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Comparative Study Of Efficacy Of Methotrexate And Apremilast In The Treatment Of Moderate To Severe Plaque Psoriasis.

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ABSTRACT

Methotrexate is an age-old drug available in the market for more than 50 years. Most of the clinicians prescribe methotrexate as the first line of management. Apremilast was recently approved in the year 2014 by FDA as monotherapy for the treatment of moderate to severe chronic plaque psoriasis There are only a few studies that directly compare the efficacy of methotrexate and Apremilast. To compare the efficacy of daily Apremilast with weekly Methotrexate in the management of moderate to severe plaque psoriasis patients attending the Dermatology Out-patient Department, Government Medical College, and Hospital Nagapatinnam. In the year 2023. A total of 40 patients with moderate-to-severe plaque psoriasis were included in the study. The psoriasis severity was evaluated by the psoriasis area and severity index (PASI). Baseline investigations were done initially before starting the treatment. The patients were divided into two groups; in group A (20 patients). Methotrexate was started at a dose of 7.5mg per week. In other group B (20 patients) Apremilast was started at a dose of 10mg and titrated to a maximum of 30mg which is taken twice daily. Regular biweekly checkups are done for 16 weeks looking for clinical improvement & adverse effects. Assessment is done by Psoriasis area and severity index (PASI) score at 0, 1, 2, 3,4th month of treatment. Post-treatment follow-up was done for another 6 months. The efficacy of the drugs was compared by using PASI75. Both methotrexate and Apremilast showed equal efficacy in the treatment of moderate to severe plaque psoriasis. About 85% of patients achieved PASI 75 in our study at the end of 4 months whereas at the end of 2 months 14 (35%) patients receiving methotrexate achieved PASI 75 whereas 11 patients (27.5%) achieved PASI 75. Six (15%) patients didn't achieve the PASI 75 at the end out of which 3 patients (7.5%) were in Group A and 3 patients (7.5%) were in Group B. Adverse effects are seen in 3 patients in patients taking Apremilast like nausea, headache, lower abdominal pain. No significant difference was seen in both the groups in achieving PASI 75 at the end of 4 months. Incidence of adverse effects is minimal or absent with methotrexate when compared to Apremilast at the end of 16 weeks.

Keywords: moderate to severe plaque psoriasis, Apremilast, methotrexate, Psoriasis area, and severity index.

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INTRODUCTION

Psoriasis is a chronic inflammatory skin disease that affects around 1% to 3% of the population [1]. Psoriasis vulgaris or plaque psoriasis, the most common form, accounts for more than 80% of psoriasis cases. Most patients are mildly affected and can be treated adequately with topical medication, but 10–20% of patients have moderate-to-severe disease and require phototherapy or systemic treatment [2]. Methotrexate and Apremilast are well-known systemic therapies for moderate-to-severe chronic plaque psoriasis. Methotrexate (MTX) is an immunomodulatory & anti-proliferative drug that has structural similarity to folic acid. It competitively inhibits the enzyme dihydrofolate reductase & blocks DNA Synthesis in the S phase of the cell cycle. MTX has potentially serious side effects, including myelosuppression, pulmonary fibrosis, and gastrointestinal disorders. The most prominent long-term side-effect is hepatotoxicity. Methotrexate weekly oral doses are effective & well tolerated. Methotrexate was approved by FDA for plaque psoriasis in the year 1972 [3]. Apremilast is an oral phosphodiesterase-4 (PDE4) inhibitor which has been approved by the US Food and Drug Administration (FDA) on September 24 2014 for psoriasis [4]. Its use does not need laboratory monitoring, and its oral route of administration gives it an advantage compared to biologics and other systemic anti-psoriatic drugs. The drug regulates immune responses associated with psoriasis by inhibiting PDE4, which is highly expressed in dendritic cells, monocytes, neutrophils, and keratinocytes, where it blocks the degradation of cyclic adenosine monophosphate (cAMP). The most commonly reported adverse reactions are diarrhea, nausea, upper respiratory tract infection, nasopharyngitis, and headache [5].

