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***Original Research Article***

# Efficacy of Methotrexate and Methotrexate with Apremilast in Patients with Chronic Plaque Psoriasis

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**Abstract:** *Chronic plaque psoriasis is a prevalent, immune-mediated dermatological disorder characterized by hyperproliferation and inflammation of the skin, leading to significant physical and psychological burden. Although methotrexate remains a cornerstone in systemic therapy for moderate to severe psoriasis, its efficacy may be limited in certain patients. The addition of apremilast, a phosphodiesterase-4 inhibitor, has emerged as a potential combination therapy to enhance treatment outcomes and minimize adverse effects.* ***Objective:*** *To determine the efficacy of methotrexate and methotrexate with apremilast in patients with chronic plaque psoriasis.* ***Methodology:*** *This study was carried out on 68 participants, presenting with chronic plaque psoriasis, which was diagnosed clinically and via histopathological assessment, divided equally into two groups. Group A received methotrexate (10 mg weekly) while Group B received methotrexate with apremilast after 12 weeks treatment. Mean reduction in PASI scores from the baseline after 12 weeks were recorded.* ***Results:*** *The results demonstrated a substantial reduction in PASI scores in Group B (methotrexate + apremilast) showing a greater mean reduction (10.64 ± 3.79) compared to Group A (13.72 ± 5.09) indicating enhanced efficacy with combination therapy ($p < 0.05$).* ***Conclusion:*** *The combination of methotrexate and apremilast was more effective than methotrexate alone in chronic plaque psoriasis in terms of mean reduction in PASI scores from the baseline.*

**Keywords:** Chronic plaque psoriasis, methotrexate, apremilast, PASI score

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## Introduction

Psoriasis is an ongoing inflammatory disorder that affects the skin in people who are predisposed to it. Nearly 2% of the overall population is affected, with over 50% of those affected presenting within the first three decades of life. (1-3) Chronic psoriasis unveils a diverse range of cutaneous manifestations in lesions that can vary from small, identifiable spots to extensive plaques, as well as, in some cases, erythroderma. The plaque type is the most prevalent and widely acknowledged morphological presentation of psoriasis. The lesions signal skin inflammation and angiogenesis, caused by dysregulated skin immune system reactions. Altered immunity could operate systemically, with indications of inflammation observable in areas beyond skin (4,5). Consequently, in patients with the condition, inflammation is extensive, and various comorbid conditions frequently coexist. Psoriasis is a common condition, displaying a global prevalence of up to 8%. In roughly one-third of instances, the onset occurs during childhood. Recent years have witnessed an apparent rise in the rate of childhood psoriasis. (6,7)
Methotrexate functions by preventing DNA synthesis through blockade of dihydrofolate reductase, consequently halting cellular reproduction within psoriatic lesions and contributing to hyper-proliferation noticed in psoriasis. (8,9) The drug's effect usually shows up within 4-8 weeks.. On the other hand, Apremilast is a novel drug used to manage psoriatic arthritis and psoriasis, and it is noteworthy for being the first oral medication approved by the FDA for psoriasis treatment. Apremilast is classified as a PDE4 inhibitor, acting intracellularly by enhancing the synthesis of anti-inflammatory mediators while reducing the generation of pro-inflammatory mediators. (10-13) A study compared methotrexate and methotrexate with apremilast in patients with chronic plaque psoriasis; the reduction in the severity of disease was observed in the methotrexate group (13.72+5.09) and in the methotrexate with apremilast group (10.64+3.79). (14)

Psoriasis is a chronic inflammatory skin disorder affecting millions of individuals worldwide, with chronic plaque psoriasis being the most prevalent form. Managing this condition poses a significant challenge, necessitating the exploration of various treatment modalities. However, due to the paucity of literature on this subject locally, the goal of this study is to compare the efficacy of methotrexate and apremilast in patients with chronic plaque psoriasis. The results of this study will help our medical professionals to unfold a deeper understanding of the optimal use of methotrexate and methotrexate with apremilast in psoriasis treatment, which will undoubtedly pave the way for more personalized and effective therapeutic strategies. Additionally, the investigations will explore various aspects, including the optimal dosage, treatment duration, and the patient populations that may benefit the most from this treatment approach.

