled. They were randomly assigned in a 1:1 ratio into two groups by block randomization. Group A received apremilast, and Group B received methotrexate. Twenty-four patients were enrolled in each group. Three patients from Group A and 4 patients from Group B did not follow up. Finally, 21 patients in Group A and 20 in Group B completed the study, which lasted 16 weeks, and were included in the efficacy and safety assessments.

Group A: Apremilast starter pack was started with a 10mg morning dose and then increased daily to 10mg until day 6. Afterwards, 30mg twice daily was prescribed, which was then continued till the end of the study.

Group B: Methotrexate 10-15mg orally once a week was given, this was continued until the end of the study. Folic acid 5 mg was given to the patients on methotrexate, once a week, a day before methotrexate, for 16 weeks.

No cross-over of the study drugs was allowed. Participants in both groups were treated with coconut oil as an add-on therapy. Blood samples were collected at baseline and follow-up visits to check complete blood count, liver, and kidney function tests. The Psoriasis Area and Severity Index (PASI) score and the Dermatology Life Quality Index (DLQI) score of each patient were noted at the baseline, four, eight, and sixteen weeks. The adverse events in both groups during the study duration were documented.

The PASI is extensively used as a measuring tool that grades the severity of psoriasis and treatment response, with scores ranging from 0 to 72. A 75% reduction in the PASI score (PASI 75) is the standard set by the FDA to assess the efficacy of psoriasis treatment.[8] The DLQI is a widely used tool that explores a 10-item questionnaire to assess the quality of life in patients suffering from skin diseases. It has a score of 0-30.[9] The higher the score, the greater the impairment in quality of life.

Sample size

The sample size was determined with a 1% significance level and 95% power of the test, using response rates of 86% for the methotrexate group and 29% for the apremilast group from a previous study.[10] This calculation yielded an initial sample size of 36. Factoring in a 10% dropout rate, the final sample size was adjusted to 40.

Data analysis

Statistical Program for Social Sciences (SPSS) version 26 was used for data analysis. The categorical data was presented as numbers (percentages). The continuous data were presented as either mean ± standard deviation. Results between the two groups were analyzed using the unpaired students t-test and chi-square test. Within-group comparison was carried out using paired students t-test. A P value of < 0.05 was considered statistically significant.

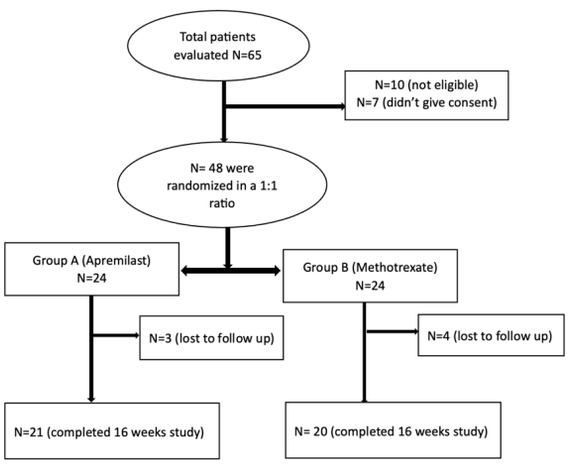

Figure:1 Showing the flow of study participants

Results

The baseline demographics of the study population are shown in Table no 1. The mean age of the study participants of Group A (Apremilast) and Group B (Methotrexate) was 44.95 ± 13.69 and 48.55 ± 11.91 years, respectively (P = 0.37). The mean duration of illness was 8.21±5.46 years and 7.11±7.09 years in Groups A and B, respectively (P = 0.57). Out of the 21 patients analyzed in Group A, 9 (42.9%) were males, and 12 (57.1%) were females. Likewise, in Group B, out of 20 patients, 10 (50%) were males and 10 (50%) were females. The mean BMI at baseline was 25.46±5.72 and 23.52±8.63 in Groups A and B, respectively (P = 0.39). The two groups were comparable at baseline.