METHODS

It is a randomized comparative study done at the dermatology outpatient department, Government Medical College, and Hospital, Nagapatinnam A total of 40 patients with moderate-to-severe plaque psoriasis were included in the study. The diagnosis of psoriasis was made on clinical grounds. A detailed history of the patient's occupation, co-morbidities, other drug intake, family history, and duration of the disease was noted. A thorough physical examination for associated skin diseases and severity of psoriasis was done. The psoriasis severity was evaluated by the psoriasis area and severity index (PASI). Baseline investigations were done initially before starting the treatment. The patients were divided into two groups; in one group A (20 patients). Methotrexate was started at a dose of 7.5mg per week after the test dose of 2.5mg in the first week. In other group B (20 patients) Apremilast was started at a dose of 10mg and titrated to a maximum of 30mg which is taken twice daily. Regular biweekly checkups are done for 16 weeks looking for clinical improvement & adverse effects. Assessment is done by Psoriasis area and severity index (PASI) score at 0, 1, 2, 3,4th month of treatment using the PASI SCORE worksheet by the British Association of Dermatologists. Post-treatment follow-up was done for another 6 months during which the patients were evaluated for duration of remission & relapse if any. The efficacy of the drugs was compared by using PASI75 at the end of 4 months.

Inclusion criteria: Both male & female plaque psoriasis patients with Ages of 15 to 70 years and Patients who could come for follow-up.

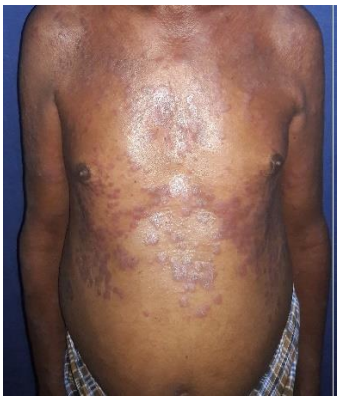
Exclusion criteria: Pregnancy, Lactating mothers, patients with diabetes, Obesity, Active pulmonary Tuberculosis, HIV patients, Immunosuppressed individuals, patients with Hematologic/hepatic/renal disorders, and Alcohol dependent patients.

RESULTS

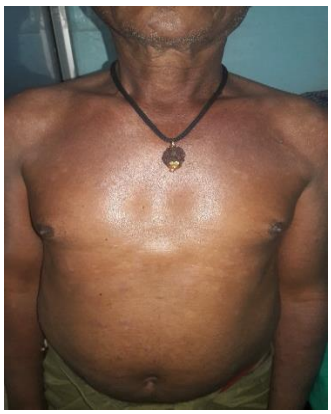
The range of age in our study was from 23 to 68 years. The mean age of treatment was 43 years in both groups. The age of onset of disease varies from 15 to 52 years. The mean age of onset in group A 36.55 and in group B 35.15. the range of disease duration of illness was from one month to 40 years. Most of the patients presented in our study were male 28/40. Only a few patients had a history of aggravating factors in which alcohol is seen in 5 patients (12.65%) followed by smoking. non veg food, trauma, sunlight. Of the patients with a history of previous topical treatment 19 (47.5%) of these patients, 3 had local treatment 2 had native treatment. co-morbidities like diabetes and hypertension were excluded from our study but 3 patients had associated diseases like Down syndrome, facial nerve palsy, kyphosis, and genu valgum. The most common site of initial onset of the lesion is the scalp followed by the trunk back 34 patients had scalp lesions during the study. 30(75%) patients had nail changes during the study in which nail pitting was seen in 21(70%) patients followed by onycholysis, sub ungula hyperkeratosis,

and nail dystrophy. Thirteen (32.5%) patients had palmoplantar involvement Four patients had psoriatic arthritis confirmed by a rheumatologist in which 2 had symmetric polyarthritis and 2 had asymmetric oligoarthritis. six patients (15%) had external genitalia involvement and STI screening was done to rule out STDs. only one patient presented with an oral mucosal lesion geographic tongue. No dose modification was done in our study; no combination of treatments was done At the end of 4 months PASI 75 was achieved in 85% of patients. The mean PASI score before starting treatment. Most of the patients had an initial PASI score above 25. Six patients (15%) didn't achieve the PASI 75 of which three of them were in group A and 3 of them in group b. six patients didn't achieve PASI 75 out of which 3 patients were in Group A and 3 in Group B Only 2 patients in Group B have defaulted. Adverse effects are seen in patients with the apremilast group. Two of them experienced nausea and headache which was treated with tab. loperamide and tab. paracetamol. One patient had lower abdomen pain and headache and was treated with tab omeprazole 20mg bd and tab. Paracetamol 500mg TDS. Apremilast was not stopped while treating symptomatically later 2 of them lost follow up. The treatment response rate was measured by comparing PASI75 at the end of 4 months. At the end of one month, only 3 (7.5%) patients achieved PASI 75. But at the end of 2nd month, the methotrexate group patients showed a higher response rate 35% than the apremilast group 27.5%. majority of patients irrespective of initial PASI score achieved PASI 75 at the end of 2 months with methotrexate 8 of them achieved whereas in apremilast 11 patients achieved. The treatment response in patients with scalp lesions in both groups was compared Three patients with methotrexate did not achieve PASI 75. The majority of patients 23 out of 34 patients with scalp lesions had an initial PASI score of more than 25. The treatment response in nail changes showed more than half of patients with nail changes 18 out of 30 had initial PASI 75 more than 25.16 of them took mtx and 14 of them took apremilast. In patients with palmoplantar involvement, all cases undergoing apremilast showed a response in 1st month of treatment but patients with methotrexate showed a slow response. One patient in the apremilast group reached PASI75 in 1st month but in 3rd month of the visit, he had multiple new lesions and an increase in PASI score following intake of alcohol. Similarly, two patients in the methotrexate group reached PASI75 at the end of 2nd month and on the next visit they showed exacerbation of lesions and raised PASI score, the reason for exacerbation could not be found.