## Methodology

This study was conducted at the Dermatology Department of Lady Reading Hospital, Peshawar, employing a randomized controlled trial design. The research commenced after obtaining ethical approval from the institute, covering the period from 09-March-2024 to 09-September-2024. Sixty-eight patients diagnosed with chronic plaque psoriasis were enrolled, with 34 participants allocated to each group using non-probability consecutive sampling and blocked randomization techniques. The sample size was calculated based on the previous values of mean PASI score (13.72±5.09)14 in the methotrexate group and (10.64±3.79)14 in the methotrexate with apremilast group in patients with chronic plaque psoriasis, with a power of 80% and a confidence interval of 95%. Consent was secured from all patients.
Data collection involved recording demographic details such as age, gender, BMI, education, profession, socioeconomic status, and residence. A structured proforma was used to document clinical assessments, which

were conducted under the supervision of a consultant with at least five years of post-fellowship experience.

Participants included adults aged 18 to 65 years diagnosed with chronic plaque psoriasis, defined clinically by the presence of erythematous, silvery-scaled plaques that have persisted for ≥12 weeks, confirmed via histopathology showing acanthosis, parakeratosis, and elongated rete ridges. At the same time, those with tinea corporis, dermatomyositis, or chronic liver/renal diseases were not selected. Group A received oral methotrexate at a dosage of 10 mg once weekly for 12 weeks, while Group B received a combination of methotrexate (10 mg weekly) and apremilast (administered via a starter pack) for the same duration. Efficacy was assessed by comparing the mean reduction in Psoriasis Area and Severity Index (PASI) scores from baseline to 12 weeks post-treatment.

Statistical analysis was performed with SPSS 27. Mean and SD were used for age, BMI, baseline PASI score, and mean reduction in PASI score. For the other aforementioned demographic variables, we used frequency and percentages. The t-test was used to assess the mean reduction in PASI score in both groups, and the same test was used to stratify the mean reduction in PASI score by demographics. We kept the P value significant at ≤ 0.05.

**Results**

Sixty-eight participants were included, evenly divided into two groups: Group A (methotrexate alone) and Group B (methotrexate with apremilast), each comprising 34 cases. The mean age of participants in Group A was 38.94±11.47 years and in Group B 40.74±12.74 years. Body mass index (BMI) in group A was 25.65±1.41 kg/m² and in Group B: 25.23±1.62 kg/m². Baseline PASI scores were 20.59±4.49 for Group A and 22.71±4.25 for Group B.

Demographic characteristics revealed a balanced distribution of gender, with males 21 (61.8%) in Group A and 20 (58.8%) in Group B, while females were 13 (38.2%) and 14 (41.2%), respectively. (Table 1).

The primary outcome was the mean reduction in PASI score, calculated by subtracting the PASI score at the 12th week from the baseline in both groups, demonstrating a substantial difference between the groups. Group A achieved a reduction of 6.55±4.09, whereas Group B showed a markedly greater reduction of 11.02±4.37 (p = 0.0001). Stratifications are presented from table no 3 to table no 9.

**Table 1: Demographics**

| Demographics | | Groups | | | |
|---|---|---|---|---|---|
| | | Group A (Methotrexate) | | Group B (Methotrexate with Apremilast) | |
| | | n | % | n | % |
| Gender | Male | 21 | 61.8% | 20 | 58.8% |
| | Female | 13 | 38.2% | 14 | 41.2% |
| Education | Educated | 18 | 52.9% | 20 | 58.8% |
| | Uneducated | 16 | 47.1% | 14 | 41.2% |
| Occupation | Labour | 3 | 8.8% | 4 | 11.8% |
| | Office job | 21 | 61.8% | 15 | 44.1% |
| | Business | 8 | 23.5% | 9 | 26.5% |
| | Other | 2 | 5.9% | 6 | 17.6% |
| Socioeconomic background | Lower Class | 10 | 29.4% | 7 | 20.6% |
| | Middle class | 20 | 58.8% | 18 | 52.9% |
| | Upper class | 4 | 11.8% | 9 | 26.5% |
| Residence area | Urban | 18 | 52.9% | 23 | 67.6% |
| | Rural | 16 | 47.1% | 11 | 32.4% |

**Table 2: Comparison of mean reduction in PASI score in both groups**

| Mean reduction in PASI score | Groups | N | Mean | Std. Deviation | P value |
|---|---|---|---|---|---|
| | Group A (Methotrexate) | 34 | 6.5588 | 4.09872 | 0.0001 |
| | Group B (Methotrexate with Apremilast) | 34 | 11.0294 | 4.37960 | |

