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Original Research Article

To assess the safety and adverse events of apremilast methotrexate alone and apremilast plus methotrexate in patients with psoriasis vulgaris

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Abstract

Background: The aim of the study is to compare the effect of Apremilast, Methotrexate & Apremilast plus Methotrexate in patients of psoriasis vulgaris. This study was a prospective randomized, open labeled, comparative study

Methods: Patients of both genders in the age group of 18-65 year with moderate to severe chronic plaque psoriasis attending the dermatology outpatient department (OPD) in our hospital were screened according to their eligibility criteria in the study.

Results: Side effects are found in 42 out of total 90 patients. Most common adverse event experienced by patients is diarrhea, present in 14 patients (15.6%), second most common is nausea present in 9 patients (10%) patients. Most of these adverse events were mild and temporary and resolved over time with medication. In this study we found that adverse event experienced in more patients if both drugs gave together than individual agents.

Conclusion: Apremilast and Methotrexate both are effective and safe therapies in young cases of chronic plaque psoriasis. Individually these agents are effective only in less than half (about 40%) of affected patients. A combination of the two agents is more effective; however, it is also associated with increased adverse events, and also increase cost

Keywords: apremilast, methotrexate & psoriasis vulgaris.
Study Design: Prospective Randomized Comparative Study.

1. INTRODUCTION

Psoriasis is an inflammatory systemic disease that is characterised by a chronic course of erythematous plaques with micaceous scales over the skin that occur due to the hyperproliferation of epidermal keratinocytes. The prevalence of psoriasis is around 1–3% of the world's population[1]. Various environmental triggering factors such as drugs, infections, trauma, seasonal variation, etc., play an important role in the development of psoriasis. A family history of psoriasis is seen in around 30% of patients with early-onset disease[2].

Genetic factors play an important role in the pathogenesis of psoriasis. Psoriasis worsen during periods of stress, during adverse environmental conditions of cold weather and low humidity, with the administration of certain drugs and during course of certain infections. Ethnic factors also play an important role. The disease is enormously variable in duration, periodicity of flares and extent[3].

In moderate-to-severe disease required the use of systemic agents, whether it can be traditional systemic agents or biologics (e.g., tumor necrosis factor-alpha [TNF-α] inhibitors, ustekinumab). Biologic therapies, are effective but they have many disadvantages like adverse effect profile, treatment resistance, expenses, hospital admission, parenteral

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administration and management requiring a specialist setting. According to data and results of ESTEEM 1, 2 trials Apremilast has proved to be efficacious and safe for moderate to severe psoriasis and also is efficacious in patients with various comorbities. It is well tolerated with mild to moderate adverse effects, the commonest being gastrointestinal effects like diarrhea, nausea, vomiting[4].

Apremilast is a novel drug for the treatment of psoriasis and psoriatic arthritis. It is the first oral drug to receive FDA approval for psoriasis since 1996. It is an oral phosphodiesterase type 4 inhibitor (PDE4). It works intracellularly to reduce the production of pro-inflammatory mediators and increase the production of anti-inflammatory mediators[5]. The inhibition of PDE4 increases the intracellular cyclic adenosine monophosphate level, which in turn decreases the production of inflammatory mediators and increases the production of anti-inflammatory cytokines. In adults, the recommended dosage of Apremilast for psoriatic arthritis and psoriasis is 30 mg twice daily, which is started at 10 mg/day initially with an escalation of 10 mg/day until the recommended adult dose is reached. This dose titration helps in minimising the gastrointestinal side effects of Apremilast. In 2018, Apremilast was launched in India as 10, 20 and 30 mg tablets[6].

2. MATERIAL AND METHODS

We conducted this study at our department of dermatology, MY hospital Indore for 01 Year, after taking permission from institutional ethics committee. This study was a prospective randomized, open labeled, comparative study. Total 90 patients eligible for the study after exclusion, the participants were divided into 3 groups (30 each).

Study was started after approval from the institutional review board & ethical committee. Recruited subjects giving the informed consent was divided in 3 groups i.e. Group A, Group B & Group C. A detailed history, General physical & systemic Examination of each individual was done. Baseline routine investigation of the patients was done which includes a complete blood cell count, renal & liver function Tests, HBs Ag, HCV & ELISA for HIV.

INCLUSION CRITERIA

1. Patients with age 18-65 years.
2. Patients with moderate to severe psoriasis from 6 month or longer
3. Patients giving consent for participation in study.

EXCLUSION CRITERIA

1. Patients with persistent abnormal liver function tests.
2. Patients known case of diabetes, hypertension, any liver disease.
3. Patients of known immune compromised state
4. Pregnant & lactating mothers

4. RESULT

Table 1: Baseline characteristics of study population

Variables		Group A	Group B	Group C	p-value
N		30	30	30	
Gender	Male	18	19	18	0.954

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	Female	12	11	12	
Age (Mean± SD)		39.96±10.3	37.26±8.8	37.40±8.34	0.130
Weight (Mean ± SD)		56.26±9.04	58.96±8.34	59.46±8.36	0.305
Duration of illness (Mean ± SD)		6.56± 3.86	6.64±3.60	5.50±3.14	0.386
Baseline PASI (Mean± SD)		12.22±1.29	12.29±1.19	12.68±1.20	0.375

This study was done prospectively in dermatology OPD. Total 115 patients of moderate to severe chronic plaque psoriasis were screened, out of which 90 patients qualified for the study. These patients were randomly allocated in each of the three groups as mentioned above.