Picture 1: Before treatment with Apremilast



Picture 2: After treatment at week 16 with Apremilast



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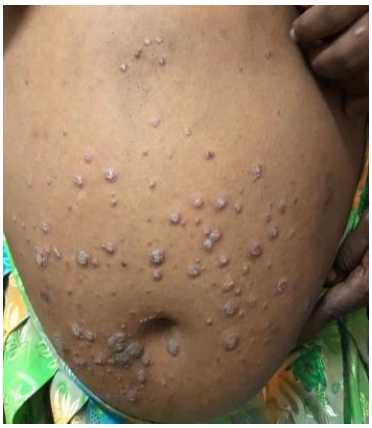
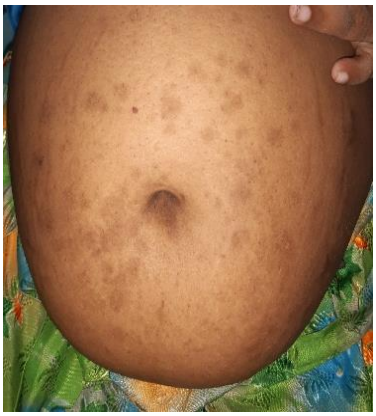
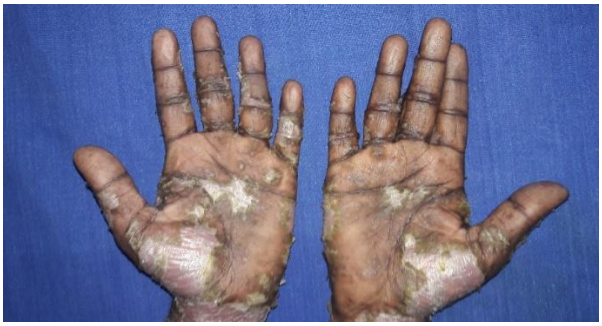
Picture 3: Before treatment with apremilast



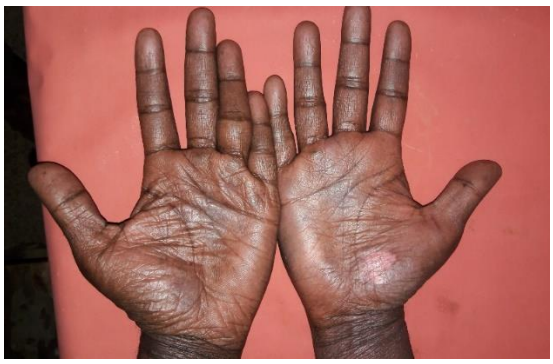
Picture 4: After treatment at week 16 with apremilast



Picture 5: Before treatment with apremilast in palms and soles



Picture 6: After treatment at week 16



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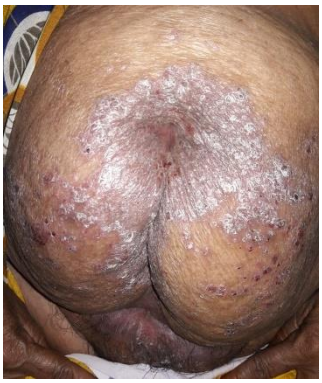
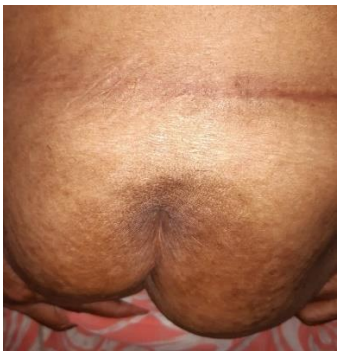
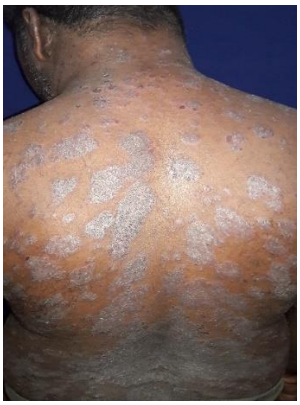
Picture 7: Psoriatic plaques before treatment with methotrexate



