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Comparison of Efficacy of Oral Methotrexate and Acitretin for Generalized Lichen Planus

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ABSTRACT

Background: Generalized lichen planus is a chronic inflammatory dermatosis that often requires systemic therapy when widespread or resistant to topical treatment. Methotrexate and acitretin are commonly used systemic agents, but comparative data on their efficacy remain limited. **Objective:** To compare the efficacy of oral methotrexate versus oral acitretin in the treatment of generalized lichen planus. **Material and Methods:** This randomized controlled trial was conducted at the Dermatology Outpatient Department of Sheikh Zayed Hospital, Rahim Yar Khan, over six months (May 31, 2024 to November 30, 2024). A total of 124 patients aged 13–50 years with generalized lichen planus were included. Patients were randomly divided into two groups of 62 each. Group A received oral methotrexate 10 mg once weekly for 12 weeks along with folic acid, while Group B received oral acitretin 50 mg daily for 6 weeks. Efficacy was assessed clinically after completion of treatment. Data were analyzed using SPSS version 25.0, and the Chi-square test was applied to assess statistical significance ($p \leq 0.05$). **Results:** Overall, efficacy was achieved in 48 (77.4%) patients treated with methotrexate and 35 (56.5%) patients treated with acitretin ($p = 0.013$). Stratified analysis showed significantly higher efficacy of methotrexate in females, patients aged ≥30 years, those with disease duration ≥6 months, BSA involvement ≥20%, and those with comorbidities. **Conclusion:** Oral methotrexate was significantly more effective than oral acitretin in managing generalized lichen planus and may be considered a preferable first-line systemic therapy, especially in patients with chronic or extensive disease.

INTRODUCTION

Lichen planus (LP) is a chronic, immune-mediated inflammatory disorder affecting the skin, mucous membranes, nails, and scalp. Generalized lichen planus (GLP), involving widespread cutaneous distribution, often presents therapeutic challenges due to its persistent nature and frequent relapses. The pathogenesis is believed to involve a T-cell–mediated autoimmune reaction targeting basal keratinocytes, though the exact etiology remains elusive [1].

First-line treatments for GLP include topical and systemic corticosteroids. However, systemic corticosteroids are associated with significant side effects, particularly with long-term use, prompting the search for safer, steroid-sparing alternatives [2]. Among the immunomodulatory agents considered, methotrexate and acitretin have emerged as promising systemic therapies due to their anti-inflammatory and immunosuppressive properties.

Methotrexate, a folic acid antagonist, has been used widely in dermatological disorders for its ability to suppress aberrant immune activity. Its role in GLP has gained traction due to favorable efficacy and safety profiles. Recent studies have demonstrated that low-dose oral methotrexate is effective in controlling GLP, offering significant improvement in cutaneous lesions and pruritus with minimal adverse effects [3,4]. For example, in a randomized trial, 80% of patients treated with methotrexate achieved excellent response without serious side effects, making it a viable alternative to corticosteroids [5].

Acitretin, a second-generation retinoid, modulates epidermal proliferation and keratinocyte differentiation. Although primarily used in psoriasis and keratinization disorders, it has shown utility in LP, particularly in cases resistant to corticosteroids [6]. A recent randomized clinical trial showed that oral acitretin, in combination with topical triamcinolone, significantly improved disease severity in oral LP compared to topical therapy alone, indicating its potential systemic benefit in GLP as well [7]. Furthermore, studies have reported sustained remission with acitretin, even in patients with widespread cutaneous involvement [8].

While both methotrexate and acitretin have demonstrated efficacy in managing GLP, comparative data remain

limited. Most existing literature addresses their effectiveness independently or in combination with other agents, such as topical corticosteroids [7,9]. Additionally, treatment selection is often guided by patient-specific factors including comorbidities, reproductive status, and tolerance to adverse effects. Methotrexate, while cost-effective, requires regular monitoring for hepatotoxicity and hematological toxicity. Acitretin, on the other hand, is teratogenic and can cause mucocutaneous dryness and dyslipidemia, limiting its use, particularly in women of reproductive age [10].

