

A Comparative Study on the Efficacy of Oral Methotrexate versus Oral Apremilast in Chronic Plaque Psoriasis

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Abstract:

Background: Chronic plaque psoriasis is a persistent inflammatory skin disorder associated with considerable physical and psychosocial morbidity. Methotrexate remains an established systemic treatment, whereas apremilast, an oral phosphodiesterase-4 inhibitor, provides a targeted non-biologic therapeutic option. Comparative evidence regarding their effectiveness and tolerability in routine clinical practice remains relevant.

Aim: To compare the efficacy and safety of oral methotrexate and oral apremilast in patients with chronic plaque psoriasis.

Methods: This prospective comparative study included 58 patients with chronic plaque psoriasis treated over 1.5 years. Patients were divided into two groups of 29 each. Group A received oral methotrexate 10–15 mg once weekly with folic acid supplementation, while Group B received oral apremilast, titrated to 30 mg twice daily. Disease severity was assessed using the Psoriasis Area and Severity Index (PASI), while quality of life was assessed using the Dermatology Life Quality Index (DLQI). Assessments were performed at baseline, 8, 16 and 24 weeks. Adverse events and relevant laboratory parameters were recorded.

Results: The mean baseline PASI was 18.6 ± 4.7 in the methotrexate group and 18.9 ± 4.9 in the apremilast group ($p=0.812$). At 24 weeks, PASI decreased to 5.1 ± 2.7 and 3.9 ± 2.3 , respectively ($p=0.048$). Mean percentage PASI reduction was 72.6% with methotrexate and 79.4% with apremilast ($p=0.041$). PASI-75 response was achieved by 62.1% and 72.4% of patients, respectively ($p=0.412$). DLQI improved significantly in both groups, with no significant between-group difference at 24 weeks ($p=0.286$). Gastrointestinal adverse effects were more frequent with apremilast, whereas elevated liver enzymes and nausea were more frequent with methotrexate. Apremilast demonstrated numerically greater reduction in PASI but no statistical significant difference was seen.

Conclusion: Both methotrexate and apremilast produced substantial improvement in psoriasis severity and quality of life. Apremilast demonstrated a numerically greater reduction in PASI and favorable tolerability, although both treatments remain useful systemic options depending on comorbidities, monitoring requirements and patient preference.

Keywords: Chronic Plaque Psoriasis, Methotrexate, Apremilast, PASI, DLQI, Systemic Therapy, Efficacy, Adverse Effects.

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Introduction

Psoriasis represents a persistent, immune-driven inflammatory condition distinguished by recurring red, sharply defined lesions with a characteristic silvery scale layer. Chronic plaque psoriasis constitutes the predominant clinical manifestation and can significantly impair physical function, mental health status, and overall quality of life. Although the condition primarily affects the skin, psoriasis is now recognized as a systemic inflammatory disorder linked to various comorbid

conditions such as obesity, type 2 diabetes mellitus, hypertension, abnormal lipid profiles, cardiovascular pathology, and psoriatic arthritis. As a result, therapeutic interventions target not merely the amelioration of cutaneous manifestations but also the reduction of overall disease impact and enhancement of health-related quality of life. Therapeutic approaches are determined by disease severity, distribution extent, prior therapeutic interventions, concurrent medical conditions, and

individual patient preferences. Standard systemic treatment modalities encompass methotrexate, cyclosporine, and acitretin, whereas contemporary targeted oral agents and biologic therapeutics have broadened the therapeutic armamentarium [1, 2].

Methotrexate continues to be extensively utilized due to its demonstrated effectiveness, cost-effectiveness, and substantial clinical evidence base. The medication functions through immunomodulatory and anti-inflammatory mechanisms via suppression of folate-dependent enzymatic pathways and augmentation of extracellular adenosine-mediated signaling. Nevertheless, therapeutic administration necessitates rigorous clinical monitoring, as potential complications including hepatic toxicity, hematologic derangements, and gastrointestinal side effects may develop. Apremilast is an oral small-molecule phosphodiesterase-4 inhibitor that elevates intracellular cyclic adenosine monophosphate levels and regulates the production of inflammatory mediators. It has demonstrated clinical efficacy in treating moderate-to-severe plaque psoriasis and provides the practical benefit of oral dosing without the routine laboratory monitoring obligations associated with methotrexate [3, 4].

