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RESEARCH ARTICLE
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COMPARISON OF SAFETY AND EFFICACY OF ORAL PIOGLITAZONE VERSUS ORAL METHOTREXATE IN THE MANAGEMENT OF PATIENTS WITH PLAQUE-TYPE PSORIASIS: A RANDOMIZED CONTROL STUDY

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Abstract

Background: Psoriasis is a chronic, immune-mediated inflammatory skin disorder affecting quality of life. Plaque-type psoriasis, its most common form, requires long-term management balancing efficacy and safety. Methotrexate, while effective, presents risks such as hepatotoxicity and hematological side effects. Pioglitazone, a thiazolidinedione, has shown potential as a safer alternative, but evidence remains inconclusive. Thus, the study aimed to compare the safety and efficacy of oral Pioglitazone versus oral Methotrexate in patients with plaque-type psoriasis.

Materials & Methods: The study was conducted on plaque psoriasis patients at Hassan Institute of Medical Sciences. It followed an open-label randomized control design with 34 participants, split into two groups of 17 each. Group 1 received Methotrexate (7.5 mg) weekly with folic acid, while Group 2 received Pioglitazone (30 mg) daily. PASI scores were measured at baseline and reassessed at weeks 4, 8, and 12. Appropriate tests were performed to assess potential adverse events.

Results: Methotrexate patients had a mean age of 56.12 years versus 50.76 years for pioglitazone ($p = 0.177$). Both groups had similar gender distributions ($p = 0.697$), illness duration ($p = 0.914$), and nail involvement ($p = 0.486$). Baseline PASI scores were 15.36 for methotrexate and 14.32 for pioglitazone, decreasing to 5.42 and 6.32 respectively by week 12 ($p = 0.033$). Methotrexate showed a 68.15% PASI improvement, while pioglitazone had 57.03% ($p = 0.021$). Six patients in the

methotrexate group experienced adverse effects, compared to only three in the pioglitazone group (p = 0.117).
Conclusion: Although methotrexate demonstrated superior efficacy in treating plaque-type psoriasis compared to pioglitazone, the pioglitazone group had a lower incidence of side effects. However, the difference in the adverse effect profiles between the two groups was not statistically significant.

Key Words: Plaque-type psoriasis, Methotrexate, Pioglitazone, Psoriasis Area and Severity Index (PASI), Adverse reactions

INTRODUCTION

Psoriasis is a long-term inflammatory skin condition characterized by recurring episodes and papulosquamous lesions. [1] It impacts 2-3% of the worldwide population and is often observed in individuals with a genetic predisposition, with environmental factors primarily influencing the skin, nails, and joints. [2]

The pathogenesis of plaque psoriasis involves a complex interaction between genetics, environmental factors, and the immune system. The immune response is crucial in the development of the disease, as activated T cells accumulate in the skin, leading to inflammation. Key cytokines, including interleukin-17 (IL-17), tumor necrosis factor-alpha (TNF-alpha), and interleukin-23 (IL-23), contribute to this inflammatory response by promoting keratinocyte proliferation and differentiation, resulting in psoriatic plaques. Additionally, genetic factors play a significant role, notably HLA-Cw6, which is associated with an increased risk of psoriasis, as well as other immune response genes like IL-12 and IL-23. [3,4]

Traditionally, psoriasis has been treated with immunosuppressive and non-biologic disease-modifying drugs, including methotrexate, cyclosporine, retinoids, and phototherapy. Combining newer therapies with conventional treatments presents a promising strategy for achieving prolonged remission and enhancing quality of life (QoL). [5]

Among these, methotrexate, a folate antagonist, is commonly considered a first-line treatment because of its immunosuppressive properties. Methotrexate suppresses the proliferation of rapidly dividing cells, such as T cells and keratinocytes, by inhibiting dihydrofolate reductase, which reduces DNA synthesis and inflammation. However, its long-term use is restricted due to serious potential side effects, including hepatotoxicity, myelosuppression, and pulmonary toxicity. This highlights the need for alternative therapies that offer similar efficacy with a better safety profile.[6]

Pioglitazone, a thiazolidinedione class drug traditionally used in the management of type 2 diabetes mellitus, has recently garnered attention for its potential role in treating psoriasis.[7] The rationale for using Pioglitazone in psoriasis stems from its ability to modulate the peroxisome proliferator-activated receptor gamma (PPAR-γ), a nuclear receptor involved in regulating inflammation and immune responses.[8] Activation of PPAR-γ has been shown to inhibit the release of pro-inflammatory cytokines, reduce the infiltration of immune cells into the skin, and promote the differentiation of keratinocytes.[9]