	Group AApremilast	Group B Methotrexate	P-value
Age (years) Mean ± SD	44.95 ± 13.69	48.55 ± 11.91	0.37
Gender Male	9 (42.9%)	10 (50%)	0.64
Female	12 (57.1%)	10 (50%)	
Duration of illness	8.21±5.46	7.11±7.09	0.57
BMI	25.46±5.72	23.52±8.63	0.39

Table 1: Baseline demographics of study population

Mean PASI score	Group A (Apremilast) Mean ± SD (% reduction of PASI from baseline)	Group B (Methotrexate) Mean ± SD (% reduction of PASI from baseline)	P- value
Baseline	17.22 ± 8.61	18.64 ± 9.02	0.61
4 weeks	15.26 ± 7.81 (11%)	15.39 ± 6.89 (17%)	0.95
8 weeks	10.53 ± 6.08 (39%)	12.19 ± 6.70 (31%)	0.41
16 weeks	3.90 ± 2.92 (77%)	5.95 ± 2.89 (68.07%)	0.02
P- value	< 0.001	< 0.001	

Table 2: PASI scores of the study population at baseline and follow-up at 4, 8, and 16 weeks

Efficacy:

The PASI scores of the study population at each time point of assessment are demonstrated in Table 2. The mean baseline PASI scores of Group A and Group B were 17.22 ± 8.61 and 18.64 ± 9.02, respectively (P = 0.61). The PASI scores at baseline, 4 weeks and 8 weeks between the two groups were comparable (P > 0.05). However, the intergroup comparison showed a statistically significant difference in PASI score at 16 weeks between the two groups (P = 0.02), with group A showing a higher reduction in PASI score (77%) than group B (68.07%). The intragroup comparison showed a gradual decline of PASI in both groups at 4, 8 and 16 weeks, respectively. At 16 weeks, both groups demonstrated a highly significant decrease in PASI score from their baseline (P = <0.001).

Efficacy was assessed as a reduction in PASI score from baseline to the completion of 16 weeks.

The drug is considered efficacious if the reduction in PASI from baseline is ≥75%. PASI 75 was achieved by 11 patients (52.30 %) in the group A and 8 patients (40 %) in the group B.

Mean DLQI	Group A Apremilast (Mean ± SD)	Group B Methotrexate (Mean ± SD)	P-value
Baseline	11.47 ± 5.35	13.20 ± 5.61	0.32
4 weeks	10.06±5.07	11.20±5.77	0.50
8 weeks	5.81±3.65	7.95±4.33	0.09
16 weeks	3.76±2.64	4.19±2.97	0.62
P-value	< 0.001	< 0.001	

Table 3: DLQI scores of the study population at baseline and follow-up at 4, 8 and 16 weeks

Quality of life:

The DLQI scores of the study population at each time point of assessment are demonstrated in Table 3. The mean baseline DLQI scores of Group A and Group

B were 11.47 ± 5.35 and 13.20 ± 5.61, respectively (P = 0.32). Intergroup comparison of DLQI scores at baseline, 4, 8, and 16 weeks between the two groups were comparable. The intragroup comparison showed a gradual reduction of DLQI in both groups at 4, 8, and 16 weeks respectively. At 16 weeks, both groups demonstrated a highly significant decrease of DLQI score from their baseline (P = <0.001).

Side effects	Group A Apremilast (N=21)	Group B Methotrexate (N=20)
Headache	6 (28.5%)	3 (15%)
Nausea/vomiting	8 (33.3%)	4 (20%)
Diarrhea	3 (14.2%)	2 (10%)
Abdominal pain	4 (19%)	7 (35%)
Fatigue	4 (19%)	5 (25%)
Anemia	1 (4.7%)	7 (35%)
Altered liver enzymes	2 (10%)	8 (40%)

Table 4: Side effects of both drugs

Side effects:

The side effects profile of the study population with both drugs is illustrated in Table 4. Patients in Group B experienced a higher incidence of side effects compared to those in Group A. Group A experienced more headache, nausea, vomiting, and diarrhea as compared to Group B. Nausea and vomiting were particularly common with apremilast but were short-lived, occurring soon after taking the drug; no additional treatment was required for most patients. However, in a few cases, a dose reduction was implemented. Conversely, side effects like abdominal pain, fatigue, anemia and altered liver enzymes were experienced more by patients treated under group B. Altered liver enzymes were commonly observed with methotrexate. However, these elevations were mild in all patients and normalized after reducing the methotrexate dose for 2-3 weeks. The original dose was then resumed once normalization occurred. Other drug-related side effects were mild and were managed with symptomatic treatment.