**Table 3: Stratification of comparison of mean reduction in PASI score in both groups with age**

| Age distribution (Years) | | Groups | N | Mean | Std. Deviation | P value |
|---|---|---|---|---|---|---|
| 18 to 35 | Mean reduction in PASI score | Group A (Methotrexate) | 16 | 7.1875 | 4.21456 | 0.0001 |
| | | Group B (Methotrexate with Apremilast) | 14 | 13.0000 | 3.76216 | |
| 36 to 50 | Mean reduction in PASI score | Group A (Methotrexate) | 11 | 5.3636 | 3.52910 | 0.02 |
| | | Group B (Methotrexate with Apremilast) | 12 | 10.0000 | 5.08116 | |
| > 50 | Mean reduction in PASI score | Group A (Methotrexate) | 7 | 7.0000 | 4.83046 | 0.32 |
| | | Group B (Methotrexate with Apremilast) | 8 | 9.1250 | 3.13676 | |

**Table 4: Stratification of comparison of mean reduction in PASI score in both groups by gender**

| Gender | | Groups | N | Mean | Std. Deviation | P value |
|---|---|---|---|---|---|---|
| Male | Mean reduction in PASI score | Group A (Methotrexate) | 21 | 6.1905 | 4.15474 | 0.0001 |
| | | Group B (Methotrexate with Apremilast) | 20 | 11.9000 | 4.61006 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Female | Mean reduction in PASI score | Group A (Methotrexate) | 13 | 7.1538 | 4.09972 | 0.0001 |
| | | Group B (Methotrexate with Apremilast) | 14 | 9.7857 | 3.84665 | |

**Table 5: Stratification of comparison of mean reduction in PASI score in both groups with education**

| Education | | Groups | N | Mean | Std. Deviation | P value |
|---|---|---|---|---|---|---|
| Educated | Mean reduction in PASI score | Group A (Methotrexate) | 18 | 6.5556 | 3.83823 | 0.0001 |
| | | Group B (Methotrexate with Apremilast) | 20 | 12.0500 | 4.16091 | |
| Uneducated | Mean reduction in PASI score | Group A (Methotrexate) | 16 | 6.5625 | 4.50139 | 0.07 |
| | | Group B (Methotrexate with Apremilast) | 14 | 9.5714 | 4.41526 | |

**Table 6: Stratification of comparison of mean reduction in PASI score in both groups with occupation**

| Occupation | | Groups | N | Mean | Std. Deviation | P value |
|---|---|---|---|---|---|---|
| Labour | Mean reduction in PASI score | Group A (Methotrexate) | 3 | 3.6667 | 1.52753 | 0.001 |
| | | Group B (Methotrexate with Apremilast) | 4 | 11.2500 | 1.25831 | |
| Office job | Mean reduction in PASI score | Group A (Methotrexate) | 21 | 6.5238 | 4.62189 | 0.007 |
| | | Group B (Methotrexate with Apremilast) | 15 | 11.1333 | 5.01237 | |
| Business | Mean reduction in PASI score | Group A (Methotrexate) | 8 | 7.1250 | 3.39905 | 0.12 |
| | | Group B (Methotrexate with Apremilast) | 9 | 9.8889 | 3.58624 | |
| Other | Mean reduction in PASI score | Group A (Methotrexate) | 2 | 9.0000 | 1.41421 | 0.45 |
| | | Group B (Methotrexate with Apremilast) | 6 | 12.3333 | 5.50151 | |

**Table 7: Stratification of comparison of mean reduction in PASI score in both groups with socioeconomic status**

| Socioeconomic background | | Groups | N | Mean | Std. Deviation | P value |
|---|---|---|---|---|---|---|
| Lower Class | Mean reduction in PASI score | Group A (Methotrexate) | 10 | 5.4000 | 4.08792 | 0.007 |
| | | Group B (Methotrexate with Apremilast) | 7 | 11.2857 | 3.35233 | |
| Middle class | Mean reduction in PASI score | Group A (Methotrexate) | 20 | 7.2000 | 3.99473 | 0.01 |
| | | Group B (Methotrexate with Apremilast) | 18 | 10.4444 | 3.77643 | |
| Upper class | Mean reduction in PASI score | Group A (Methotrexate) | 4 | 6.2500 | 5.12348 | 0.13 |
| | | Group B (Methotrexate with Apremilast) | 9 | 12.0000 | 6.20484 | |

**Table 8: Stratification of comparison of mean reduction in PASI score in both groups with residence**

| Residence area | | Groups | N | Mean | Std. Deviation | P value |
|---|---|---|---|---|---|---|
| Urban | Mean reduction in PASI score | Group A (Methotrexate) | 18 | 6.8333 | 4.31482 | 0.01 |
| | | Group B (Methotrexate with Apremilast) | 23 | 10.4783 | 4.44020 | |
| Rural | Mean reduction in PASI score | Group A (Methotrexate) | 16 | 6.2500 | 3.95811 | 0.001 |
| | | Group B (Methotrexate with Apremilast) | 11 | 12.1818 | 4.21469 | |