Several studies have suggested that Pioglitazone exerts anti-inflammatory and immunomodulatory effects that may benefit patients with psoriasis, particularly in reducing the severity and extent of plaques. Importantly, Pioglitazone is associated with a lower risk of serious adverse effects compared to methotrexate, making it an attractive candidate for long-term use.[10]

Despite the promising role of pioglitazone, the evidence supporting its efficacy in the treatment of psoriasis is limited, with conflicting results from clinical trials and observational studies.[11] Studies directly comparing Methotrexate and Pioglitazone in the treatment of plaque-type psoriasis are scarce. This highlights the need for well-designed, randomized controlled trials to definitively assess the safety and efficacy of pioglitazone in comparison to established therapies such as methotrexate.

Given the rising prevalence of psoriasis and the limitations of existing treatments, identifying safe and effective alternatives is crucial. This study aims to evaluate whether Pioglitazone, a well-tolerated drug with metabolic benefits, can be a viable option for managing plaque psoriasis. If effective,

Pioglitazone may provide a new therapeutic approach for patients intolerant or unresponsive to methotrexate.

To address this gap, a randomized controlled trial was conducted to compare the safety and efficacy of oral Pioglitazone with oral Methotrexate in patients with plaque psoriasis. The primary objective was to assess the improvement in PASI scores at 12 weeks, while secondary objectives included monitoring adverse events and laboratory parameters to evaluate the safety profiles of both treatments.

Materials & Methods

This open-label, randomized controlled trial was conducted in the Department of Dermatology at Hassan Institute of Medical Sciences, Hassan. The study lasted approximately 24 weeks, including 12 weeks of treatment per patient. An additional period was allocated for patient recruitment, baseline assessment, and data analysis.

Before initiating the study, Ethical approval was obtained, and written informed consent was taken from all participants, adhering to the Declaration of Helsinki. A total of 34 patients were enrolled in the study.

Inclusion criteria:

1. Patients of either sex with a clinical diagnosis of plaque-type psoriasis covering ≥10% of body surface area (BSA).
2. Patients aged 18 years and above.
3. Patients willing to provide written informed consent.

Exclusion criteria:

1. Pregnant or lactating women.
2. Patients with significant comorbid conditions, including malignancies, diabetes mellitus, hepatic, renal, cardiovascular diseases, or other autoimmune/inflammatory diseases.
3. Immunocompromised patients.
4. Patients with active guttate, erythrodermic, pustular psoriasis, or psoriatic arthritis.
5. Patients who had received systemic treatment or phototherapy for psoriasis in the last six months.
6. Patients unwilling to comply with study protocols or provide informed consent.

Methodology

Participants meeting the inclusion criteria were randomized into two groups using simple randomization in a 1:1 ratio. Baseline clinical assessments included a complete medical history, physical examination, body mass index assessment, and evaluation of psoriasis severity using the Psoriasis Area and Severity Index (PASI). Baseline investigations included Random Blood Sugar (RBS), Complete Blood Counts (CBC), Liver Function Tests (LFT), Renal Function Tests (RFT), HIV, Chest X-ray (CXR), urine routine, and Mantoux test.

Group 1: Participants in this group received oral Methotrexate 7.5 mg weekly for 12 weeks. To mitigate the potential side effects of Methotrexate, participants received folic acid 1 mg daily, except on the days they took methotrexate.

Group 2: Participants in this group received oral Pioglitazone 30 mg once daily for 12 weeks.

During the study period, no concurrent antipsoriatic drug, topical or systemic was permitted in both groups except for bland emollients. PASI scores and laboratory investigations were reassessed at 4,8 and 12 weeks for safety and efficacy measurements. Therapeutic success was evaluated based on the change in PASI score from baseline to 12 weeks of treatment.

Patients were withdrawn from the study if they experienced severe weight gain and edema during follow-up, significant changes in blood cell count, a marked increase in hepatic enzymes (over 2.5 times the baseline), nausea and vomiting unresponsive to symptomatic treatment, or any persistent abnormalities in blood biochemistry or urinalysis (e.g., hematuria or proteinuria).

