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Original Article

Comparison Between Oral Methotrexate and Tofacitinib in the Treatment Of Chronic Plaque Psoriasis

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ABSTRACT

Background: Chronic plaque psoriasis is a systemic immune-mediated inflammatory disease requiring effective systemic therapy in patients with moderate-to-severe disease or inadequate response to topical treatment. Methotrexate remains widely used because of affordability and availability, while tofacitinib offers targeted oral Janus kinase inhibition with potential efficacy in plaque psoriasis. Objective: To compare the efficacy and short-term safety of oral tofacitinib and oral methotrexate in patients with chronic plaque psoriasis. Methods: This randomized controlled trial was conducted at the Department of Dermatology, Lahore General Hospital, Lahore, from February 2025 to June 2025. Seventy-five patients aged 18–70 years with chronic plaque psoriasis of at least 6 months' duration, PASI score ≥10 or body surface area involvement ≥10%, and inadequate response to topical therapy were included. Group A received oral tofacitinib 5 mg twice daily, while Group B received oral methotrexate once weekly, starting at 10 mg and titrated according to response and tolerance. Patients were followed for 12 weeks. The primary outcome was PASI-75 achievement at week 12. Results: Tofacitinib was given to 38 patients and methotrexate to 37 patients. Mean PASI decreased from 18.6 ± 4.4 to 4.9 ± 3.1 with tofacitinib and from 18.2 ± 4.6 to 6.7 ± 3.7 with methotrexate. Mean percentage PASI reduction was higher with tofacitinib than methotrexate. PASI-75 was achieved by 23 patients (60.5%) receiving tofacitinib and 16 patients (43.2%) receiving methotrexate. Any adverse event occurred in 10 patients (26.3%) in the tofacitinib group and 12 patients (32.4%) in the methotrexate group. Conclusion: Both oral tofacitinib and methotrexate improved PASI score over 12 weeks. Tofacitinib produced greater mean PASI reduction and numerically higher PASI-75 response, although categorical response superiority was not statistically confirmed. Both drugs were generally tolerated during short-term follow-up. Keywords: Chronic plaque psoriasis, Methotrexate, Tofacitinib, PASI-75, Safety, Lahore General Hospital.

INTRODUCTION

Chronic plaque psoriasis is a persistent immune-mediated inflammatory skin disease characterized by sharply demarcated erythematous plaques covered with silvery scales and a relapsing clinical course. Although the disease primarily presents with cutaneous lesions involving the scalp, trunk, extensor surfaces, nails, and sometimes joints, it is increasingly recognized as a systemic inflammatory disorder because of its association with psoriatic arthritis, metabolic syndrome, cardiovascular disease, obesity, diabetes mellitus, and psychological morbidity. The World Health Organization has described psoriasis as chronic, painful, disfiguring, and disabling non-communicable disease with substantial impairment of health-related quality of life, while contemporary clinical reviews emphasize the need to evaluate psoriasis beyond skin involvement alone (1,2).

The pathogenesis of chronic plaque psoriasis involves a complex interaction between genetic susceptibility, environmental triggers, innate immune activation, adaptive immune dysregulation, and

cytokine-mediated keratinocyte proliferation. The interleukin-23/T-helper 17 axis plays a central role in maintaining psoriatic inflammation through downstream cytokine signaling, epidermal hyperproliferation, and persistent plaque formation. These immunological mechanisms provide the biological rationale for systemic and targeted therapies in patients whose disease is moderate to severe or insufficiently controlled with topical treatment alone (3,4). Current treatment guidelines recommend systemic therapy for patients with moderate-to-severe plaque psoriasis, extensive body surface area involvement, high Psoriasis Area and Severity Index scores, functional impairment, or inadequate response to topical therapy, with treatment selection guided by disease severity, comorbidities, previous response, patient preference, affordability, and monitoring feasibility (5).

