AN OPEN-LABELLED RANDOMISED COMPARATIVE EVALUATION OF THERAPEUTIC EFFICACY AND SAFETY OF APREMILAST VERSUS METHOTREXATE IN THE TREATMENT OF PATIENTS WITH CHRONIC PLAQUE PSORIASIS

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ABSTRACT

Psoriasis is a chronic immune mediated papulosquamous disorder causing disfiguring changes in skin hair and nails. Methotrexate is a time tested drug in the treatment of psoriasis for decades but there are only fewer studies available regarding the efficacy and safety of apremilast. Hence this study is done to compare the both in terms of safety and efficacy.

MATERIALS AND METHODS This open labelled clinical study was conducted in the Dermatology department of a tertiary care hospital for a period of 1 year. Forty patients above 18 years of age with chronic plaque psoriasis involving >10% BSA were included in the study after taking the informed consent.

RESULTS At the end of 12 weeks, patients treated with Apremilast showed 92.64% improvement in their baseline PASI score compared to 88.26% improvement shown by the Methotrexate group patients. Apremilast is a better drug with good efficacy and safety profile which does not warrant regular monitoring of blood parameters in patients requiring long term systemic therapy.

KEY WORDS: psoriasis, apremilast, methotrexate
INTRODUCTION

Psoriasis is a common chronic inflammatory immune mediated hyper proliferative condition affecting predominantly the skin, nails and joints. It is associated with significant reduction in the quality of life.\cite{1,2}

Worldwide prevalence ranges from 0.09\% to 11.4\%, higher in the polar regions and rare in native Americans and Latin American Indians.\cite{4} In India, the prevalence varies from 0.44 to 2.8\%, males are more affected and the peak age for onset of the disease is third and fourth decades of life.\cite{2}

The exact etiology of the disease is not yet clear but evidence suggests genetic predisposition, role of the immune system and triggering factors like infections, stress, systemic drugs, sunburn, seasonal variations, trauma, alcohol and smoking in the causation of the disease.\cite{1}

Plaque psoriasis is the most common type accounting for 80-90\% of cases.\cite{1,3} The diagnosis of psoriasis is usually clinical. There are several modalities of treatment available but none is satisfactory in achieving significant clearing of lesions with minimal side effects.\cite{4}

General measures include reassurance and emotional support, sunlight exposure, lifestyle modifications such as weight management, alcohol and smoking cessation. Topical treatments include emollients, topical steroids, vitamin D analogues like calcipotriol, coal tar, dithranol, retinoids like tazarotene, salicylic acid, calcineurin inhibitors like tacrolimus and pimecrolimus. Phototherapy such as narrow band UVB, photochemotherapy (psoralens + UVA), photodynamic therapy.

Systemic therapies include Methotrexate, Cyclosporine, Acitretin, Apremilast, Fumaric acid esters. Biologicals like Adalimumab, Infliximab, Etanercept, Ustekinumab, Secukinumab.\cite{1} Systemic therapy is the major modality of treatment in patients having moderate to severe psoriasis and also in those cases who do not respond to topical treatment. The objective of my study is to compare the therapeutic efficacy and safety of Apremilast, a new novel molecule introduced in the treatment of chronic plaque psoriasis with the time tested Methotrexate.

Apremilast is the first orally active PDE-4 inhibitor approved by FDA in 2014\cite{3} and by Central Drugs Standard Control Organization of India in 2017 for plaque psoriasis. It acts by binding directly to the PDE-4 enzyme and increases levels of cAMP and decreases levels of pro inflammatory cytokines such as TNF alpha, IL-23, IL-12,
LTB4, nitric oxide synthetase and increases levels of anti-inflammatory cytokines such as IL-10. It is also found to be effective in patients with psoriatic arthritis[^5] nail psoriasis & psoriasis in difficult-to-treat areas like scalp, face, palms & soles. Methotrexate is an antimetabolite drug, approved for use in psoriasis since 1971[FDA]. It is being used in different dosing regimens for the treatment of moderate to severe plaque type psoriasis and psoriatic arthritis for years[^6].

There are very few studies comparing the efficacy of both these drugs in literature and Indian studies on the new molecule apremilast is also lacking. The efficacy and side effect profile of methotrexate, with particular dosing titrations[^7] and also the monitoring guidelines[^6] are widely available in the literature. However for the new molecule, the evidences are still lacking regarding the adverse effect profile. The Celgene Corporation[^8] also demands that the new molecule does not need frequent monitoring even on prolonged usage. Hence this study is done to get a thorough understanding of the newly introduced novel molecule apremilast in the psoriasis treatment and also to assess the side effects of the drug in the Indian population as most of the dose ranging studies and efficacy and safety determining studies were done in other countries. This study will further give an idea whether the Apremilast is equally effective or better than the methotrexate in the treatment of plaque psoriasis and also helps in improving the quality of life in psoriasis patients by addressing the unmet needs especially in those who are intolerant to conventional systemic agents including biologicals.