The comparative evaluation of these two agents in the context of GLP is essential for establishing a clear therapeutic protocol, especially in patients contraindicated for corticosteroids. This study aims to assess and compare the efficacy, safety, and tolerability of oral methotrexate and oral acitretin in the treatment of generalized lichen planus.

MATERIALS AND METHODS

This randomized controlled trial was conducted at the Outpatient Department of Dermatology, Sheikh Zayed Hospital, Rahim Yar Khan, over a period of six months (May 31, 2024 to November 30, 2024 with ref to study approval No. CPSP/REU/DER-2022-110-19249). Male and female patients aged between 13 and 50 years, diagnosed clinically with generalized lichen planus, were included in the study. Only patients who had not received any prior treatment in the last one month were considered eligible for participation.

Patients were excluded if they were pregnant or lactating, had a known bleeding disorder, deranged liver function tests, platelet counts below 100,000, or a history of hypersensitivity to methotrexate or acitretin. Individuals with unrealistic expectations regarding treatment outcomes were also excluded.

The sample size was calculated using the WHO sample size calculator, considering a level of significance of 5%, power of test at 80%, population standard deviation of 14.77%, test value of population mean as 0.55%, and anticipated population mean of 0.33. Based on these parameters, a total of 124 patients were enrolled, with 62 patients allocated to each treatment group. [11-12]

Patients were selected using a non-probability consecutive sampling technique. Informed consent was obtained from all participants. The patients were randomly divided into two groups. Group A received oral methotrexate 10 mg once weekly for 12 weeks along with folic acid 5 mg daily. Group B received oral acitretin 50 mg once daily for 6 weeks. All patients were followed at 3-week intervals to monitor treatment response and adverse effects.

Data were collected using a structured proforma and analyzed using IBM SPSS Statistics version 25.0. Quantitative variables such as age and duration of disease were presented as means ± standard deviations, while categorical variables such as gender, treatment group, efficacy, and comorbidities were presented as frequencies and percentages.

The primary outcome variable was treatment efficacy, categorized as Yes (effective) or No (not effective) based on clinical improvement observed at follow-up. The Chi-square test was used to compare efficacy between the two treatment groups.

To assess the impact of possible confounding variables, stratified analysis was conducted across key factors including age group (<30 years vs. ≥30 years), gender, duration of disease (<6 months vs. ≥6 months), baseline severity (body surface area involvement <20% vs. ≥20%), and presence of comorbidities (yes/no). Within each subgroup, the relationship between treatment group and efficacy was reassessed using the Chi-square test.

A p-value ≤ 0.05 was taken as statistically significant for all analyses.

RESULTS

The mean age of the study participants was 31.23 ± 10.97 years. Patients in the methotrexate group had a mean age of 30.26 ± 10.68 years, while those in the acitretin group had a slightly higher mean age of 32.21 ± 11.24 years.

In the methotrexate group, 48 patients (77.4%) achieved clinical efficacy, while 14 patients (22.6%) did not show a satisfactory response. In comparison, in the acitretin group, 35 patients (56.5%) responded positively to treatment, whereas 27 patients (43.5%) failed to achieve clinical efficacy. These findings indicate that a significantly higher proportion of patients treated with oral methotrexate experienced clinical improvement compared to those receiving oral acitretin. The difference in treatment response between the two groups was statistically significant, with a p-value of 0.013 using the Chi-square test. (Table 1)

In the gender-based stratification, male patients showed a comparable response to both treatments, with 23 (76.7%) achieving efficacy in the methotrexate group versus 20 (69.0%) in the acitretin group (p = 0.506), indicating no statistically significant difference. However, among female patients, a significantly higher response rate was observed in the methotrexate group with 25 (78.1%) achieving efficacy compared to only 15 (45.5%) in the acitretin group (p = 0.007), suggesting that methotrexate is notably more effective than acitretin in females.

