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Original Research Article

# Effectiveness of Methotrexate and Apremilast in the Management of Moderate to Severe Plaque Psoriasis: A Comparative Study

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**Abstract:**

**Introduction:** Psoriasis chronic inflammatory skin disorder typically characterized by erythematous papules and plaques. Methotrexate acts by inhibiting dihydrofolic reductase enzyme and apremilast is an oral phosphodiesterase-4 inhibitor, which are effective in the management of moderate to severe psoriasis. The current study was aimed to evaluate the effectiveness of methotrexate and apremilast in treating moderate to severe plaque psoriasis.

**Material and methods:** A total of 52 participants of both genders with moderate to severe plaque psoriasis attending outpatient department aged between 18 to 60 years were included. Participants were randomly divided in to group 1 (n=26) medicated with 7.5 mg Methotrexate per week and group 2 (n=26) medicated with Apremilast with a started dose of 10 mg and titrated to a maximum dose of 30 mg two time in a day. The participants were assessed for treatment response and adverse effects for a period of 4 months. The severity of psoriasis was assessed by psoriasis are severity index (PASI).

**Results:** The mean age of onset was 36.7 years in group 1 and 35.28 years in group 2. 73.1% were suffering with <2 years and 46.2% were suffering with >2 years. SCALP was commonly affected part (80.8% each), followed by nails (61.5% & 57.7%), palm and sole (26.9% & 30.76%). 84.61% and 80.76% patients were achieved PASI75 in group 1 and 2 respectively. Headache is common adverse event followed by nausea, vomiting and lower abdomen pain. 3.84% of patients

**Conclusion:** Methotrexate and Apremilast did not show significant difference in achieving PASI75 at the end of 4$^{th}$ month of treatment and are equally efficacious in the management of moderate to severe grade psoriasis.

**Keywords:** Methotrexate, Apremilast, Psoriasis, Efficacy, Psoriasis are severity index (PASI).



## Introduction

Psoriasis is chronic, heterogenous, papulosquamous disease influencing around 2-3% of global population [1]. Due to India's unique combination of wet and dry tropical weather, the prevalence of chronic plaque psoriasis has increased over the past ten years [2, 3]. In India, the annual incidence of psoriasis ranges from 0.44% to 2.2% [3].

Patients with psoriasis have greater impairments in social life, psychological health and quality of life. A novel oral

small molecule phosphodiesterase 4 inhibitor called apremilast has been given the go-ahead to treat adults with psoriasis and psoriatic arthritis. Two phase III clinical trials (ESTEEM and PALACE) have proven the efficacy [4, 5]. Regardless of gender or age, methotrexate is the preferred systemic treatment for mild to severe plaque psoriasis, psoriatic arthritis, and pustular psoriasis. Dihydrofolate reductase (DHFR) activity is impaired, and folic acid activation is interfered with. It limits epithelial hyperplasia, supports the death of T cells that have been activated, and prevents neutrophil chemotaxis by stopping DNA synthesis. Additionally, it is reducing the production of interleukin-1 (IL-1 [6, 7] and tumour necrosis factor (TNF).According to its severity, psoriasis is categorised as mild, affecting 3% or less of the body, moderate, affecting 3–10% of the body, and severe [8]. The psoriasis area severity index (PASI) instrument was used to gauge this severity. The PASI evaluates the lesions' severity and the affected region [9]. Gender, age, demographics, length of time with the ailment, severity of the condition, mode of therapy, and dose of medications are some of the factors that affect how psoriasis is managed [10, 11]. The goal of the current study was to evaluate the effectiveness of methotrexate and apremilast in treating moderate to severe plaque psoriasis.

## Material and Methods

The present prospective comparative study was conducted in the Department of Dermatology at Ayaan Institute of Medical Sciences, Moinabad, Telangana during September 2021 to April 2023. A total of 52 participants of both genders with moderate to severe plaque psoriasis attending outpatient department aged between 18 to 60 years were included. Participants with diabetes mellitus, pregnancy, lactation, pulmonary tuberculosis, alcohol dependents, hypertension, cardiovascular, renal complications and obesity were excluded. Written informed consent was obtained from all the participants and study protocol was approved by the institutional ethics committee.