Meta-analytical evidence has established that apremilast produces significantly superior PASI responses relative to placebo. Direct comparative assessments between these two therapeutic agents are particularly valuable because both represent oral systemic treatment options yet differ markedly in their mechanisms of action, monitoring prerequisites, and adverse-effect profiles. A randomized controlled trial conducted in India at SCB Medical College, Cuttack, evaluated methotrexate and apremilast across a 24-week period and demonstrated greater PASI improvement with apremilast, whereas DLQI improvement was comparable between treatment groups. A comprehensive network meta-analysis has similarly indicated that methotrexate and apremilast may demonstrate equivalent effectiveness for certain outcomes, though distinctions become apparent when considering specific PASI threshold levels [5].

Despite increasing availability of targeted oral therapies, real-world comparative data remain valuable, particularly in Indian dermatology practice. The present study was therefore undertaken to compare the efficacy, quality-of-life improvement and tolerability of oral methotrexate and oral apremilast in patients with chronic plaque psoriasis.

Objectives

1. To compare the efficacy of oral methotrexate and oral apremilast using PASI.
2. To compare improvement in quality of life using DLQI.

3. To compare PASI-50, PASI-75 and PASI-90 responses between treatment groups.
4. To compare the safety and adverse-effect profiles of both treatments.
5. To evaluate changes in relevant laboratory parameters during treatment.

Materials and Methods

Study design and setting: This was a prospective comparative observational study conducted in the Department of Dermatology at Mahatma Gandhi Memorial Medical College and Hospital over a period of 1.5 years.

A total of 58 patients with chronic plaque psoriasis were included.

Patients were allocated into two groups:

- **Group A:** Oral methotrexate, n=29
- **Group B:** Oral apremilast, n=29

Inclusion criteria

Patients were included if they:

- Were aged ≥ 18 years.
- Had clinically diagnosed chronic plaque psoriasis.
- Had moderate-to-severe disease requiring systemic treatment.
- We're willing to receive either methotrexate or apremilast.
- Provided written informed consent.
- Were available for follow-up.

Exclusion criteria

Patients were excluded if they had:

- Other forms of psoriasis requiring different treatment strategies.
- Significant hepatic or renal dysfunction.
- Active tuberculosis or other serious infection.
- Pregnancy or lactation.
- Previous intolerance to either study drug.
- Concomitant systemic antipsoriatic therapy.
- Uncontrolled psychiatric illness.
- Patients unable to complete scheduled follow-up.

Treatment protocol

Group A: Methotrexate: Patients received oral methotrexate 10 mg once weekly, with escalation to 15 mg weekly according to clinical response and tolerance. Folic acid supplementation was provided according to institutional practice.

Group B: Apremilast: Apremilast was initiated using the standard dose-escalation schedule and subsequently maintained at 30 mg twice daily as tolerated.

Both groups received standard supportive skin care and emollients.

Assessment of efficacy: Disease severity was assessed using the Psoriasis Area and Severity Index (PASI) at:

- Baseline
- 8 weeks
- 16 weeks
- 24 weeks

Treatment response was categorized as PASI-50, PASI-75 and PASI-90 according to the percentage reduction from baseline PASI.

Quality-of-life Assessment: The Dermatology Life Quality Index (DLQI) was assessed at baseline and at 8, 16 and 24 weeks.

Safety Assessment: Patients were questioned regarding adverse effects at each follow-up visit. Hemoglobin, total leukocyte count, platelet count, liver function tests and renal function tests were assessed according to treatment requirements.

Statistical Analysis: Data were analyzed using SPSS version 26.0. Continuous variables were expressed as mean $\pm$ SD, while categorical variables were presented as frequency and percentage. Independent-samples t-test was used for comparison of continuous variables between groups. Chi-square/Fisher's exact test was used for categorical variables. Repeated-measures analysis was used for changes over time where appropriate. A p-value <0.05 was considered statistically significant.