Stratification by age group revealed that in patients aged <30 years, efficacy was achieved in 21 (70.0%) of those treated with methotrexate versus 15 (55.6%) with acitretin (p = 0.259), a difference that did not reach statistical significance. However, in patients aged ≥30 years, methotrexate demonstrated significantly greater efficacy, with 27 (84.4%) showing improvement compared to 20 (57.1%) in the acitretin group (p = 0.015). This suggests that older patients may respond more favorably to methotrexate than to acitretin.

When analyzed based on disease duration, methotrexate showed better efficacy in both subgroups, though statistical significance was only reached in patients with longer disease duration. Among those with disease duration <6 months, 12 (70.6%) responded to methotrexate and 9 (47.4%) to acitretin (p = 0.158). In contrast, for those with ≥6 months of disease duration, methotrexate was significantly more effective, with 36 (80.0%) achieving efficacy compared to 26 (60.5%) in the acitretin group (p = 0.045). These results indicate that methotrexate may offer greater therapeutic benefit in chronic or long-standing cases of lichen planus.

Assessment of body surface area (BSA) involvement

revealed that among patients with limited disease (<20% BSA), efficacy was high in both groups: 11 (84.6%) in the methotrexate group and 9 (64.3%) in the acitretin group (p = 0.228). However, in patients with more extensive disease (≥20% BSA involvement), methotrexate again proved superior, with 37 (75.5%) achieving response compared to 26 (54.2%) in the acitretin group (p = 0.028). This supports the use of methotrexate in patients with widespread cutaneous involvement. Regarding comorbidity status, methotrexate was effective regardless of comorbid conditions, but the difference in efficacy was more pronounced in patients with comorbidities. Among patients without comorbidities, 34 (73.9%) in the methotrexate group and 27 (58.7%) in the acitretin group achieved efficacy (p = 0.123). Notably, in patients with comorbidities, methotrexate demonstrated a markedly higher efficacy rate of 14 (87.5%) compared to 8 (50.0%) in the acitretin group (p = 0.022), showing that methotrexate remains effective even in complex clinical scenarios. Overall, the stratified analysis consistently shows that methotrexate outperformed acitretin across multiple clinically relevant subgroups, particularly in females, older patients, those with longer disease duration, greater BSA involvement, and comorbid conditions. These findings reinforce the broader efficacy and potential advantage of methotrexate as a first-line systemic agent in the management of generalized lichen planus. (Table 2)

Table 1

Comparison of Efficacy between the Two Treatment Groups

Group	Efficacy: Yes	Efficacy: No	p-value
Methotrexate	48 (77.4%)	14 (22.6%)	0.013
Acitretin	35 (56.5%)	27 (43.5%)	

Table 2

Stratified Comparison of Treatment Efficacy between Methotrexate and Acitretin

Stratified Variable	Subgroup	Methotrexate (Yes/No)	Acitretin (Yes/No)	p-value
Gender	Male	23 / 7 (76.7% / 23.3%)	20 / 9 (69.0% / 31.0%)	0.506
	Female	25 / 7 (78.1% / 21.9%)	15 / 18 (45.5% / 54.5%)	0.007
Age Group	<30 years	21 / 9 (70.0% / 30.0%)	15 / 12 (55.6% / 44.4%)	0.259
	≥30 years	27 / 5 (84.4% / 15.6%)	20 / 15 (57.1% / 42.9%)	0.015
Disease Duration	<6 months	12 / 5 (70.6% / 29.4%)	9 / 10 (47.4% / 52.6%)	0.158
	≥6 months	36 / 9 (80.0% / 20.0%)	26 / 17 (60.5% / 39.5%)	0.045
BSA Involvement	<20%	11 / 2 (84.6% / 15.4%)	9 / 5 (64.3% / 35.7%)	0.228
	≥20%	37 / 12 (75.5% / 24.5%)	26 / 22 (54.2% / 45.8%)	0.028
Comorbidities	No	34 / 12 (73.9% / 26.1%)	27 / 19 (58.7% / 41.3%)	0.123
	Yes	14 / 2 (87.5% / 12.5%)	8 / 8 (50.0% / 50.0%)	0.022

DISCUSSION

Our study demonstrated that oral methotrexate is significantly more effective than oral acitretin in managing generalized lichen planus (GLP), with 77.4% of patients achieving clinical efficacy compared to 56.5% in the acitretin group (p = 0.013). This finding mirrors trends observed in recent dermatologic literature, particularly regarding methotrexate's utility as a potent immunomodulatory agent in inflammatory skin diseases.