The sociodemographic details of participants were collected and advised for basic laboratory investigations. The severity of psoriasis was assessed by psoriasis are severity index (PASI). Study participants were randomly divided in to two groups. Group 1 (n=26) was administered with 7.5 mg Methotrexate per week and group 2 (n=26) was administered with Apremilast with a started dose of 10 mg and titrated to a maximum dose of 30 mg two time in a day. The participants were assessed for treatment response and adverse effects for a period of 4 months. The outcome of psoriasis was assessed by using psoriasis are severity index. The participants were followed up at least for 6 months after the treatment procedure to check the remission and relapse. The collected data was analysed by using SPSS version 23.0. Categorical variables were represented in frequency and percentages. Comparative analysis was conducted using fisher's exact test. $P<0.05$ was considered as statistical significance.

## Results

**Table 1: Socio-demographic details of study participants**

| Parameter | Group 1 (n=26) | | Group 2 (n=26) | | p-value |
|---|---|---|---|---|---|
| | Frequency | Percentage | Frequency | Percentage | |
| **Age (In years)** | | | | | |
| 18-30 | 03 | 11.5% | 01 | 3.84% | 0.325 |
| 31-40 | 06 | 23.07% | 14 | 53.84% | |
| 41-50 | 09 | 34.61% | 07 | 26.92% | |
| 51-60 | 08 | 30.76% | 04 | 15.38% | |

| | | | | | |
|---|---|---|---|---|---|
| **Gender** | | | | | |
| Male | 16 | 61.54% | 15 | 57.7% | 0.672 |
| Female | 10 | 38.46% | 11 | 42.3% | |
| Weight (In Kg) | 74.38 | | 72.56 | | 0.0941 |
| BMI (kg/m$^2$) | 26.01 | | 24.80 | | 1.852 |
| **Onset of illness** | | | | | |
| Below 30 | 06 | 23.1% | 05 | 19.2% | 0.104 |
| 31-45 | 13 | 50% | 15 | 57.7% | |
| >45 | 07 | 26.9% | 06 | 23.1% | |
| **Time period of illness (In years)** | | | | | |
| Below 2 | 19 | 73.1% | 12 | 46.2% | 0.0286 |
| Above 2 | 07 | 26.9% | 14 | 53.8% | |

**Table 2: Details of different body parts involved in psoriasis lesions**

| Parameter | Group 1 (n=26) | | Group 2 (n=26) | | p-value |
|---|---|---|---|---|---|
| | Frequency | Percentage | Frequency | Percentage | |
| SCALP | 21 | 80.8% | 21 | 80.8% | 0.750 |
| Nails | 16 | 61.5% | 15 | 57.7% | 0.694 |
| Palm & sole | 07 | 26.9% | 08 | 30.76% | 0.885 |
| External genitalia | 06 | 23.1% | 03 | 11.5% | 0.098 |
| Joints | 03 | 11.5% | 02 | 7.7% | 0.322 |

