

Comparison of Efficacy of Methotrexate Versus Acitretin in the Treatment of Chronic Plaque Psoriasis

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Abstract

Objective: To compare the efficacy of methotrexate versus acitretin in the treatment of chronic plaque psoriasis

Method: Randomized Controlled Trial conducted in Dermatology Department, Services Hospital Lahore, on 60 patients after informed consent, divided into two groups. Group A was given methotrexate 0.3-0.5mg/kg orally and Group B was given acitretin 0.4mg/kg orally. Efficacy was ascertained by reduction in PASI score, calculated at baseline and at 12 weeks

Results : Patients of Group A achieved a reduction in PASI score from baseline 13.13 ± 2.047 to 6.20 ± 2.024 (efficacy 76.7%) while in Group B, PASI score dropped from 13.53 ± 2.047 to 7.00 ± 1.857 (efficacy 56.7%) . Adverse effects for both groups were minimal.

Conclusion: Both methotrexate and acitretin are highly effective drugs in treating chronic plaque psoriasis. However, methotrexate showed greater efficacy and faster reduction in PASI as compared to acitretin.

Keywords: Efficacy, Methotrexate, Acitretin, Chronic Plaque Psoriasis

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Introduction

Psoriasis is a common, chronic, inflammatory condition of the skin, characterized by red, scaly, sharply demarcated, indurated plaques, present particularly over the extensor surfaces of the skin and scalp. The disease varies in its graveness over time and in individuals during life. It is polygenic in predisposition and is influenced by environmental triggers such as trauma, infection, or medication.¹

Psoriasis is prevalent in different populations varying from 0.27% to 11.4%, more common in high income countries and elderly, often presenting in bimodal distribution, in both genders, with women affecting a little earlier than men.²

Psoriasis Area and Severity Index (PASI) is used to assess the severity of psoriasis. We scan four areas of the body (head, trunk, upper and lower limbs) in relation to erythema, induration (thickness), desquamation (scaling) of the plaques and body surface area involved. Scores are assigned from 0 to 4 based on intensity of erythema, induration and scaling to figure out severity of psoriasis.³ Oral methotrexate, an antimetabolite, is an effective immunomodulator used for treating psoriasis over. The drug competitively inhibits enzyme dihydrofolate reductase resulting in lower nucleic acid production through folate, in a dose dependent manner. Low dose weekly administration inhibits proliferation of lymphoid tissue in psoriatic plaques.⁵

The oral retinoids are vitamin-A derivatives, possess immunomodulatory and anti-inflammatory activity, used for treating psoriasis. The drug modulates epidermal proliferation and differentiation. Etretnate was the first retinoid introduced now replaced by acitretin which is its active metabolite.⁴

Naldi et al., studied methotrexate in chronic plaque psoriasis and reported a reduction of 75% in their PASI

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score values.⁶ In Pakistan Sabiha et al., recorded an almost complete remission in 40% of patients during eight weeks of treatment with methotrexate at a dosage of 7.5mg weekly.⁷

Borghi A et al., retrospectively evaluated the efficacy and safety of acitretin in moderate to severe plaque psoriasis concluded that acitretin at an initial low (10 mg/day, gradually increased (<50 mg/day) than maintaining at the minimal effective dose, is a suitable treatment option for plaque psoriasis.⁸ Acitretin in combination with TNF- α monoclonal antibodies has a synergistic effect alleviates secondary no response to the biologics, improves drug efficacy, accelerate the remission and reduce the costs of disease reduces the incidence of cardiovascular events and mortality.⁹ While comparing both drugs with each other Noor SM et al., found excellent response with methotrexate in 53.5% against 25.3% in acitretin group in chronic plaque psoriasis.¹⁰

Therefore, we have conducted this research in our set up to find out which drug is more efficacious among the two, thus enabling healthcare professionals in developing a good treatment protocol for the disease with profound psychosocial impact.

Methods

This randomized controlled trial was carried out in the Dermatology Department, Services Hospital Lahore in total sixty patients, of either gender and age ranging from 18-50 years suffering from chronic plaque psoriasis, of any duration with PASI \geq 10 were enrolled through non probability convenient sampling and equally divided into two groups of 30 patients each.