Source of the Data

The primary source of data for this study was the clinical records of patients with plaque-type psoriasis attending the outpatient department of Dermatology, Venereology, and Leprosy at Hassan Institute of Medical Sciences. Baseline data was collected during routine clinical visits and recorded on standardized case report forms.

STATISTICAL ANALYSIS

Data analysis was performed using Statistical Package for the Social Sciences (SPSS) software, version 22. Descriptive statistics included mean and standard deviation for continuous variables, and frequency and percentage for categorical variables. Inferential statistics involved the chi-square test to compare proportions, the unpaired t-test to compare age and duration of illness, and the Mann-Whitney U test to compare PASI scores between groups. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Table 1: Baseline Characteristics of Patients

Parameter	Methotrexate (n=17)	Pioglitazone (n=17)	p-value
Age (mean ± SD)	56.12 ± 8.53	50.76 ± 13.53	0.177
Sex (Male/Female)	12/5	13/4	0.697
Duration of Illness (mean ± SD)	4.76 ± 4.54	4.61 ± 3.18	0.914
Nail Involvement (Present/Absent)	11/6	9/8	0.486

The baseline characteristics in Table 1, show that the Methotrexate group had a mean age of 56.12 (± 8.53), while the Pioglitazone group had a slightly younger mean age of 50.76 years (± 13.53) with a mean difference of 5.36 years (p=0.177). The mean duration of illness in the Methotrexate group was 4.76 years (± 4.54), closely comparable to the Pioglitazone group at 4.61 years (± 3.18), with a negligible difference of 0.15 years (p=0.914). The sex distribution showed 12 males and 5 females in the Methotrexate group, compared to 13 males and 4 females in the Pioglitazone group (p=0.697). The number of males was more than twice that of females in both groups. Nail involvement was present in 11 Methotrexate patients. At the same time, in the Pioglitazone group, it was present in 9 patients (p=0.486).2 patients in the Pioglitazone group and 1 in the Methotrexate group were lost to follow-up and were not included in efficacy measurements.

Table 2: PASI Scores Comparison

PASI Time Points	Methotrexate(n=16) (mean ± SD)	Pioglitazone(n=15) (mean ± SD)	Mean Difference	p-value
PASI-0 (Baseline)	15.81 ± 2.91	14.85 ± 2.06	0.96	0.358
PASI-4 (Week 4)	12.58 ± 2.79	12.83 ± 1.71	-0.25	0.626
PASI-8 (Week 8)	8.33 ± 2.81	9.22 ± 2.15	-0.89	0.093
PASI-12 (Week 12)	5.15 ± 2.56	6.47 ± 1.84	-1.32	0.033

The PASI score progression over time as shown in Table 2, Figure 1 reveals that at baseline (PASI-0), the Methotrexate group had a mean score of 15.82 (± 2.91), while the Pioglitazone group had a mean of 14.85 (± 2.06), with a mean difference of 0.96 (p=0.358). At Week 4 (PASI-4), Methotrexate patients had a mean score of 12.58 (± 2.79) compared to 12.83 (± 1.71) in the Pioglitazone group (p=0.626). By Week 8 (PASI-8), the Methotrexate group had a score of 8.33 (± 2.81) while Pioglitazone showed 9.22 (± 2.15) (p=0.093). At Week 12 (PASI-12), the Methotrexate group's score decreased further to 5.15 (± 2.56), compared to 6.47 (± 1.84) for Pioglitazone (p=0.033), showing greater improvement in the Methotrexate group.

Table 3: Percentage reduction in PASI Scores

Time Points	Methotrexate (mean ± SD)	Pioglitazone (mean ± SD)	Mean Difference	p-value
% PASI-4 (Week 4)	20.63 ± 7.28	13.15 ± 7.65	7.48	0.009
% PASI-8 (Week 8)	47.82 ± 10.57	37.56 ± 12.86	10.26	0.019
% PASI-12 (Week 12)	68.15 ± 12.75	57.03 ± 12.22	11.12	0.021

The percentage reduction in PASI scores in Table 3 shows that at Week 4, Methotrexate patients experienced a mean reduction of 20.63% (± 7.28). In contrast, the Pioglitazone group had a reduction of 13.15% (± 7.47) with a significant mean difference of 7.47% (p=0.009). By Week 8, Methotrexate patients showed a greater reduction of 47.82% (± 10.57) compared to 37.56% (± 12.86) in the Pioglitazone group, yielding a mean difference of 10.26% (p=0.019). At Week 12, the Methotrexate group had a mean reduction of 68.15% (± 12.75), while Pioglitazone patients showed a reduction of 57.03% (± 12.22), with a mean difference of 11.11% (p=0.021), indicating superior efficacy for Methotrexate over time (**Figure 1**).