Discussion

This study was a prospective, randomized, open-labeled study comparing the efficacy and safety of apremilast versus methotrexate after 16 weeks of intervention in patients with chronic stable plaque psoriasis. Our study revealed a highly significant decline in PASI score from baseline to 16 weeks with both apremilast and methotrexate (P = <0.001). However, the intergroup comparison between apremilast and methotrexate showed a higher reduction in PASI score with apremilast than methotrexate at 16 weeks (P = 0.02). This result was akin to a randomized trial conducted by Panda et al., that demonstrated a significant reduction of median PASI scores with apremilast and methotrexate (P = 0.002) after 24 weeks. However, the reduction was significantly higher with apremilast than with methotrexate. Their study concluded that apremilast was more effective than methotrexate in chronic plaque psoriasis.[11] The same study showed that both drugs significantly improved the quality of life of the patients with no intergroup difference (P = 0.079) at 24 weeks. This finding was compatible with our study in which both drugs demonstrated a significant reduction in DLQI scores at 16 weeks compared to their baseline, with comparable DLQI scores in each visit.

A comparative study has demonstrated that the percentage of improvement in PASI after 16 weeks of treatment for chronic plaque psoriasis was 76.8% with methotrexate and 71.5% with apremilast.[12] Their study concluded that the efficacy of methotrexate was high as compared to apremilast. In contrast, our study elucidated greater efficacy with apremilast at 16 weeks of treatment, with 77% and 68% improvement in PASI score from baseline with apremilast and methotrexate, respectively. Another single-blind, randomized, controlled study for psoriatic arthritis revealed no difference in the efficacy between methotrexate and apremilast. Both the drugs were well tolerated and had similar adverse event profiles.[13] Further, an interventional study between apremilast and methotrexate for palmoplantar psoriasis revealed significant improvement with both drugs after 16 weeks of treatment without statistically significant differences between them in terms of efficacy and safety.[14]

PASI-75 is defined as a 75% improvement from the baseline PASI score. An article published by Yélamos and Puig highlighted that with oral methotrexate, the PASI-75 response rate varies and is influenced by both the dosage and the duration of treatment (measured in weeks). With a lower dose (7.5-15mg/week), PASI-75 was achieved in 24% at week 12.[6] In our study, we gave oral methotrexate at the dose of 10-15mg/week, and 40% of patients achieved PASI-75 at week 16. Our results were comparable to the study by Saurat et al., in which 35.6% had achieved PASI-75 with methotrexate at 16 weeks of treatment.[15] Weekly doses of MTX are safe and should be used at the minimal dose necessary to control the disease.[6] However, up to 60% of patients may develop mild and reversible side effects like gastrointestinal intolerance, asthenia, arthralgias, and fever, which can be minimized with the administration of folic or folinic acid. Few patients can develop significant side effects, such as bone marrow toxicity.[6] In our study, frequently reported side effects with MTX were altered liver enzymes, anemia, and abdominal pain. However, none of these side effects were severe or fatal.

The two important phase 3 clinical trials entitled, the Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM 1) and ESTEEM 2, demonstrated that apremilast 30 mg twice daily

reduced the severity and extent of moderate-to-severe plaque psoriasis in adults at 16 weeks and these benefits were sustained over 52 weeks after treatment.[16,17] PASI-75 was achieved in 33.1% and 28.8% in ESTEEM 1 and ESTEEM 2, respectively, at 16 weeks. Also, the apremilast was generally well-tolerated, and most adverse effects occurred within the first week of dosing and self-resolved within one month. The most commonly reported adverse events were diarrhea, nausea, upper respiratory tract infection, and headache.[7,12] In contrast, our study achieved the PASI-75 in 52.3% of the study population taking apremilast at 16 weeks. Side effects like headache, nausea, and vomiting were seen in the majority of patients taking apremilast in our study.

Limitations

Our study had a few limitations. The sample size was smaller and was performed in a single-center setting. Also, the patients could only be followed up for a short time, limiting the assessment of relapse rate and long-term side effects of the drugs.

Conclusion

We conclude that apremilast was more efficacious than methotrexate in treating chronic plaque psoriasis. The quality of life improved well with both drugs. Adverse effects like nausea and vomiting were frequently reported with apremilast while, altered liver enzymes and abdominal pain were reported frequently with methotrexate. However, these side effects were mild and well tolerated.

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