Psoriasis: Patients having characteristic erythematous, scaly, indurated lesions over extensor surfaces of the skin, with PASI \geq 10. Patients suffering comorbidities like eczema, lichen planus, systemic illnesses like chronic liver disease, lung disease, anemia, alcoholics, drug allergy, using any topical treatment within 2 weeks, or systemic therapy before 4 weeks of study, pregnant or lactating female, having abnormal lipid profile (cholesterol more than 230mg/dl and triglycerides more than 200mg/dl) or suffering from Hepatitis B/Hepatitis C/HIV were excluded. Distributed into two groups A and B using lottery method. **Methotrexate:** An antimetabolite, administered to group A in the form of a tablet 0.3-0.5mg/kg, orally once a week for 12 weeks. Tablet folic acid 5mg once daily was given to patients to minimize systemic side effects. **Acitretin:** Vitamin A derivative, administered to group B, as a capsule 0.4mg/kg orally, daily for 12 weeks. **Efficacy:** was assessed as a reduction

in PASI score which was assessed at baseline and the completion of study 12 weeks later. Drug was considered efficacious if the reduction in PASI from baseline will be \geq 50%.

$$\% \text{ Reduction} = \frac{\text{Baseline PASI} - \text{Post-treatment PASI}}{\text{Baseline PASI}} \times 100$$

Efficacy was assessed at baseline and after 12 weeks. Information regarding demographic data and outcome variables recorded in a predesigned proforma. Data was analyzed using SPSS version 22. Quantitative variables like age and duration was assessed as mean \pm standard deviation. Both groups were compared using the chi-square test. Qualitative variables like gender and efficacy was presented as frequency and percentages. Effect modifiers such as age, gender and disease duration were controlled by stratification. Post stratification chi-square test was applied to compare the two groups. P-value of \leq 0.05 was taken as significant.

Results

A total of 60 patients were enrolled in the study. The mean age of the patients was 30.73 \pm 6.62 years with minimum and maximum age of 19 and 50 years respectively. Among patients from Group A, the mean age of the patients was 29.50 \pm 6.85 years, whereas the mean age of patients in Group B was 31.97 \pm 6.26. The number of male patients in the study was 26(43.33%) while 34(56.67%) patients were females. **(Fig 1)** In our study 33(55%) patients were married while 27(45%) patients were unmarried. Mean duration of disease of the patients was 10.15 \pm 4.51 months with minimum & maximum duration of 2 & 60 months respectively. In Group A, the mean PASI score at baseline was 13.13 \pm 2.047 which reduced to mean PASI value of 6.20 \pm 2.024 at the end of 12 weeks with a mean percentage reduction of 53.46 \pm 10.64. In group B, mean PASI at baseline was 13.53 \pm 1.717 which reduced at 12th week follow up to the mean PASI score of 7.00 \pm 1.857 with mean percentage reduction of 48.24 \pm 12.24. (Table 1) According to this study, efficacy was achieved in 40(66.67%) of the total 60 enrolled patients. **(Fig 2)** In the methotrexate group the efficacy achieved in 23(76.7%) patients. Among acitretin group the efficacy achieved in 17(56.7%) patients. Statistically both group showed insignificant difference. i.e. p value=0.100. **(Table 2)** According to the age stratification, in patients with age \leq 30 years, efficacy in methotrexate group was achieved in 15(78.9%) patients (p value=0.055) and in acitretin group it was achieved in 6(46.2%) patients. In patients with age > 30 years, in methotrexate group, efficacy was achieved in 8(72.7%)

patients (p-value=1.00). Among acitretin group the efficacy achieved in 11(64.7%) patients.(Table 3) The study results showed that in patients with duration of disease ≤ 8 months, in methotrexate group the efficacy was achieved in 7(70.0%)patients, whereas in the acitretin group, the efficacy was achieved in 8(72.7%) patients (p-value=0.890). Similarly in patients with duration of disease >8 months, in methotrexate group the efficacy achieved in 16(80.0%) patients, and among acitretin group the efficacy achieved in 9(47.4%) patients (p-value=0.048). (Table 3)

Fig 1: Distribution of Gender in Study Population

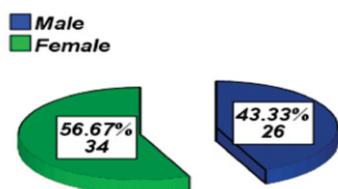


Table 1: Summary statistics of PASI score at baseline and 12 weeks along with percentage reduction between study groups

PASI	Study group		p-value
	Methotrexate 30	Acitretin 30	
Baseline	13.13±2.05	13.53±1.72	0.415
12 th week	6.20±2.02	7.00±1.86	0.116
Mean Percentage reduction	53.46	48.24	0.083
Standard deviation	10.64	12.24	