Methotrexate remains one of the most widely used systemic non-biologic therapies for moderate-to-severe plaque psoriasis because of its anti-inflammatory and antiproliferative effects, clinical familiarity, availability, and relative affordability in resource-constrained settings. Despite these advantages, methotrexate requires careful patient selection and regular laboratory monitoring because of gastrointestinal intolerance, hepatotoxicity, hematologic toxicity, renal considerations, drug interactions, and cumulative exposure concerns (6). In contrast, targeted oral therapies have expanded the therapeutic landscape for psoriasis. Tofacitinib, an oral Janus kinase inhibitor, acts by interfering with intracellular cytokine signaling involved in inflammatory pathways relevant to psoriasis. Clinical trial evidence has shown that tofacitinib can produce meaningful improvement in moderate-to-severe chronic plaque psoriasis, including in Asian populations, although infection risk, laboratory abnormalities, relapse after withdrawal, and the need for ongoing safety monitoring remain important considerations (7–11).

Direct comparative evidence between oral tofacitinib and methotrexate remains limited, particularly in South Asian tertiary-care settings where drug cost, laboratory monitoring access, and treatment availability influence real-world therapeutic decisions. Previous comparative evidence has suggested improvement in Psoriasis Area and Severity Index scores with both agents, but differences across response thresholds have not been consistently significant, and methotrexate response rates vary according to dose, escalation schedule, treatment duration, and clinical setting (12–15). Local evidence from Pakistan also indicates that psoriasis is associated with disease-related quality-of-life impairment and psychiatric morbidity, supporting the need for effective, accessible, and locally relevant systemic treatment strategies for patients with moderate-to-severe disease (16). Therefore, this study aimed to compare the efficacy and short-term safety of oral tofacitinib 5 mg twice daily versus oral methotrexate over 12 weeks in adults with chronic plaque psoriasis, using Psoriasis Area and Severity Index reduction and achievement of PASI-75 as primary measures of clinical response.

MATERIAL AND METHODS

This parallel-group randomized controlled trial was conducted at the Department of Dermatology, Lahore General Hospital, Lahore, Pakistan, from February 2025 to June 2025. Ethical approval was obtained from the institutional ethical review committee under IRB No. 2025 ERC 57, and the study was registered as Clinical Trial NCT07261306. Written informed consent was obtained from all participants before enrolment. Patient confidentiality was maintained by assigning each participant a serial identification number, and no personally identifiable information was used during data analysis or manuscript preparation.

A total of 75 patients with chronic plaque psoriasis were recruited through non-probability consecutive sampling. Patients of either gender aged 18 to 70 years were eligible if they had clinically diagnosed chronic plaque psoriasis for at least 6 months, a Psoriasis Area and Severity Index score of 10 or greater or body surface area involvement of 10% or greater, and inadequate response to topical therapy. Patients were excluded if they had other clinical forms of psoriasis, coexisting dermatological disease that could interfere with lesion assessment, use of systemic corticosteroids, biologics, or other immunosuppressive drugs within 4 weeks before enrolment, known hypersensitivity to either study drug, significant liver

disease, renal disease, hematologic disorder, acid peptic disease, immunodeficiency, history of tuberculosis, history of malignancy, pregnancy, or lactation.