Table 4: Adverse effects in patients

Adverse effects			PATIENT		p-value
			Methotrexate group	Pioglitazone group	
ADR	Nil	Count	10	12	0.117
		%	62.5%	80.0%	
	Nausea, Vomiting	Count	2	0	
		%	12.5%	0.0%	
	Fatigue	Count	2	0	
		%	12.5%	0.0%	
	Elevated liver enzymes	Count	2	1	
		%	12.5%	6.7%	
	Pedal edema	Count	0	1	
		%	0.0%	6.7%	
	Weight gain	Count	0	1	
		%	0.0%	6.7%	

As shown in Table 4 and **Figure 2**, 65% of patients in the methotrexate group did not have any adverse effects as to 80% of patients in the Pioglitazone group. In the group receiving Methotrexate (16 participants), 2 (12.5%) experienced nausea and vomiting, 2 (12.5 %) reported fatigue, and 2 (12.5 %) showed elevated liver enzymes, leading to a total of 6 adverse effects overall. In the Pioglitazone

group (15 participants), 1 (6.7%) participant experienced weight gain, 1(6.7%) had pedal edema, and 1 (6.7 %) had elevated liver enzymes with a total of 3 adverse effects. Interestingly 10 patients in the Methotrexate group and 12 in the Pioglitazone group reported no adverse effects. This shows that relatively the adverse effect profile of Pioglitazone is lesser than subjects who were on Methotrexate but not statistically significant.