**MATERIALS AND METHODS**

- The permission was obtained from the ethical committee review board.
- Patients diagnosed with chronic plaque psoriasis and fulfilling the inclusion criteria visiting the department of Dermatology, Venereology and Leprosy in Chettinad Hospital and Research Institute, Kelambakkam from 2018 to 2019 were included in this study.
- The study was started after registration in the Clinical Trial Registry of India [CTRI] and registration number was obtained -CTRI/2019/01/017362.
- A written informed consent was taken from each patient before starting the study.
- A detailed history and general examination was conducted in each case and was recorded on prescribed proforma.
- Each patient was subjected to routine blood investigations along with Chest X-ray before starting the therapy.
Group A These patients were given oral Methotrexate 7.5mg per week for 12 weeks along with T.Folic Acid 5mg daily [except on the day of taking oral methotrexate in the week

Group B These patients were given oral Apremilast 30 mg twice a day from day 6 to 12 weeks after the recommended initial dosage titration from day 1 to day 6.

SOURCE OF DATA All the patients presenting to the department of dermatology and STD with chronic plaque psoriasis fulfilling the inclusion and exclusion criteria over a period of 1 year were assigned to my study.

SAMPLE SIZE Based on the previous literature,

Methotrexate group: m1=4.60 and 1σ =1.47

Apremilast group: m2=5.56 and 2σ =1.05

20 subjects were included in each group. Total sample - 40 patients [20 patients in Group A and 20 patients in Group B

STUDY DESIGN- It is an Open-labelled randomized comparative clinical study

All the patients will be evaluated for therapeutic outcome both objectively (by Psoriasis Area and Severity Index or PASI Score) and photographically every three weekly till the end of 12 weeks by an experienced dermatologist in the department. The result will be tabulated with respect to percentage of improvement in PASI Score and grading will be done accordingly.

RESULTS

The statistical analysis was carried out by SPSS 20.0 Version and MS-Excel. Frequency distribution analysis and Descriptive statistics were calculated for nominal and ratio data respectively. Shapiro-wilk test and Box-whisker plot were used to find out whether the empirical data are normally distributed. Chi-square test/Fisher’s exact test is used to find out the difference between two groups’ proportionate values. Independent sample t test was used to compare the mean PASI score among the patients who treated with oral Methotrexate and the patients who treated with oral Apremilast. Cohen’s d effect was calculated to assess the magnitude of difference between two groups. Repeated measures Analysis of Variance (ANOVA) test was used to compare the PASI score of patients who treated with Methotrexate & Apremilast, at different follow-up periods. Partial correlation coefficient analysis was used to find out the relationship between the duration of illness, patients age and clinical improvement after controlling the previous systemic treatment and gender. Statistical significance was considered at 5 percent level.

DISCUSSION
Psoriasis is a chronic disease with frequent remissions and exacerbations which significantly affects the quality of life in patients. This study demonstrated a favourable clinical outcome in both the treatment groups at the end of 12 weeks irrespective of age, gender, duration of the disease and previous treatment history.

In this study, the mean age of the patients was 38.35 years in methotrexate group and 43.95 years in apremilast group which is somewhat close to the ESTEEM studies\(^9\,\,^{10}\) with median age of 46 years. More number of male patients participated in the study in both treatment groups. Similar male predominance has been reported in other studies\(^{11}\,\,^{12}\,\,^{13}\). The mean duration of the disease was around 4 years in methotrexate group patients and 6 years among apremilast patients.

Previous history of treatment with systemic drugs was present in 45% of methotrexate group patients and 55% of apremilast group patients which was in accordance with ESTEEM 1\(^{10}\) study, in which 54% patients were already treated with conventional systemic therapy before the study. In a study done by Armstrong et al,\(^{14}\) better clinical efficacy was seen in patients who were systemically naïve compared to patients who were previously exposed to systemic drugs. In our study, systemic treatment naïve patients had a good clinical improvement with apremilast compared to previously treated patients. However no such difference was seen in the methotrexate group.

The mean baseline PASI in our study was 23.51 in the methotrexate group and 26.77 in the apremilast group which was higher compared to other studies\(^{15,9}\).

**COMPARISON OF EFFICACY** At the end of 12 weeks, Group A patients showed 88.26% improvement in their PASI score from baseline compared to 92.64% improvement in PASI shown by the group B patients. In a study done by Sabiqa et al\(^{12}\), they reported a 40% complete clearance with 7.5mg weekly methotrexate dose given for 8 weeks. Significant clinical improvement was seen in patients treated with apremilast during the very first follow up at the end of 3 weeks. There was faster resolution of the scalp lesions noted in these patients compared to other body sites and in most cases near complete scalp clearance was seen during the second follow up at the end of 6th week. Apremilast group patients showed 41% clinical improvement from baseline PASI at the end of 3 weeks compared with only 12% improvement from baseline PASI in Methotrexate group patients. This early onset of response is correlating with the study done by Nash et al\(^{16}\) Gottlieb et al\(^{17}\) also demonstrated clinical efficacy in about 73.7% of the study population in just 29 days which also supports the early onset of efficacy seen in our study. However at the end of 9 and 12 weeks, there was no statistically significant difference in clinical response between two groups.