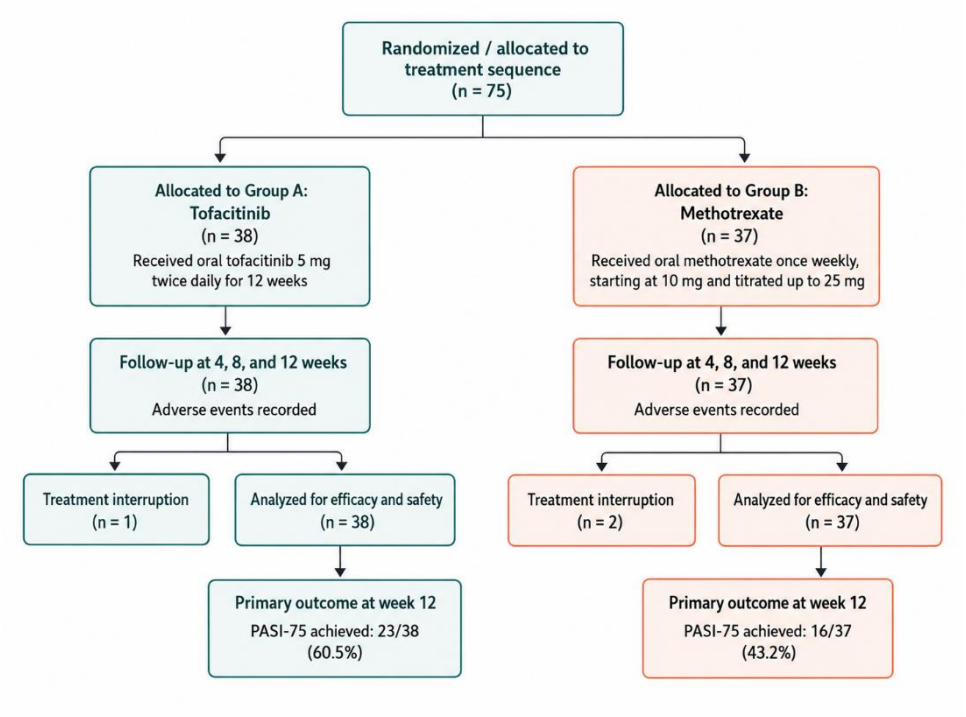

Figure 1 CONSORT Flowchart

After eligibility confirmation, baseline demographic and clinical information was recorded, including age, gender, duration of psoriasis, baseline Psoriasis Area and Severity Index score, body surface area involvement, and disease severity category. Baseline complete blood count, liver function tests, renal function tests, and relevant screening investigations were reviewed before treatment initiation to assess suitability for systemic therapy. Eligible participants were assigned to two treatment groups according to the study treatment sequence. Group A received oral tofacitinib 5 mg twice daily for 12 weeks. Group B received oral methotrexate once weekly, starting at 10 mg weekly and titrated according to clinical response and treatment tolerance up to a maximum weekly dose of 25 mg. Folic acid supplementation was prescribed to patients receiving methotrexate, except on the day of methotrexate administration.

The Psoriasis Area and Severity Index was used as the principal clinical severity measure and was assessed at baseline and at follow-up visits. The score was calculated by evaluating erythema, induration, scaling, and area involvement across four anatomical regions, yielding a total score ranging from 0 to 72, with higher scores indicating greater disease severity (17,18). Body surface area involvement was estimated using the palm method, in which the patient's palm, including the fingers, approximates 1% of total body surface area (19). Patients were followed at 4, 8, and 12 weeks. At each visit, treatment adherence was reviewed, Psoriasis Area and Severity Index score was recorded, and adverse events were documented.

The primary efficacy outcome was achievement of PASI-75 at week 12, defined as at least 75% reduction in Psoriasis Area and Severity Index score from baseline. Secondary efficacy outcomes included absolute change in Psoriasis Area and Severity Index score, percentage reduction in Psoriasis Area and Severity Index score, PASI-50 achievement, PASI-90 achievement, and treatment response category at 12 weeks. Safety outcomes included infections, gastrointestinal symptoms, hepatotoxicity or liver enzyme elevation, laboratory abnormalities, treatment interruption, serious adverse effects, and hospital admission related to drug toxicity.

Data were analyzed using SPSS version 26. Quantitative variables were summarized as mean±standard deviation, while categorical variables were summarized as frequency and percentage. Independent-

samples t-test was used to compare normally distributed quantitative variables between treatment groups, while paired-samples t-test was used to assess within-group change in Psoriasis Area and Severity Index score from baseline to week 12. Chi-square test or Fisher's exact test was applied for categorical variables, as appropriate according to cell counts. Binary logistic regression was used to evaluate the association between treatment group and PASI-75 achievement after adjustment for age, gender, baseline Psoriasis Area and Severity Index score, and disease duration. A p-value of ≤0.05 was considered statistically significant.

RESULTS

A total of 75 patients with chronic plaque psoriasis were included in the final analysis. Group A comprised 38 patients treated with oral tofacitinib, while Group B comprised 37 patients treated with oral methotrexate. Baseline demographic and clinical characteristics were comparable between the two treatment groups.

Table 1. Baseline Demographic and Clinical Characteristics by Treatment Group

Variable	Tofacitinib (n=38)	Methotrexate (n=37)	p-value
Age, years, Mean ± SD	39.7 ± 11.4	40.2 ± 10.9	0.846
Male gender, n (%)	21 (55.3)	20 (54.1)	0.918
Female gender, n (%)	17 (44.7)	17 (45.9)	0.918
Duration of psoriasis, months, Mean ± SD	38.9 ± 20.6	40.5 ± 21.4	0.742
Baseline PASI score, Mean ± SD	18.6 ± 4.4	18.2 ± 4.6	0.701
Baseline BSA involvement, %, Mean ± SD	13.5 ± 4.2	13.2 ± 4.1	0.755
Moderate disease severity, n (%)	26 (68.4)	25 (67.6)	0.938
Severe disease severity, n (%)	12 (31.6)	12 (32.4)	0.938

PASI: Psoriasis Area and Severity Index; BSA: body surface area; SD: standard deviation.