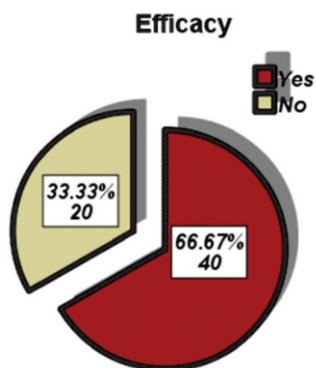


Fig 2 : Distribution of Efficacy in Study Population

Patients on methotrexate varyingly experienced nausea, headache, body aches, vertigo managed with medication. Acitretin group suffered from pruritis, mucocutaneous dryness, cheilitis, but none required treatment discontinuation.

Table 2: Distribution of efficacy between study groups

Efficacy	Study Group		Total	p-value
	Methotrexate	Acitretin		
Yes	23 76.7%	17 56.7%	40 66.7%	0.100
No	7 23.3%	13 43.3%	20 33.3%	
Total	30 100.0%	30 100.0%	60 100.0%	

Table 3: Distribution of efficacy between study groups according to age and duration of disease

Age (years)	Efficacy	Study Group		Total	p-value
		Methotrexate	Acitretin		
≤ 30	Yes	15 78.9%	6 46.2%	21 65.6%	0.055
	No	4 21.1%	7 53.8%	11 34.4%	
>30	Yes	8 72.7%	11 64.7%	19 67.9%	1.000
	No	3 27.3%	6 35.3%	9 32.1%	
Duration of disease (months)					
≤ 8	Yes	7 70.0%	8 72.7%	15 71.4%	0.890
	No	3 30.0%	3 27.3%	6 28.6%	
>8	Yes	16 80.0%	9 47.4%	25 64.1%	0.048
	No	4 20.0%	10 52.6%	14 35.9%	

Discussion

Psoriasis is a chronic skin disease. Mild disease is usually controlled with topical treatment while for moderate severe condition phototherapy, methotrexate, acitretin, ciclosporin, apremilast and biologic therapies (e.g., etanercept, infliximab, secukinumab) are good options. Combination drug therapy is used depending upon short and long-term considerations, disease severity, efficacy and side effect profile of available treatment options, quality of life of the patient and affordability.¹¹

Our study results showed that both methotrexate and acitretin were effective as evident by the decreasing scores for psoriasis area severity index, once treatment started. But after 12 weeks of treatment, methotrexate was found to be more effective of the two with a greater number of patients achieving efficacy.

The mean age of the patients in our study was 30.73 ± 6.62 years with minimum and maximum age of 19 and 50 years respectively. This was very similar to the mean age of 35.14 ± 16.16 years that was found in a study by Affandi et al, as part of a 10 year review of Malaysian Psoriasis registry.¹² Psoriasis is bi-modal with two age brackets with first peak occurring at 16-22 years, and the second at 57-60 years¹³. This was not found in our study, but our results were consistent with other study conducted in Taiwan, in which psoriasis was seen in the third decade of life.¹⁴

Our study population consisted of 26 (43.33%) male and 34(56.67%) female patients. The greater percentage of females reported is perhaps due to greater feelings of stigmatization related to disease and being more strongly impacted psychologically. Women are affected more with psoriasis; feeling unhappy (women: 18.5%; men: 11.3% lower vs. general population), stressed (women: > 60%; men: 42%), socially isolated (women: 25-28%; men: 19-24%), stigmatised (Feelings of Stigmatization Questionnaire score; women: 93.2; men: 78.0), and reduced libido (women: 33%; men: 19%) compared with men.¹⁵ That is why more women chose to seek treatment for their psoriasis in our study. In another study by Gawlik et al., 16 out of a total of 130 patients, 56.92% (70) were female. The gender distribution in this study is closer to our own. While some other studies indicated males to be affected more in Germany¹⁷ (0.76% vs 0.66%), and in United States¹⁸ [2.5% vs 1.9% with an odds ratio=1.37 (95% CI: 1.14–1.64)]. Of the total 60 patients in our study 33(55%) were married while 27(45%) patients were unmarried. Although more married chose to seek treatment in our study but in a study done by Gawlik et al., where 59.23% of the respondents were married. The impact of psoriasis was more profound in single individuals. Marital status disturbs Quality of Life (QoL) with important statistical difference among married Vs unmarried statuses (Kruskal–Wallis test: $\chi^2 = 10.411$; $df = 3$; $p = 0.034$).¹⁶ As such, marital status may influence which patients choose to seek treatment.