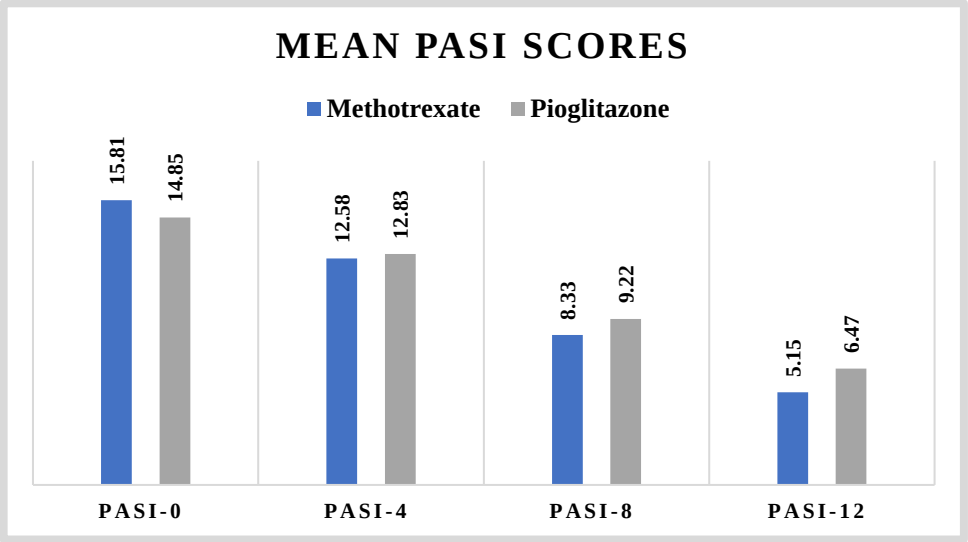

Figure 1: Mean PASI scores from baseline to week 12

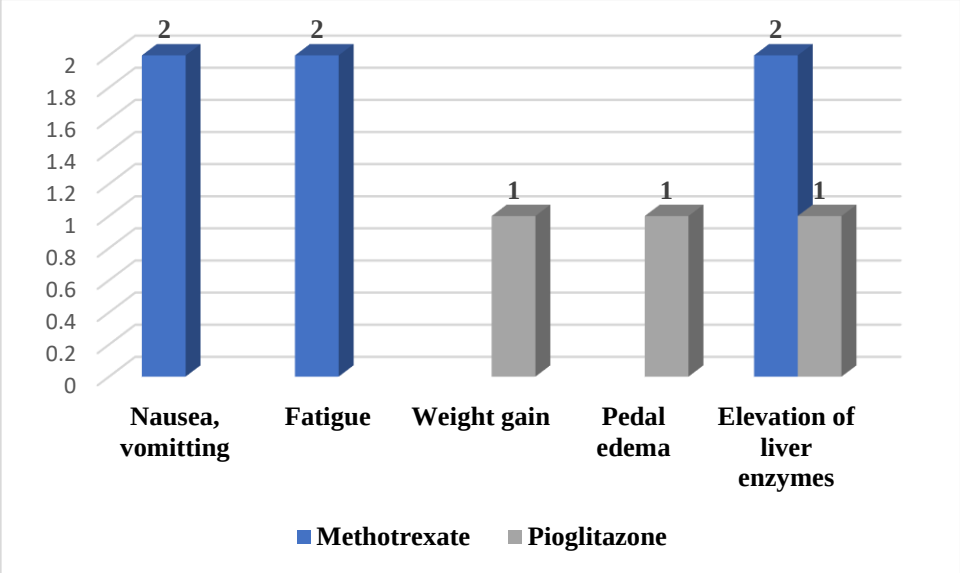

Figure 2: Adverse effects

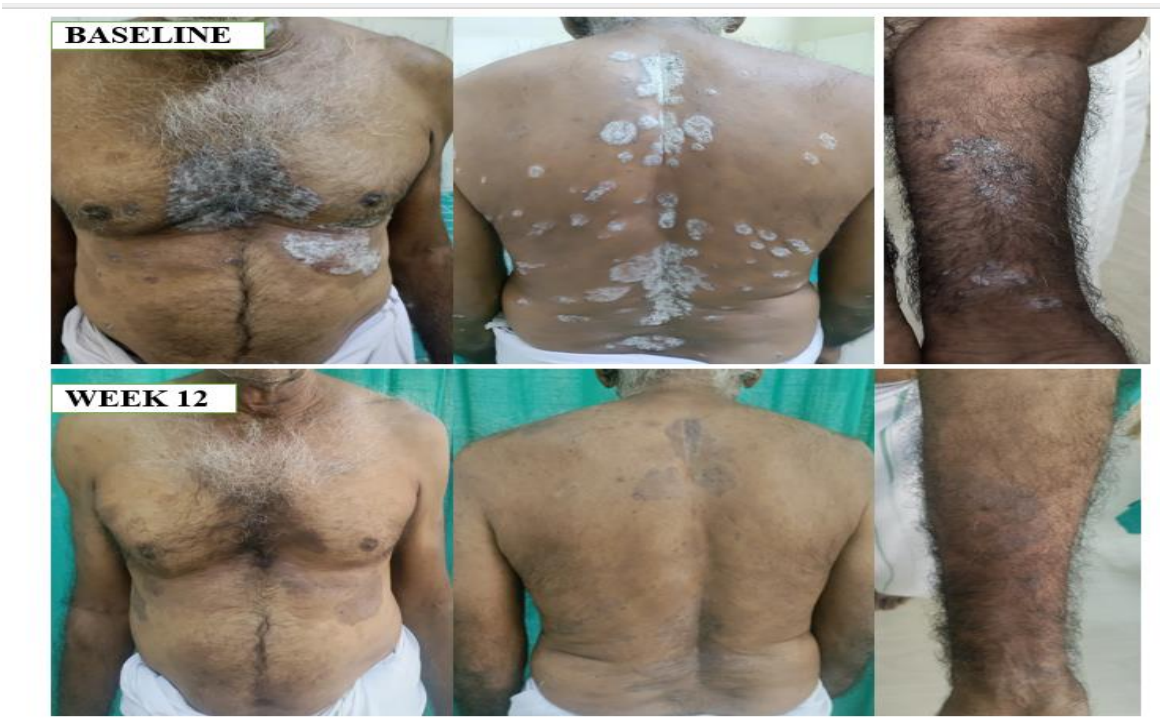

Figure 3: At week 12, the Methotrexate group showed improvement in lesions compared to baseline. Scaling decreased, and lesions healed with some remaining hyperpigmentation.