The mean age was 39.7 ± 11.4 years in the tofacitinib group and 40.2 ± 10.9 years in the methotrexate group. Baseline PASI score was also similar between groups, with mean values of 18.6 ± 4.4 and 18.2 ± 4.6, respectively. The proportions of patients with moderate and severe disease were nearly identical across groups, supporting baseline comparability before treatment initiation.

Table 2. Change in PASI Score Over 12 Weeks

PASI Assessment	Tofacitinib (n=38), Mean ± SD	Methotrexate (n=37), Mean ± SD	Mean Difference	95% CI	Cohen's d	p-value
Baseline PASI	18.6 ± 4.4	18.2 ± 4.6	0.4	-1.67 to 2.47	0.09	0.701
PASI at 4 weeks	12.1 ± 4.2	12.8 ± 4.5	-0.7	-2.70 to 1.30	-0.16	0.489
PASI at 8 weeks	7.1 ± 3.6	8.9 ± 3.9	-1.8	-3.53 to -0.07	-0.48	0.041
PASI at 12 weeks	4.9 ± 3.1	6.7 ± 3.7	-1.8	-3.37 to -0.23	-0.53	0.025
Absolute PASI reduction	13.7 ± 5.0	11.5 ± 5.4	2.2	-0.20 to 4.60	0.42	0.071
Percentage PASI reduction	73.1 ± 17.4	62.5 ± 20.1	10.6	1.93 to 19.27	0.56	0.016
Within-group p-value	<0.001	<0.001	—	—	—	—

PASI: Psoriasis Area and Severity Index; CI: confidence interval; SD: standard deviation. Mean difference was calculated as tofacitinib minus methotrexate. Negative values for follow-up PASI indicate lower PASI score in the tofacitinib group. Cohen's d was derived using pooled standard deviation from the reported aggregate data.

PASI scores decreased substantially in both treatment groups over 12 weeks. At week 8, mean PASI was lower in the tofacitinib group than in the methotrexate group, with a mean difference of -1.8 points and a 95% CI from -3.53 to -0.07. At week 12, the between-group difference remained -1.8 points, with a 95% CI from -3.37 to -0.23. The percentage reduction in PASI was 73.1 ± 17.4% with tofacitinib and 62.5 ± 20.1% with methotrexate, yielding a mean difference of 10.6 percentage points and a moderate standardized effect size.

At week 12, PASI-75 was achieved by 23 patients in the tofacitinib group and 16 patients in the methotrexate group. The relative risk for PASI-75 achievement was 1.40, with a 95% CI from 0.89 to 2.19.

PASI-50 and PASI-90 responses were also numerically higher with tofacitinib, but the confidence intervals for categorical response outcomes crossed the null value, indicating statistical uncertainty despite clinically visible differences.

Table 3. Clinical Efficacy Outcomes at 12 Weeks

Outcome	Tofacitinib (n=38), n (%)	Methotrexate (n=37), n (%)	Risk Difference	95% CI	Relative Risk	95% CI	p-value
PASI-50 achieved	32 (84.2)	27 (73.0)	0.11	-0.07 to 0.30	1.15	0.91 to 1.47	0.235
PASI-75 achieved	23 (60.5)	16 (43.2)	0.17	-0.05 to 0.40	1.40	0.89 to 2.19	0.133
PASI-90 achieved	8 (21.1)	5 (13.5)	0.08	-0.09 to 0.25	1.56	0.56 to 4.33	0.387

PASI-50, PASI-75, and PASI-90 indicate at least 50%, 75%, and 90% reduction in Psoriasis Area and Severity Index score from baseline, respectively. Risk difference and relative risk were derived from the reported group-wise frequencies.