Mean duration of disease in patients was 10.15 ± 4.51 months in our study. This was very low in contrast to what noted by Colombo et al., in Italy where the mean time of disease duration was 18.7 years. This difference can be due to the fact that the study from Italy recruited psoriasis of all severity and there was no minimum body surface area involvement, whereas in our study, a minimum of 10% of BSA (Body Surface Area) involvement

was required for eligibility.¹⁹ It is possible that patients with greater area severity sought treatment earlier in the course of disease.

Regarding PASI, patients in the methotrexate group had a mean PASI of 13.13 ± 2.047 (p-value=0.415). At week 12, the mean PASI score was 6.20 ± 2.024 (p-value = 0.116). In this group, the mean PASI reduction from baseline to week 12 was $53.46 \pm 10.64\%$.

For those in the acitretin group, the mean PASI score at baseline was 13.53 ± 1.717 (p-value=0.415), which had dropped to a mean of 7.00 ± 1.857 (p-value= 0.116) at week 12. The mean percentage reduction in PASI was $48.24 \pm 10.24\%$.

Efficacy was achieved in 76.7% (23) of patients in the methotrexate group, whereas in patients being given acitretin, 56.7%(17) patients achieved a 50% or greater reduction in PASI compared to baseline. Statistically both groups showed insignificant difference. i.e. p value = 0.100.

In a study by Naldi et al., it was concluded that use of methotrexate resulted in clinical improvement of 75% of patients, which is comparable to the results of our study.⁶ Similarly, Sabiqha Haider et al., found that methotrexate satisfactorily controlled disease within 5-7 weeks (mean 6 ± 0.89 weeks).⁷ The mean baseline PASI reduced from 14.8 ± 4.2 to 4.9 ± 4.3 (reduction in PASI of 95%) in 29(40%) patients. Partial remission (reduction in PASI of 75%) was achieved in 44 (60%) patients. In our study, 76.7% of patients of methotrexate were able to achieve a 50 percent or greater reduction in PASI scores. This is greater than the 60% of patients that were able to achieve a partial remission in the study by Sabiqha et al., possibly because a different end point was used. We declared the drug efficacious at 50% reduction in PASI from baseline whereas the other study in question used a 75% reduction in score from baseline to declare partial remission. Hence, the results are comparable. In another study by Heydendael et al., partial remission was achieved by 60% of patients on methotrexate after 16 weeks of treatment. The end point employed by this study was also a 75% reduction in PASI score from baseline, which was higher than the percentage reduction used in our study.²⁰

In our study, 56% of patients achieved efficacy on acitretin. The result is comparable to Murray et al., who observed a response in 60% of the patients.²¹

According to a study conducted by Parsam et al., comparing methotrexate versus acitretin in palmoplantar

psoriasis, concluded that oral methotrexate clears condition faster than acitretin with statistically significant reduction in scores. The MPASI score in group I was 57.15 ± 17.17 at baseline and 14.50 ± 13.55 at the end of 3rd month. While MPASI score in group II was 57.76 ± 18.60 at baseline and 21.30 ± 8.168 at the end of 3rd month.²² The study results were very close to our own, which could be due to the fact that our sample size and doses of methotrexate and acitretin used in both studies were very similar.

Noor et al., conducted a study in Pakistan comparing the efficacy of methotrexate and acitretin in the treatment of chronic plaque psoriasis. They concluded that methotrexate is a better option than acitretin for patients of moderate to severe chronic plaque psoriasis. In their study of 142 patients, 53.5% of patients achieved an excellent response (PASI75) on methotrexate while 25.3% of patients on acitretin were able to achieve an excellent response.¹⁰ The results are in line with our study, as a greater percentage of patients on methotrexate were able to achieve efficacy compared to those on acitretin.

Conclusion

From our present work we conclude that both methotrexate and acitretin are efficacious in treating chronic plaque psoriasis and can be used alone or in combination with other therapies especially biologics to achieve sustained remission. These drugs are cost effective alternatives to expensive biological therapies.

Conflicts of Interest

None

Funding Source

None

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Authors Contribution

SS: Conceptualization of Project

SS,AA: Data Collection

SS,AA: Literature Search

SS: Statistical Analysis

SS: Drafting, Revision

SS: Writing of Manuscript