**Table 9: Stratification of comparison of mean reduction in PASI score in both groups with BMI**

| BMI (Kg/m2) | | Groups | N | Mean | Std. Deviation | P value |
|---|---|---|---|---|---|---|
| 18 to 24.99 | Mean reduction in PASI score | Group A (Methotrexate) | 11 | 7.5455 | 3.61562 | 0.01 |
| | | Group B (Methotrexate with Apremilast) | 16 | 11.8125 | 4.60751 | |
| 25 to 29.99 | Mean reduction in PASI score | Group A (Methotrexate) | 23 | 6.0870 | 4.30553 | 0.003 |
| | | Group B (Methotrexate with Apremilast) | 18 | 10.3333 | 4.17274 | |

**Discussion**

In our study, the mean reduction in PASI scores was notably higher in the combination therapy group (Group B: 11.02±4.37) compared to methotrexate monotherapy (Group A: 6.55±4.09) (P = 0.0001). This

finding is consistent with the results of Hassanandani et al., who observed a marked improvement in PASI scores in patients receiving combination therapy for palmoplantar psoriasis. Their study reported a 43% achievement of m-PPPASI-75 in the combination group compared to 30% in the methotrexate-only group, underscoring the superior efficacy of the combined approach. (15) Similarly, Srivastava et al. found that the combination of methotrexate and apremilast led to an 89.4% improvement in PASI scores over 12 weeks compared to 65.1% with methotrexate alone, further supporting our results. (14)

The demographic characteristics of our study participants, such as mean age and gender distribution, were comparable to those in other studies. For instance, Shetty et al. (2018) reported a mean age of 39.78±2.07 years in their methotrexate group and 39.42±3.15 years in the apremilast group, with a male predominance in both groups. (16) These similarities suggest that our cohort was representative of the broader population studied in other trials, reinforcing the generalizability of our findings.

The safety profiles of Apremilast have shown that 31.3% of patients experienced treatment-related adverse effects, primarily gastrointestinal disorders, leading to discontinuation in only 11.6% of cases, as documented by Khan et al.(17). Hassanandani et al noted that diarrhea and nausea were the most common side effects in their combination group, yet these did not impact treatment adherence. (15) The tolerability of apremilast, as highlighted in these studies, suggests that it can be safely combined with methotrexate without exacerbating adverse effects.

Hassanandani et al assessed Quality of life improvements as measured by tools like the Dermatology Life Quality Index. They reported a notable reduction in DLQI scores in their combination group (5.26±1.43) compared to methotrexate alone (6.80±2.15). The Palmoplantar Quality of Life Index (ppQLI) also showed greater improvement in the combination group, particularly for hand involvement, which is critical for patients' daily functioning. (15) These results highlight the holistic benefits of combination therapy extending beyond clinical metrics to encompass patient-reported outcomes.

Comparatively, the study by Khurram et al. evaluated methotrexate versus apremilast monotherapy and found apremilast to be more effective, achieving a 58% reduction in PASI scores compared to 52% for methotrexate. (18) However, their study did not explore the combination of the two drugs, which our research and others have shown to yield superior outcomes. This suggests that while apremilast alone may outperform methotrexate, their combination offers additive or synergistic benefits, particularly in resistant cases.

Our findings also resonate with the mechanistic rationale for combining these therapies. Methotrexate, which is a dihydrofolate reductase inhibitor, reduces cellular proliferation and inflammation, while apremilast, a PDE4 inhibitor, modulates immune responses by increasing anti-inflammatory cytokines. This dual mechanism likely explains the enhanced efficacy observed in our and other studies. In light of these comparisons, our study contributes to the developing evidence that methotrexate and apremilast combination therapy is a viable and effective option for moderate to severe chronic plaque psoriasis.

## Conclusion

We conclude that the efficacy, measured by the mean reduction in PASI score from baseline, was substantially better in the methotrexate with apremilast group than in the methotrexate alone group. Further studies shall explore the efficacy of a longer follow-up duration.

## Declarations

**Data Availability statement**
All data generated or analysed during the study are included in the manuscript.

**Ethics approval and consent to participate**
Approved by the department concerned. (IRB-38/LRH/MTI)

**Consent for publication**
Approved

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**Conflict of interest**

The authors declared the absence of a conflict of interest.

**Author Contribution**

**A (Postgraduate Resident)**
*Data Collection, Manuscript review, Manuscript drafting and final approval of draft*
**SMN (Professor)**
*Supervision, Development of Research Methodology Design, Critical guidance, and final approval of draft*
**MMP (Professor)**
*Literature review, and Critical input*
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*All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.*

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