Results

Table 1: Baseline demographic and clinical characteristics

Parameter	Methotrexate (n=29)	Apremilast (n=29)	p-value
Age, years	42.3 $\pm$ 10.1	40.8 $\pm$ 9.7	0.568
Male, n (%)	18 (62.1)	17 (58.6)	0.791
Female, n (%)	11 (37.9)	12 (41.4)	0.791
Disease duration, years	7.1 $\pm$ 3.8	6.8 $\pm$ 3.5	0.752
Family history, n (%)	8 (27.6)	7 (24.1)	0.766
Hypertension, n (%)	6 (20.7)	5 (17.2)	0.739
Diabetes mellitus, n (%)	4 (13.8)	3 (10.3)	0.688
Baseline PASI	18.6 $\pm$ 4.7	18.9 $\pm$ 4.9	0.812
Baseline DLQI	19.8 $\pm$ 4.6	20.2 $\pm$ 4.8	0.748

The two treatment groups were comparable at baseline with respect to demographic characteristics, disease duration, PASI and DLQI.

Table 2: Change in PASI score during follow-up

Time point	Methotrexate	Apremilast	p-value
Baseline	18.6 $\pm$ 4.7	18.9 $\pm$ 4.9	0.812
8 weeks	13.2 $\pm$ 4.1	12.1 $\pm$ 3.8	0.291
16 weeks	8.4 $\pm$ 3.2	7.0 $\pm$ 2.8	0.081
24 weeks	5.1 $\pm$ 2.7	3.9 $\pm$ 2.3	0.048
Mean percentage reduction	72.6 $\pm$ 12.4%	79.4 $\pm$ 10.7%	0.041

Both treatments produced significant reductions in PASI over time, with a greater reduction observed in the apremilast group at 24 weeks.

Table 3: PASI response at 24 weeks

Treatment response	Methotrexate (n=29)	Apremilast (n=29)	p-value
PASI-50, n (%)	24 (82.8)	27 (93.1)	0.226
PASI-75, n (%)	18 (62.1)	21 (72.4)	0.412
PASI-90, n (%)	9 (31.0)	13 (44.8)	0.282
PASI-100, n (%)	3 (10.3)	5 (17.2)	0.445
PASI <5 at 24 weeks, n (%)	19 (65.5)	23 (79.3)	0.248

Although response rates were numerically higher with apremilast, differences in categorical PASI responses were not statistically significant.

Table 4: Change in DLQI during treatment

Time point	Methotrexate	Apremilast	p-value
Baseline	19.8 $\pm$ 4.6	20.2 $\pm$ 4.8	0.748
8 weeks	13.7 $\pm$ 4.0	14.1 $\pm$ 4.2	0.707
16 weeks	8.1 $\pm$ 3.4	7.5 $\pm$ 3.1	0.482
24 weeks	4.2 $\pm$ 2.6	3.7 $\pm$ 2.4	0.286
Mean reduction	15.6 $\pm$ 4.1	16.5 $\pm$ 4.3	0.424

Both treatments produced significant improvement in quality of life, with no statistically significant difference between groups at 24 weeks.

Table 5: Adverse effects during treatment

Adverse event	Methotrexate (n=29)	Apremilast (n=29)	p-value
Nausea/vomiting	5 (17.2)	2 (6.9)	0.228
Diarrhea	1 (3.4)	6 (20.7)	0.045
Headache	2 (6.9)	4 (13.8)	0.390
Fatigue	4 (13.8)	3 (10.3)	0.688
Elevated liver enzymes	4 (13.8)	1 (3.4)	0.157
Anemia	2 (6.9)	0 (0.0)	0.149
Treatment discontinuation	2 (6.9)	1 (3.4)	0.554

Gastrointestinal adverse effects, particularly diarrhea, were more frequent with apremilast, while laboratory abnormalities were more commonly observed with methotrexate.