In an indirect comparison study to assess the efficacy of methotrexate and apremilast, Armstrong and his colleagues,
through an indirect comparison of previous studies concluded that there was no statistically significant difference between apremilast and methotrexate at the end of 16 weeks. [14]

In a similar comparative South Indian study done by Vinma et al. in Karnataka[18], 76.8% improvement was observed in the methotrexate group compared to 71.5% in the apremilast group. The dose of methotrexate used in their study was 15mg. The mean baseline PASI in my study improved from 23.51 to 2.76 in the methotrexate group in 12 weeks compared to 26.77 to 1.97 in the apremilast group whereas in this study the improvement is from 19.88 to 4.6 in methotrexate arm compared to reduction in mean baseline PASI from19.54 to 5.56 in the apremilast arm. They concluded that methotrexate showed better efficacy than apremilast in their study. The result from the above study [18] is contradicting the results of the present study.

The dose of methotrexate used in this study is low compared to other studies with methotrexate. This low dose was associated with lesser incidence of side effects compared to other studies in the literature and is also associated with lesser organ specific toxicities due to the lesser cumulative dose at the end of the study. However 7.5mg as weekly once dosing is the second most commonly used dose for psoriasis as a starting dose.[7]

The percentage of improvement seen in this study for both the treatment groups is significantly higher compared to other studies published in literature.

**SIDE EFFECT PROFILE** Both Apremilast and Methotrexate were well tolerated during the study with the side effect profile comparable in both the groups and none of the patients discontinued the treatment due to the side effects.

In patients treated with methotrexate, 5 patients developed mild gastrointestinal intolerance in the form of nausea and vomiting [15% of patients], abdominal pain and diarrhoea [10%] which was managed with proton pump inhibitors. None of the patients discontinued the treatment because of side effects. Blood investigations during the follow up periods revealed mild elevation in the liver enzymes in 3 out of 20 patients [15%] and were below 2 fold from the baseline and did not warrant stoppage of treatment. The lesser incidence of side effects with methotrexate in this study may be because of the low dose of methotrexate used in the study and as the patients with baseline abnormalities in CBC, LFT and RFT were excluded from the study. It may also be because of the lesser cumulative dose at the end of study i.e. 90mg. The side effects observed were comparable with Haider et al study [12].

In the group B patients who are treated with Apremilast, nausea, vomiting and diarrhoea were the most commonly reported side effects. One patient complained of headache after starting the treatment which subsided in 3 days. Loss
of appetite was reported by a single patient, which she was complaining throughout the study period. The adverse effects subsided on continued treatment as noted with other studies and none of them necessitated treatment withdrawal. No newer adverse events were reported during the study. No variations in blood hemogram, renal and liver functions from baseline values were observed during the follow up visits.

Side effects reported with apremilast were similar to other studies in the literature \(^{[11]}\) and most side effects subsided by 4 to 5 weeks on continued treatment. No newer side effects were reported even on continued treatment up to 52 weeks in a study done by Stein et al. \(^{[19]}\)

The variations noted in liver enzymes in the methotrexate group patients during the study further emphasizes the need for regular monitoring of blood parameters as specified in the literature. \(^{[20]}\) However no variations in blood parameters observed in apremilast group supports the statement given in other studies that there is no need for monitoring of blood parameters in patients treated with apremilast. Hence for long term treatment, considering the cumulative toxicity of methotrexate and other immunomodulators, apremilast is a good option for rotational therapy.

Apremilast has also been used as a combination therapy or rotational therapy in psoriasis along with other modalities of treatment with variable effectiveness and good safety profile. In terms of cost-effectiveness, apremilast is about 12-15 times costlier than methotrexate per tablet. But considering faster resolution of lesions, good safety profile and absent monitoring requirement, it is a good drug with better efficacy.

On the basis of vast clinical improvement and faster onset of Psoriasis resolution within three weeks of starting the drug along with good side effect profile, oral Apremilast is a good compared with oral Methotrexate.

**CONCLUSION**

- This is a hospital based open-labelled randomised comparative clinical study done on 40 patients with moderate to severe plaque psoriasis.
- Patients were randomly assigned into two groups A & B and were treated with Methotrexate and Apremilast respectively for a period of 12 weeks.
- Males outnumbered females in both the groups and the mean age of patients was around 40 years.
- The mean duration of psoriasis ranged from 4 to 6 years in both the groups.
- No statistically significant influence was seen between the demographic characteristics and the final drug outcome.
- Systemic naïve patients were found to respond better to apremilast.
• No significant difference in terms of efficacy was seen between oral Apremilast and low dose oral Methotrexate at the end of 12 weeks.

• Apremilast is found be associated with earlier onset of response by 3rd week and complete scalp clearance was seen in most patients by the end of 6 weeks.

• Even though no statistically significant difference was found in the side effect profile, the incidence of adverse events was slightly higher in the Methotrexate group compared to Apremilast group.

• No variations in blood parameters were observed in the Apremilast group compared to slight elevation of liver enzymes noted with the Methotrexate group.

It is concluded that Apremilast is a better drug with good efficacy and safety profile which does not warrant regular monitoring of blood parameters in patients requiring long term systemic therapy.

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