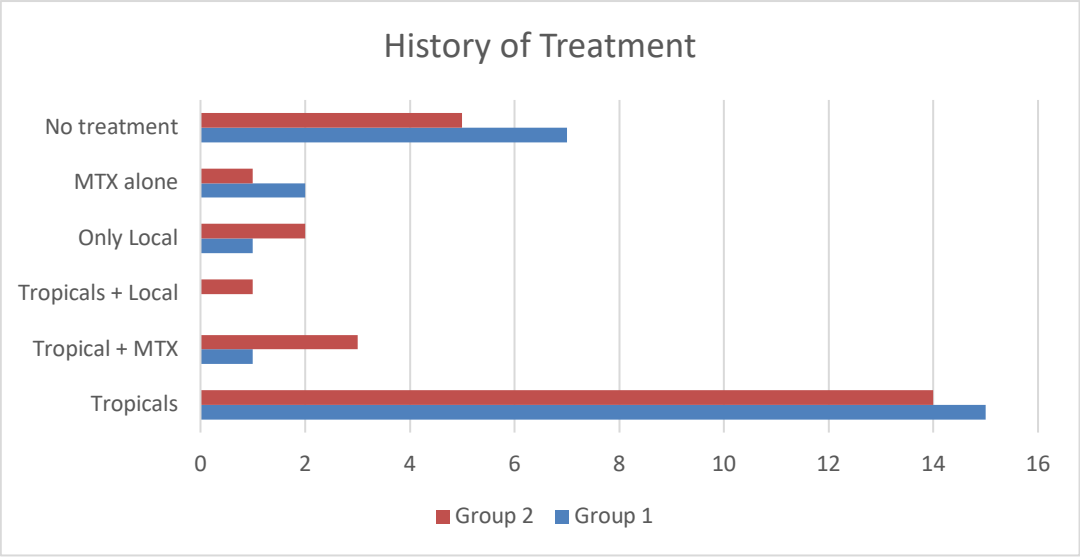


**Figure 1: Details of treatment history in the study participants**

**Table 3: Details of PASI score before and after treatment.**

| Duration | <15 | | 16-25 | | >25 | | P value |
|---|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 1 | Group 2 | Group 1 | Group 2 | |
| **At the beginning** | 05 | 03 | 04 | 10 | 17 | 13 | 0.257 |
| **1st month** | 06 | 04 | 04 | 20 | 16 | 02 | 0.342 |
| **2nd month** | 08 | 06 | 10 | 19 | 06 | 01 | 0.760 |
| **3rd month** | 08 | 18 | 16 | 08 | 02 | - | 0.564 |
| **4th month** | 17 | 22 | 07 | 04 | 02 | - | 0.078 |

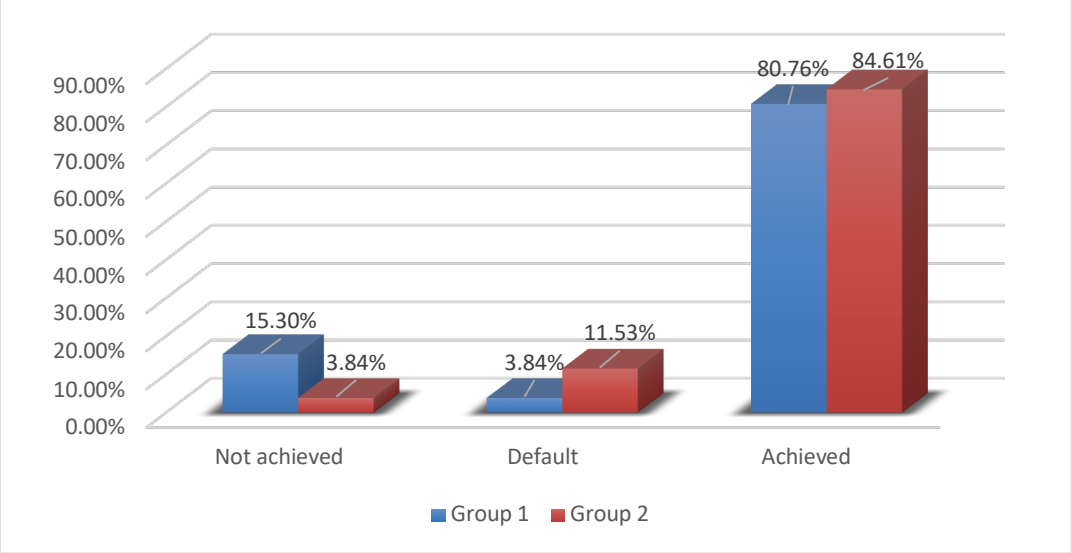


**Figure 2: Details of participants achieved the PASI75 in both study groups**

**Table 4: Details of adverse effects**

| Adverse effects | Group 1 | | Group 2 | |
|---|---|---|---|---|
| | Frequency | Percentage | Frequency | Percentage |
| Headache | - | - | 03 | 11.53% |
| Nausea | - | - | 01 | 3.84% |
| Vomiting | - | - | 01 | 3.84% |
| Lower abdomen pain | - | - | 01 | 3.84% |
| Vertigo | - | - | - | - |

## Discussion

The majority of study participants were aged between 41-50 years (34.61%) and 51-60 years (30.76%) in group 1 and 31-40 years (53.84%) and 41-50 years in group 2 (26.92%) with mean age of 42.4 years in group 1 and 37.8 years in group 2 ($p>0.05$). Male participants were common than females in both the groups. The mean age of onset of psoriasis was 36.7 years in group 1 and 35.28 years in group 2. Majority participants were suffering from the condition less than two years in group 1 (73.1%) and more than 2 years in group 2 (46.2%) (Table 1). A study by Lubna Khondker found a mean age of 45.72 years in Methotrexate group and 37.28 years in Apremilast group with more male participants [12]. Kaplan et al., reported a mean age of 49.2 years in Apremilast group and 49.5 years in Methotrexate group [13]. A study by Hassanandani et al., included 64 patients with palmoplantar psoriasis to assess the efficacy and safety of apremilast and methotrexate (group A) compared with methotrexate monotherapy (Group B) found a mean age of 40.87 years in group A and 44.47 years in group B with more male participants than females. The mean age of onset of illness was 34.53 and 36.60 years in group and B respectively. The mean duration of illness was 6.33 and 7.86 years in group A and B respectively [14]. Panda G et al., found a mean age of 40.86 years in apremilast and 41.34 years in methotrexate groups with more male participants. The disease duration was above 5 years in 25.71% and 28.58% and below 5 years in 74.29% and 71.42% in apremilast and methotrexate groups respectively [15].