Discussion

The present prospective comparative study evaluated the efficacy and tolerability of oral methotrexate and apremilast in 58 patients with chronic plaque psoriasis. Both treatments produced substantial improvements in disease severity and quality of life over 24 weeks. Apremilast demonstrated a numerically greater reduction in PASI, while improvement in DLQI was comparable between the two groups. The baseline demographic and clinical characteristics of both treatment groups demonstrated substantial similarity, encompassing age, disease duration, baseline Psoriasis Area and Severity Index (PASI), and Dermatology Life Quality Index (DLQI) scores. This baseline equivalence is critical for the valid interpretation of subsequent disparities in therapeutic outcomes [6].

The mean baseline PASI score approximated 19 across both groups, reflecting a patient population with clinically meaningful disease severity that warranted systemic therapeutic intervention. At the 24-week assessment point, both treatment groups exhibited substantial reductions in PASI scores. The percentage reduction achieved was 72.6% in the methotrexate cohort and 79.4% in the apremilast cohort, representing a statistically significant difference in mean percentage reduction. These observations align with findings from a randomized controlled trial conducted in India by Panda et al., which evaluated apremilast and methotrexate over an identical 24-week period and demonstrated significantly superior median PASI improvement with apremilast. In that investigation, the median PASI change was -37.25 for apremilast compared with -34.75 for methotrexate ($p=0.006$). Conversely, categorical PASI response rates in the current investigation revealed no statistically significant differences between groups [7].

Although PASI-75 and PASI-90 response rates demonstrated numerically higher values in the apremilast group, the sample size of 58 participants may have lacked sufficient statistical power to establish statistically significant differences. This observation is consistent with existing literature

demonstrating that treatment efficacy comparisons may yield variable conclusions depending on the specific efficacy threshold employed. A network meta-analysis indicated no meaningful difference between apremilast and methotrexate across certain efficacy measures, whereas subsequent analyses have identified methotrexate as superior to apremilast for attaining PASI-90 response in particular comparative assessments. Both treatment groups exhibited substantial improvements in DLQI scores. Notably, no statistically significant difference was observed between the groups at the 24-week assessment point. This result is consistent with findings from an Indian randomized controlled trial, wherein the median DLQI reduction demonstrated no significant difference between apremilast and methotrexate treatment arms ($p=0.079$) [8, 9].

Consequently, enhancements in cutaneous disease severity do not necessarily correspond to proportional differences in quality-of-life outcomes between treatment modalities. The adverse-effect profiles demonstrated distinct differences between the two therapeutic agents. Diarrhea occurred with significantly greater frequency in the apremilast group, whereas elevated hepatic enzymes and anemia were predominantly associated with methotrexate administration. This differential pattern aligns with established pharmacological mechanisms and underscores the distinct monitoring protocols required for these oral systemic medications. Systematic reviews have established that apremilast maintains an acceptable safety profile overall, despite a higher incidence of adverse events relative to placebo. In summary, both therapeutic agents demonstrated clinically significant benefits. These findings advocate for individualized therapeutic selection informed by disease severity, presence of comorbid conditions, monitoring requirements, tolerability considerations, and patient preference [10].

Conclusion

This prospective comparative study demonstrated that both oral methotrexate and apremilast effectively reduced disease severity and improved quality of life in patients with chronic plaque psoriasis over 24 weeks. Apremilast demonstrated a superior average decrease in PASI scores and

showed numerically greater PASI-50, PASI-75, and PASI-90 response rates, though Apremilast demonstrated numerically greater reduction in PASI but no statistical significant difference was seen. Both therapeutic agents resulted in marked and equivalent enhancements in DLQI measurements. The adverse event profiles exhibited notable differences, with gastrointestinal side effects occurring more frequently in the apremilast group and laboratory abnormalities, including hepatic enzyme elevation and anemia, manifesting more commonly in the methotrexate group.

These results underscore the importance of tailoring systemic therapy selection according to disease severity, underlying comorbid conditions, safety considerations, monitoring obligations, financial implications, and individual patient preferences. The investigation is constrained by its limited participant population, single-institution setting, observational methodology, and 24-week observation period. Expanded multicenter investigations are necessary to validate these observations and assess extended clinical outcomes.

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