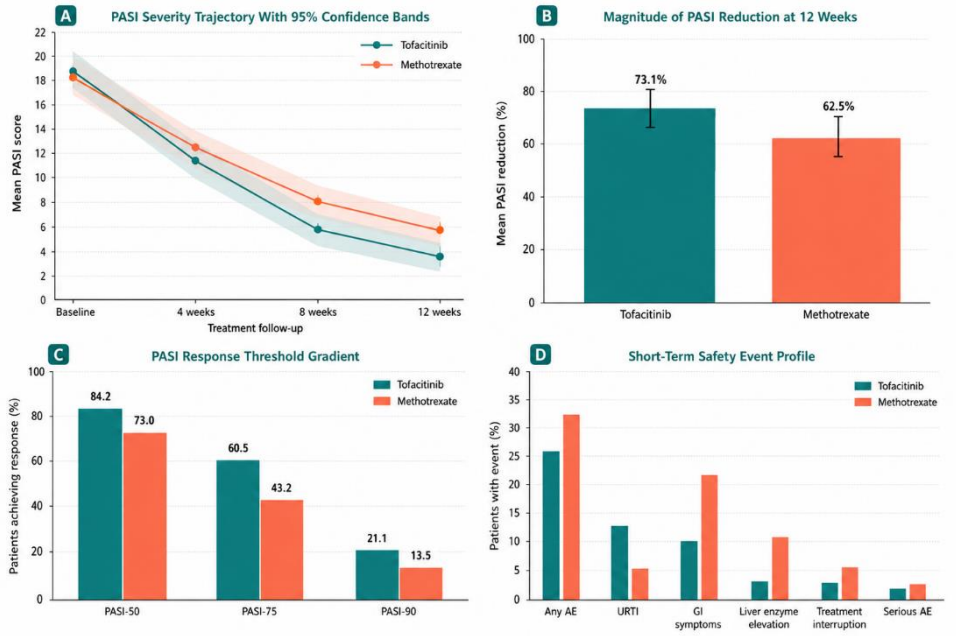

Figure 2 Comparative efficacy and short-term safety of oral tofacitinib versus methotrexate in chronic plaque psoriasis. Tofacitinib showed lower mean PASI scores from week 8 onward, greater mean PASI reduction at 12 weeks, and numerically higher PASI-50, PASI-75, and PASI-90 response rates. Safety outcomes showed more upper respiratory tract infections with tofacitinib, whereas gastrointestinal symptoms and liver enzyme elevation were more frequent with methotrexate during 12-week follow-up.

Table 4. Safety Outcomes During 12-Week Treatment

Safety Outcome	Tofacitinib (n=38), n (%)	Methotrexate (n=37), n (%)	Risk Difference	95% CI	Relative Risk	95% CI	p-value
Any adverse event	10 (26.3)	12 (32.4)	-0.06	-0.27 to 0.14	0.81	0.40 to 1.64	0.562
Upper respiratory tract infection	5 (13.2)	2 (5.4)	0.08	-0.05 to 0.21	2.43	0.50 to 11.77	0.240
Gastrointestinal symptoms	4 (10.5)	8 (21.6)	-0.11	-0.28 to 0.05	0.49	0.16 to 1.48	0.187
Hepatotoxicity/liver enzyme elevation	1 (2.6)	4 (10.8)	-0.08	-0.19 to 0.03	0.24	0.03 to 2.08	0.165
Treatment interruption	1 (2.6)	2 (5.4)	-0.03	-0.12 to 0.06	0.49	0.05 to 5.14	0.610
Serious adverse effect	0 (0.0)	1 (2.7)	-0.03	-0.08 to 0.03	—	—	0.493
Hospital admission due to drug toxicity	0 (0.0)	0 (0.0)	—	—	—	—	—

CI: confidence interval. Risk difference and relative risk were derived from the reported group-wise frequencies. Relative risk was not calculated where one or both groups had zero events.

Any adverse event was reported in 10 patients receiving tofacitinib and 12 patients receiving methotrexate. Upper respiratory tract infection occurred more often in the tofacitinib group, whereas gastrointestinal symptoms and liver enzyme elevation occurred more often in the methotrexate group. One serious adverse effect was reported in the methotrexate group, and no hospital admission due to drug toxicity was reported in either group during the 12-week follow-up.