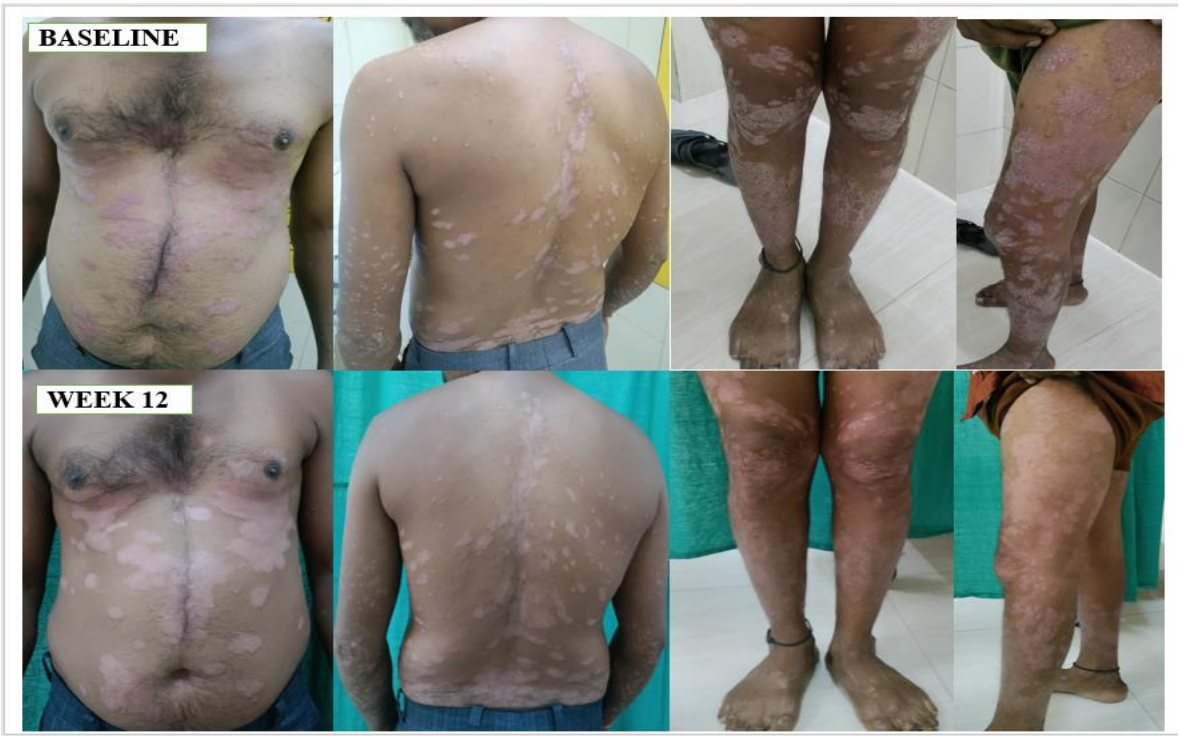

Figure 4: By the end of week 12, the Pioglitazone group showed reduction in erythema and scaling, with lesions healing accompanied by hypopigmentation compared to baseline.

Discussion

The baseline characteristics reveal no significant differences between the two groups. This comparability ensures that the results observed in treatment efficacy and safety can be attributed to the interventions rather than underlying demographic differences. The average age in the Methotrexate group was slightly higher (56.12 years) than in the Pioglitazone group (50.76 years), but this difference was not statistically significant (p=0.177). Both groups were balanced in terms of

gender distribution. The number of males was more than twice that of females in both groups (0.697). This was similar to a study by Dogra et al[12]. The duration of illness was also comparable, with 4.76 years for Methotrexate patients and 4.61 years for Pioglitazone patients (p=0.914). Nail involvement, a common feature of psoriasis, was present in 64.7% of Methotrexate patients and 52.9% of Pioglitazone patients, with no significant difference between the groups (p=0.486). These findings align with the study by Canal-García et al[13], which reported prevalence rates of nail involvement in psoriasis ranging from 47.4% to 78.3%.

The primary efficacy measure in this study was the reduction in Psoriasis Area and Severity Index (PASI) scores. Although the baseline PASI scores were slightly higher in the Methotrexate group (15.81 vs. 14.83), this difference was not statistically significant (p=0.358). By week 4, the PASI score had decreased to 12.58 in the Methotrexate group and 12.83 in the Pioglitazone group (p=0.626). At week 8, Methotrexate reduced PASI scores to 8.31, while Mioglitazone patients had a slightly higher PASI of 9.22(p=0.093). By week 12, the final PASI scores were 5.15 for Methotrexate and 6.47 for Pioglitazone(p=0.033), indicating that while both drugs were effective, Methotrexate had a slightly better outcome (Depicted in **Figure 3**) in terms of overall PASI score reduction and was statistically significant. Similar findings were noted by Drateln et al [14] who reported superior PASI reductions in patients treated with Methotrexate compared to Pioglitazone at the end of the study.