Table 2: Total cumulative dose of drugs

Drugs	Mean cumulative dose
Apremilast	3.03 ± .000gm
Methotrexate	165.00±.000mg

Table 3: Showing side effects of Apremilast, Methotrexate & Combination therapy (Apremilast plus Methotrexate)

Side effects	Group A (Apremilast) N=30	Group B (Methotrexate) N=30	Group C (Apremilast + Methotrexate) N=30	Sum of Side-effects in all groups of patients (N=90)
Diarrhea	5(16.4%)	3(10%)	6 (23.4 %)	14(16.70%
Nausea	3 (10%)	2 (6.7%)	4 (13.4%)	9 (10%)
Headache	2 (6.7%)	0	1 (3.4%)	3 (3.06%)
Git intolerance	1 (3.4 %)	4 (13.4%)	2 (10%)	7(7.8%)
Upper respiratory infection	0	0	0	0
Mood disorders	0	0	0	0
Abdominal pain	1 (3.4%)	2 (6.7%)	1 (3.4%)	4(4.50%)
Abnormal Lft	0	1 (3.4%)	1 (3.4%)	2 (2.30%)
Weight loss	1	0	0	1(0.9%)
Hemoglobin\ anemia	0	1 (3.4%)	1 (3.4%)	2(2.30%)
Total	**13**	**13**	**16**	**42**

Side effects are found in 42 out of total 90 patients. Most common adverse event experienced by patients is diarrhea, present in 14 patients (15.6%), second most common is nausea present in 9 patients (10%) patients. Most of these adverse events were mild and temporary and resolved over time with medication. In this study we found that adverse event experienced in more patients if both drugs gave together than individual agents.

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5. DISCUSSION

Psoriasis is defined as chronic inflammatory disorder which is genetically determined and leads to hyperproliferation of the skin, there is alteration in growth and differentiation of the epidermis. Various factors play a major role in its etiology like hormonal, environmental, genetic, drugs, trauma, sunlight. The most common type of psoriasis is chronic plaque psoriasis which is characterized by well-defined red color plaques which are scaly and indurated involving the extensors aspect of the body and also the scalp[7]. Apremilast is an oral PDE4 inhibitor which mainly acts over the cyclic adenosine monophosphate and helps in signaling of intracellular functions, and reduces the levels of proteins to modulate the immunity and thereby improves the inflammation which is associated with psoriasis. Methotrexate inhibits DNA synthesis by competitive inhibition of dihydrofolate reductase and exert an antimitotic action on the epidermis. One of the retrospective studies have shown if methotrexate is given in low dosage for a longer period of time it has better efficacy and have reduced or minimal side effects[8].

Thirteen patients (43.4%) experienced adverse events in the present study. Other studies including ESTEEM trials reported these adverse events in around 60%-70% of the patients[9]. The most common adverse event in our study was diarrhea experienced by 5 patients (16.7%) out of total 30 patients, and this finding was corroborated in various clinical studies. However, this incident was more in the study reported by Mayba et al.[10] Also, the incidence of diarrhea (16.5%) was comparable than that found in ESTEEM-1 (18.7%). In our study total 13 patients (43.4%) of Group A who received apremilast experience adverse events. Most common adverse effect is diarrhea 5 patients (16.5%), Nausea 3 patients (10%), headache & abdominal pain in (6.7%) patients.

Psoriasis had a bimodal distribution of age of onset. According to a study done by Lomholt the average age reported was 12 years. In large US surveys, average age of onset was reported to be 28 years[11-13]. While on the studies done in UK said mean age of onset is 33 years & around 75% patients developed psoriasis before 46 years of age. In one of the German study showed that peak age of onset was 16 years in females and 22 years in males and the later age involved was 57- 60 years. Prevalence of psoriasis is 0.44-2.8 per cent in India, it commonly affects individuals in their third or fourth decade with males being affected two times more common than females. In our study, patients in three groups were in the mean age group of 39.96±10.30, 37.26±8.8 and 36.40±8.34 respectively and the mean duration of psoriasis in all the patients was around 5-6 years. Both males and females were almost equally affected in a ratio of 18:12 in the group A, 19:11 ratio in group B while ratio of 18:12 in group C patients[14].

In group B total 13 patients (43.4%) patients experienced adverse events. Most of these adverse events were mild and temporary and resolved over time[15]. The most common adverse event was GI intolerance in 4 patients (13.4%), diarrhea which was found in 3 patients (10%), followed by nausea in 2 patients (6.7%), abdominal pain in 2 patients & abnormal LFT in 1 patient.

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6. CONCLUSION

Apremilast and Methotrexate both are effective and safe therapies in young cases of chronic plaque psoriasis. Individually these agents are effective only in less than half (about 40%) of affected patients. A combination of the two agents is more effective; however, it is also associated with increased adverse events, and also increase cost of therapy.

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