Table 5. Logistic Regression for PASI-75 Achievement at 12 Weeks

Variable	Adjusted OR	95% CI	p-value
Tofacitinib treatment	2.21	0.85 to 5.74	0.105
Age ≥40 years	0.91	0.36 to 2.32	0.845
Male gender	1.18	0.47 to 2.97	0.724
Baseline PASI ≥20	0.76	0.29 to 2.00	0.577
Disease duration ≥36 months	0.68	0.27 to 1.74	0.421

OR: odds ratio; CI: confidence interval; PASI: Psoriasis Area and Severity Index. The model was adjusted for age, gender, baseline PASI score, and disease duration.

For age, gender, baseline PASI score, and disease duration, treatment with tofacitinib was associated with higher odds of PASI-75 achievement compared with methotrexate, with an adjusted odds ratio of 2.21. However, the 95% CI ranged from 0.85 to 5.74 and the p-value was 0.105, indicating that the adjusted association did not reach statistical significance. Age, gender, baseline PASI score, and disease duration were not independently associated with PASI-75 achievement in the adjusted model.

DISCUSSION

The present randomized controlled trial compared oral tofacitinib and oral methotrexate in patients with chronic plaque psoriasis treated over 12 weeks at a tertiary-care dermatology department. Both interventions produced substantial reduction in PASI score from baseline, indicating clinically relevant improvement with either systemic therapy. However, tofacitinib was associated with a greater mean percentage PASI reduction and lower mean PASI score at weeks 8 and 12. The categorical PASI-75 response was also numerically higher with tofacitinib than with methotrexate, although this difference did not reach statistical significance. These findings suggest that tofacitinib may provide a stronger short-term reduction in objective disease severity, but the available sample size does not support a definitive conclusion of superiority for the primary categorical endpoint.

The baseline comparability of the two treatment groups strengthens the internal interpretation of the observed treatment response. Mean age, gender distribution, duration of psoriasis, baseline PASI score, baseline body surface area involvement, and disease severity category were similar between groups. This balance reduces the likelihood that the observed differences in PASI response were driven by major pretreatment clinical differences. PASI is widely used in psoriasis trials because it integrates erythema, induration, scaling, and regional area involvement into a single severity score, although it remains partly dependent on clinical assessment and therefore requires standardized and preferably blinded outcome evaluation in randomized studies (17,18).

The greater reduction in PASI score observed with tofacitinib is biologically plausible because Janus kinase inhibition interferes with intracellular cytokine signaling involved in inflammatory pathways relevant to plaque psoriasis. Previous phase III evidence in Asian patients reported meaningful improvement in moderate-to-severe chronic plaque psoriasis with tofacitinib 5 mg twice daily and 10 mg twice daily, with higher response at the larger dose but clinically relevant activity also observed at 5 mg twice daily (7). Long-term extension evidence has shown that responses may be maintained in a subset of patients, although infections, laboratory abnormalities, and treatment discontinuation remain important monitoring concerns (8). Placebo-controlled phase III trials have also shown that tofacitinib improves PASI responses in moderate-to-severe chronic plaque psoriasis, supporting the efficacy signal observed in the present study (9). Subgroup evidence from Japanese patients further supports the potential relevance of tofacitinib in Asian populations (10). The present PASI-75 response of 60.5% with tofacitinib 5 mg twice daily is broadly consistent with prior evidence, while remaining within the range expected for short-term systemic treatment.

The current findings also align with active-comparator and pooled evidence on tofacitinib. In a phase III non-inferiority trial, tofacitinib was compared with etanercept and placebo in moderate-to-severe chronic plaque psoriasis, and the 10 mg twice-daily dose showed stronger efficacy than the 5 mg twice-daily dose (20). Longer-term studies and meta-analytic evidence have similarly supported the efficacy of tofacitinib

in improving PASI outcomes, while emphasizing the need for patient selection and safety monitoring because of infection risk and laboratory abnormalities (21,22). The present study adds local comparative data using the 5 mg twice-daily dose, which is clinically relevant in settings where oral targeted therapy may be considered but treatment decisions are influenced by cost, access, comorbidities, and monitoring feasibility.