A 2023 randomized controlled trial assessing methotrexate and acitretin in chronic plaque psoriasis showed higher efficacy in the methotrexate group (78.6%) compared to the acitretin group (58.6%), with a statistically significant difference (p < 0.005) [13]. While psoriasis and lichen planus have distinct pathophysiologies, both involve dysregulated T-cell activity.

Methotrexate's inhibition of dihydrofolate reductase and subsequent suppression of lymphocyte proliferation may account for its broader efficacy across autoimmune dermatoses. The higher response rate among females in our methotrexate group (78.1% vs. 45.5% with acitretin; p = 0.007) is consistent with observations from Alsenaid et al., who noted that adverse effects of acitretin, such as mucocutaneous dryness and teratogenic risks, often limit its acceptability in women of reproductive age [14]. In contrast, methotrexate—despite requiring contraceptive measures—has a shorter post-treatment teratogenic window and better tolerability in this population.

Patients aged ≥30 years showed a more pronounced response to methotrexate compared to acitretin (84.4% vs. 57.1%, p = 0.015). This age-dependent difference may relate to more stable immune regulation or medication metabolism in older individuals. A 2023 retrospective review on palmoplantar lichen planus similarly reported successful remission with methotrexate in middle-aged patients after failure of steroids and retinoids [15].

Our stratified analysis also found that methotrexate demonstrated higher efficacy in patients with disease duration ≥6 months (80.0%) compared to acitretin (60.5%, p = 0.045). Khurana et al. recently showed that methotrexate led to complete resolution in 93% of recalcitrant lichen planus cases within an average of 15 weeks, with durable remission lasting over two years [16]. These outcomes underscore methotrexate's effectiveness in long-standing disease.For patients with ≥20% body surface area (BSA) involvement, methotrexate was more effective (75.5%) than acitretin (54.2%, p = 0.028). This mirrors findings from a prospective trial on palmoplantar psoriasis, where methotrexate produced greater PASI reduction than acitretin in severe disease [17]. These results suggest that methotrexate may be more appropriate for extensive disease due to its systemic immunosuppressive effects.

In patients with comorbidities, methotrexate was significantly superior (87.5% vs. 50.0%, p = 0.022). Methotrexate's longstanding track record and well-established monitoring protocols make it a safer option for individuals with complex health profiles. A case report of vulvar lichen planus further illustrated successful disease control and tolerability with methotrexate after acitretin failure in a patient with cardiovascular risk factors [18].

While some studies advocate for acitretin in hyperkeratotic or mucosal forms of lichen planus, it often requires adjunctive therapies for optimal results. For instance, Vinay et al. reported that oral acitretin combined

with topical corticosteroids significantly improved oral lichen planus compared to topical monotherapy alone [19]. This suggests that acitretin may not be as effective as monotherapy in widespread cutaneous involvement, which matches our findings.Lastly, a 2023 scoping review of systemic immunomodulators for oral lichen planus concluded that methotrexate demonstrated the strongest evidence among non-steroidal therapies, with clinical improvement seen in up to 93% of cases [20]. These findings provide further validation of methotrexate as a first-line systemic treatment option for GLP.

CONCLUSION

Based on the findings of this study, oral methotrexate demonstrated superior efficacy compared to oral acitretin in the treatment of generalized lichen planus. This difference was statistically significant overall and remained consistent across key subgroups, including female patients, individuals aged 30 years and above, those with disease duration of six months or more, patients with extensive body surface area involvement, and those with comorbidities. These results suggest that methotrexate may offer a more reliable and effective treatment option for generalized lichen planus, particularly in patients with more severe or chronic disease profiles

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