SCALP was commonly affected part (80.8% each), followed by nails (61.5% & 57.7%), palm and sole (26.9% & 30.76%), external genitalia (23.1% & 11.5%) and joints (11.5% & 7.7%) in group 1 and group 2 (Table 2). Exposing to sunlight is the most common aggravating factor

observed in the study participants followed by alcohol consumption with smoking and meat.

Majority participants were under tropical treatment in both the study groups (Graph 1). 84.61% and 80.76% patients were achieved PASI75 in group 1 and 2 respectively. 3.84% in group 1 and 11.53% in group 2 were defaulted and 15.3% and 3.84% of patients were not achieved PASI75 in group 1 and group 2 respectively (Graph 2). The patients administered with 7.5 mg Methotrexate were not reported adverse events, but cases treated with Apremilast were exhibited headache in 11.53%, nausea, vomiting and lower abdomen pain in 3.84% of patients each (Table 4). According to Lubna Khondker, nausea (4% and 12%), vomiting (4% and 8%), headaches (4% each), and vertigo (4% in the Apremilast group) were the most frequent side events in the Methotrexate and Apremilast groups, respectively [12]. According to a study by Hassanandani et al., 43% of the cases in group A and 30% of the cases in group B reached PASI75 at 16 weeks. Diarrhoea, nausea & vomiting, headache, gastrointestinal intolerance, UPTI, abnormal liver function test and mood disorders were commonly observed in both study groups [14]. Panda G et al., stated that the common adverse event was diarrhoea, nausea/vomiting, URTI, anaemia, rashes, tension headache and deranged liver enzymes [15]. The most frequent adverse events, according to Strober B et al., were vomiting, nausea, headache, and upper respiratory tract infections [16]. When Ighani A. et al. evaluated the effectiveness of apremilast monotherapy in the treatment of psoriasis, they discovered headache in 32.4% of patients, nausea in 20.6%, diarrhoea in 14.7%, weight loss in 8.8% of patients, and loose stools in 8.8% of patients [17]. The results of preset study were similar with the findings of above study where headache, nausea, vomiting, and lower abdominal pain were the commonly observed adverse events.

According to Strober B et al., Apremilast considerably improved quality of life, was efficacious and well tolerated, and was linked to high patient satisfaction in systemic-naive, post-topical patients with mild plaque psoriasis [16]. Premilast monotherapy, according to Ighani A et al., can dramatically lessen the severity of moderate to severe plaque psoriasis [17]. According to Paul C et al., Apremilast was successful in treating moderate to severe plaque psoriasis for 52 weeks [18]. According to Kaplan et al., apremilast usage may postpone the start of a biologic in psoriasis patients, suggesting superior symptom management and results compared to methotrexate [13]. For the treatment of moderate to severe palmoplantar psoriasis, Hassanandani et al. [14] found that the combination of apremilast and methotrexate has higher efficacy and a similar safety profile as compared to methotrexate monotherapy. Apremilast exhibits similar efficacy to methotrexate, according to Spencer KR et al. [19], and it can be administered in conjunction with methotrexate to treat palmoplantar psoriasis. Kt S et al., reported that the Apremilast showed a comparable efficacy and safety profile to methotrexate in the management of palmoplantar psoriasis [20]. Samanta J et al., stated that methotrexate and apremilast are equally efficacious, safe and not exhibiting any adverse events and no significant difference between study groups [21]. Panda et al., concluded that apremilast was safe and effective in the management of chronic plaque psoriasis compared to methotrexate. While, the present study results showed similar efficacy of both drugs at 4$^{th}$ month follow up. The present study has limitations in terms of low sample size with minimal duration of follow up. Further long-term follow-up studies with larger sample size is required to assess the multiple drug

combination with various dosage levels in the management of psoriasis.

## Conclusion

The results exhibited that methotrexate and apremilast had similar efficacy in the management of moderate to severe grade psoriasis. The treatment response to the SCALP lesions, palmoplantar lesions, psoriasis of nails, and joint lesions were comparable between two drug groups. At the end of 4th month, methotrexate and apremilast groups did not show significant difference in achieving PASI75. Hence, study concluded that low dose methotrexate and apremilast were equally efficacious in the management of moderate to severe grade psoriasis.

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