Methotrexate also produced clear clinical improvement in this study, with a PASI-75 response of 43.2% and mean percentage PASI reduction of 62.5% at 12 weeks. This finding is consistent with the established role of methotrexate as a systemic non-biologic therapy for moderate-to-severe plaque psoriasis. Previous evidence has shown that methotrexate response varies according to weekly dose, escalation strategy, folic acid use, patient characteristics, and duration of treatment. Dogra et al. reported that 25 mg weekly was more effective than 10 mg weekly in severe plaque-type psoriasis, highlighting the importance of dose intensity in clinical response (13). In the CHAMPION study, methotrexate achieved PASI-75 in 35.5% of patients at week 16, while real-world evidence has reported variable response rates depending on the analysis population and treatment continuation (14,15). The methotrexate response observed in this study is therefore within a clinically plausible range.

The numerical advantage of tofacitinib over methotrexate was more evident for continuous PASI reduction than for categorical PASI-75 achievement. At week 12, tofacitinib produced a greater mean percentage PASI reduction, while PASI-75 showed a 17.3 percentage-point absolute difference that did not achieve statistical significance. This pattern may reflect limited statistical power, modest sample size, and variability in patient-level response. PASI-75 is a stricter dichotomous endpoint than mean PASI change; therefore, clinically visible differences may fail to reach statistical significance when the sample is small. The adjusted logistic regression similarly showed higher odds of PASI-75 achievement with tofacitinib, but the confidence interval crossed the null value, reinforcing the need for cautious interpretation.

The short-term safety findings were consistent with the known clinical profiles of both treatments. Any adverse event occurred in 26.3% of patients receiving tofacitinib and 32.4% of patients receiving methotrexate. Upper respiratory tract infection was more frequent with tofacitinib, whereas gastrointestinal symptoms and liver enzyme elevation were more frequent with methotrexate. These findings are directionally consistent with previous safety concerns for Janus kinase inhibition and methotrexate therapy. However, the 12-week follow-up period is insufficient to evaluate delayed or cumulative toxicity, including serious infections, cardiovascular events, malignancy risk, relapse after withdrawal, cumulative hepatotoxicity, and long-term drug survival. Therefore, the present safety findings should be interpreted as short-term tolerability data rather than evidence of long-term comparative safety.

The study has practical relevance for dermatology practice in Pakistan and similar resource-limited settings. Methotrexate remains widely used because it is affordable, familiar, and accessible, but its use requires laboratory monitoring and caution in patients with hepatic, renal, hematologic, gastrointestinal, or pregnancy-related contraindications. Tofacitinib may offer a useful oral alternative in selected patients who require systemic therapy and can undergo appropriate screening and monitoring. Treatment selection should remain individualized according to disease severity, comorbidities, reproductive considerations, baseline laboratory profile, affordability, availability, monitoring capacity, and patient preference.

Several limitations should be considered. The sample size was modest, and the study may have been underpowered to detect statistically significant differences in PASI-75 despite numerical separation between groups. Follow-up was limited to 12 weeks, preventing evaluation of long-term efficacy, relapse pattern, cumulative toxicity, and drug survival. The study was conducted at a single tertiary-care hospital, which may limit generalizability to other clinical settings. Quality-of-life assessment using Dermatology Life Quality Index or another patient-reported outcome measure was not included. The manuscript

would also be strengthened by fuller reporting of random sequence generation, allocation concealment, blinding or open-label status, sample-size calculation, methotrexate dose escalation schedule, final achieved methotrexate dose, adherence assessment, and laboratory monitoring thresholds. Despite these limitations, the study provides useful local comparative evidence on two oral systemic treatment options for chronic plaque psoriasis and supports the need for larger, methodologically rigorous trials with longer follow-up.

CONCLUSION

Oral tofacitinib and oral methotrexate both produced substantial improvement in PASI score among patients with chronic plaque psoriasis over 12 weeks. Tofacitinib was associated with greater mean percentage PASI reduction and lower PASI scores at later follow-up, while PASI-75 achievement was numerically higher but did not reach statistical significance. Both treatments were generally tolerated during short-term follow-up; upper respiratory tract infection occurred more frequently with tofacitinib, whereas gastrointestinal symptoms and liver enzyme elevation were more frequent with methotrexate. Larger randomized trials with transparent allocation procedures, adequate statistical power, blinded outcome assessment, patient-reported outcomes, and longer follow-up are required to confirm comparative efficacy, durability of response, relapse pattern, and long-term safety.

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