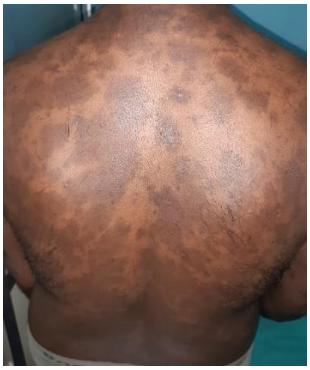
Picture 8: After treatment at the 16th week



Picture 9: Before treatment with methotrexate



Picture10: After treatment at week 12



DISCUSSION

The initial response of the drug is better in Apremilast, but the initial response of methotrexate is not appreciable. But at the end of 4 months both the groups showed similar efficacy to treatment. The mean age of onset of psoriasis in our study is 35.85. The mean duration of disease in our study was 6 years in Group A and 7.5 years in Group B whereas the mean duration of psoriasis was around 13-14 years in the. In our study, 34 patients had psoriatic lesions over the scalp. Only 4 patients didn't achieve remission of scalp lesions even after treatment which included 2 patients from group A and another 2 from group B [6]. Totally 30 patients in our study showed nail changes 14 patients were under group A and 16 were under group B, out of which 10 patients had persistent nail changes even after 16 weeks of treatment. Eight patients on methotrexate and 2 patients on Apremilast had persistent nail changes even after treatment [7]. Only 4 patients had joint involvement, two from each group. Asymmetrical oligoarthritis and symmetrical polyarthritis were the findings seen in these patients. Out of the four patients, two patients, one from each group showed poor response to treatment at the end of 4 months. Thirteen patients in our study had palmoplantar involvement and all patients responded to both methotrexate and Apremilast [8]. The treatment response of this study is measured by PASI 75. PASI 75 is a reduction of 75% of initial PASI score (PASI 0). In our study, 34 patients (85%) achieved the PASI 75. Only 6 (15%) patients didn't achieve the PASI 75, out of which 3 patients (7.5%) were in Group A and 3 patients (7.5%) were in Group B. Out of the three patients in Group B two defaulted [9]. In our study methotrexate was given in the dose of 7.5mg/week in three divided doses 12 hours apart for 4 months and 85% of patients achieved the treatment response. Due to the Adverse effects of the drug patients from the Apremilast group dropped out. Out of the 40 patients, only 3 (7.5%) patients developed side effects. All the 3 patients belonged to the Apremilast group. Headache was the most common side effect followed by nausea and lower abdominal pain. Many trials reported that diarrhea and nausea as the major adverse effects [10]. None of the patients taking methotrexate developed adverse effects. The probable reason for the absence of side effects may be due to the low dosage of Methotrexate and folic acid supplementation and in fact, high-risk patients were excluded from the inclusion criteria. [11] Defaulters are more in Apremilast than methotrexate probably again due to low dosage regimen and supplement folic acid therapy During the follow-up period two of the patients in the methotrexate group had relapse after 2 months then they were treated with methotrexate in higher doses [12]. Four patients in the Apremilast group showed exacerbation of lesions out of which one patient developed relapse after 3 months and was switched to methotrexate, one patient had a relapse within one month started with cyclosporine and another two had minimal scaling in 2 months and were treated symptomatically and with topical emollients [13-15]

CONCLUSION

Both methotrexate and Apremilast showed equal efficacy in the treatment of moderate to severe plaque psoriasis. Incidence of adverse effects is minimal or absent with methotrexate when compared to Apremilast at the end of 16 weeks. Apremilast showed a very good response to nail psoriasis than methotrexate. Both Apremilast and methotrexate showed similar responses for scalp lesions and Palmoplantar lesions. Methotrexate is a cost-effective drug available in our setting. Though it carries many adverse effects and life-threatening toxicities, it can be used safely by frequent lab monitoring, low-dose regimens, and folic acid supplementation. Three patients who failed to achieve PASI 75 with 7.5mg of methotrexate might have achieved the same with higher doses. No significant difference was seen in both the groups in achieving PASI 75 at the end of 4 months. To the best of our knowledge, ours is the only comparative study using low dose of methotrexate i.e. 7.5mg/week. While all other studies used 15mg/week as an initial dose.

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