However, it is important to note that Pioglitazone still demonstrated considerable efficacy in reducing PASI scores (14.83 to 6.47 by the end of 12 weeks) (As shown in **Figure 4**). This was similar to results noted by Shafiq N [15], Singh S[16] et al who observed a significant reduction in PASI scores in patients treated with Pioglitazone when compared to the placebo arm.

The percentage reduction in PASI scores provides further insight into the relative efficacy of the two treatments. At Week 4, Methotrexate patients experienced a significantly greater reduction in PASI scores (20.63% vs. 13.15%, p=0.009), demonstrating its superior efficacy early in treatment. By Week 8, the gap in PASI reduction had widened, with Methotrexate showing a reduction of 47.82% compared to 37.56% in the Pioglitazone group (p=0.019). At Week 12, Methotrexate maintained its superiority with a mean reduction of 68.15% compared to 57.03% for Pioglitazone (p=0.021). According to Czarnecka et al [17], Methotrexate typically requires a minimum of 4–8 weeks to reach its full therapeutic effect. Similarly, improvement in PASI scores was noted as early as 4 weeks in the Methotrexate group in our study. These results indicate that Methotrexate offers more rapid and sustained improvements in PASI scores compared to Pioglitazone, particularly after the initial 4 weeks of treatment.

Safety is a critical consideration in the management of chronic conditions like psoriasis, which often require long-term treatment. In this study, the frequency of adverse reactions was reported more in the Methotrexate group compared to Pioglitazone. Hepatotoxicity, a known side effect of Methotrexate, was observed in 2 patients from the Methotrexate group and 1 patient from the Pioglitazone group, manifesting as elevated liver enzymes. The elevation was less than 1.5 times the baseline level. Weight gain and pedal edema were common in the Pioglitazone group affecting 2 patients. Other minor side effects such as nausea and fatigue were reported in 2 Methotrexate patients. It is important to note that 10 patients in the Methotrexate group and 12 in the Pioglitazone group reported no adverse effects. 2 patients were lost-to-follow-up in Pioglitazone and 1 in the Methotrexate group. The overall distribution of adverse reactions in both groups was not statistically significant but patients on Pioglitazone showed fewer adverse effects. In a study done by Pengfei Chen et al[18], the risk of common adverse events in both groups was similar, such as an elevated liver enzyme, fatigue, nausea, and weight gain, and concluded that Pioglitazone is an effective and safe drug in the treatment of patients with psoriasis vulgaris.

Weight gain, a common side effect of Pioglitazone, remains a concern, particularly in patients with metabolic comorbidities such as diabetes or obesity. Careful patient selection and monitoring are essential when considering pioglitazone for psoriasis treatment.

The overall findings of this study suggest that while both Methotrexate and Pioglitazone are effective in treating plaque-type psoriasis, Methotrexate offers superior efficacy in reducing PASI scores,

particularly over time. The faster and greater percentage reduction in PASI scores seen with Methotrexate could be attributed to its well-established mechanism of action. Pioglitazone, as a PPAR-γ agonist, may take longer to exert its full effects, which could explain the slower improvement in PASI scores.

Methotrexate, with its faster and more pronounced efficacy, may be more suitable for patients requiring rapid improvement in their psoriasis symptoms. However, for patients who may not tolerate Methotrexate due to its known toxicities, Pioglitazone represents a viable alternative, especially for those who prefer a drug with a lesser side effect profile.

A limitation of our study was the relatively small sample size and its single-center design.

Conclusion

This study demonstrates that Methotrexate offers superior efficacy in the management of plaque-type psoriasis compared to Pioglitazone, as evidenced by the faster and greater reduction in PASI scores over time. By Week 12, Methotrexate resulted in a significantly higher percentage reduction in PASI scores, indicating its effectiveness in achieving rapid improvement. However, Pioglitazone had lesser adverse effect profiles which was not statistically significant. This makes Pioglitazone a viable alternative drug to Methotrexate which can help in reducing the dose of methotrexate for patients who may not tolerate higher doses of Methotrexate. Future studies should focus on long-term outcomes and quality of life measures to better understand the sustained effects of these treatments. Additionally, larger sample sizes and diverse patient populations could provide more comprehensive data on the comparative effectiveness of these therapies. Exploring combination therapies involving both Methotrexate and Pioglitazone might also offer new avenues for improving patient outcomes, particularly for those with resistant forms of psoriasis.

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