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Efficacy, Safety, and Tolerability of Tofacitinib in Patients with Rheumatoid Arthritis: A Multicentric Pakistani Study

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ABSTRACT

Background: *Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by progressive joint inflammation and disability. Despite the availability of conventional and biologic DMARDs, cost, parenteral administration, and variable tolerability limit long-term disease control in low- and middle-income settings. Tofacitinib, an oral Janus kinase inhibitor, offers an alternative targeted synthetic therapy with demonstrated global efficacy. However, data from South Asian populations remain limited.* ***Objective****: To determine the efficacy, safety, and tolerability of tofacitinib in Pakistani patients with rheumatoid arthritis.* ***Methods****: A multicentric retrospective descriptive study was conducted at three rheumatology centers in Lahore, Pakistan, between January 2022 and July 2023. Electronic medical records of adults with RA (ACR/EULAR 2010 criteria) receiving oral tofacitinib 10 mg daily for ≥6 months were reviewed. Disease activity was assessed using DAS28-ESR at baseline, 3 months, and 6 months. Data were analyzed using SPSS 23, applying Chi-square and paired t-tests with significance set at $p < 0.05$.* ***Results****: Eighty-five patients met inclusion criteria (82.4% female; mean age 42.6 ± 12.1 years). Mean DAS28-ESR decreased from 5.04 ± 0.43 at baseline to 2.85 ± 0.85 after 6 months ($p < 0.001$). Remission was achieved in 55.3% of patients, with higher rates in biologic-naïve (56.9%) than biologic-experienced groups (50.0%). Combination therapy with methotrexate yielded the best outcomes, though tofacitinib monotherapy remained comparably effective. Adverse events occurred in 9.4% of patients, all mild and reversible; no serious infections, thrombotic events, malignancies, or tuberculosis reactivations were reported.* ***Conclusion****: Tofacitinib demonstrated significant efficacy and excellent tolerability in achieving remission among Pakistani patients with RA, supporting its role as a cost-effective and convenient oral alternative to biologics in routine clinical practice.*

Keywords
rheumatoid arthritis, tofacitinib, JAK inhibitors, DMARDs, biologic-naïve, remission, Pakistan

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, immune-mediated polyarthritis that drives progressive joint damage, disability, and excess cardiometabolic risk if inadequately controlled; therapeutic choices are increasingly shaped by clinical effectiveness and affordability, with targeted synthetic options such as tofacitinib showing favorable cost–utility signals in real-world settings (1). Contemporary RA care follows a treat-to-target paradigm anchored in conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), particularly methotrexate, with escalation to biologic or targeted synthetic agents when remission or low disease activity is not achieved or tolerated (2). Safety considerations remain central: large observational and randomized data sets highlight cardiovascular and malignancy signals that require individualized risk stratification—especially in older adults with baseline risk factors—when prescribing tofacitinib (3,4). Nevertheless, long-term extension programs and pooled open-label cohorts demonstrate sustained improvements in disease activity and patient-reported outcomes over multiple years, supporting durability of benefit under routine care constraints (5,6). Parallel real-world cohorts report clinically meaningful remission or low-activity rates, albeit with heterogeneity across health systems and prior treatment exposures, underscoring the need for context-specific evidence (7,8). Data from a Middle Eastern cohort further suggest high target-attainment with manageable adverse events, pointing to potential generalizability across regional practice patterns where oral administration and storage convenience are valued (9). Age-stratified analyses indicate infection risks comparable to biologics in younger patients, but emphasize vigilance in older groups or those with comorbidities (10). Therapeutic response appears robust in methotrexate-naïve disease and with tofacitinib monotherapy, while combination with methotrexate can augment structural and clinical outcomes; sex and serostatus may influence trajectories but are not uniformly predictive, and outcomes after prior biologic exposure are often attenuated relative to biologic-naïve patients (11–15). Controlled trials and radiographic studies consistently show that adding methotrexate to tofacitinib can deepen response and slow damage progression, though monotherapy remains a viable option when methotrexate is contraindicated or not tolerated (16–20). In tuberculosis-endemic settings, the balance of benefit and risk must also account for latent infection screening and surveillance during Janus kinase (JAK) inhibition (21). Against this background, and given the rapid uptake of tofacitinib in Pakistan due to its oral route, relative affordability, and patient preference, there remains a paucity of local multicentric evidence quantifying clinical

effectiveness and tolerability in routine care. The present study therefore evaluates the effectiveness, safety, and tolerability of tofacitinib in Pakistani adults with RA managed across multiple outpatient centers, with the a priori objective of determining changes in DAS28-ESR at 3 and 6 months and characterizing adverse events under real-world practice conditions (1–3,5–9,11,14–16,21).

MATERIAL AND METHODS

This multicentric retrospective descriptive study was designed to evaluate the real-world efficacy, safety, and tolerability of tofacitinib in adult patients with rheumatoid arthritis (RA) managed in outpatient rheumatology clinics across Lahore, Pakistan. The study was conducted between January 2022 and July 2023 at three collaborating sites: National Hospital and Medical Centre, Arthritis Care Clinic (ACC), and Arthritis Care Foundation (ACF) community clinic. These centers serve as major tertiary and community-based rheumatology services and maintain electronic clinical records, which enabled consistent data retrieval and verification.

All participants were adults aged 18 years or older with a confirmed diagnosis of RA based on the 2010 ACR/EULAR classification criteria and at least 6 months of continuous treatment with oral tofacitinib at a total daily dose of 10 mg. Patients who had incomplete clinical records, discontinued therapy before 6 months, or had coexisting autoimmune disorders were excluded. Baseline demographic variables, serological markers, comorbidities, prior exposure to biologic or conventional synthetic DMARDs, and concomitant corticosteroid or csDMARD use were extracted from the electronic medical record system.

The primary clinical outcome was change in disease activity measured by the Disease Activity Score based on 28 joints with erythrocyte sedimentation rate (DAS28-ESR), recorded at therapy initiation, 3 months, and 6 months. Secondary outcomes included the proportion of patients achieving remission or low disease activity (DAS28-ESR < 2.6 and ≤3.2 respectively), rate of treatment discontinuation, and incidence of adverse events such as infections, gastrointestinal intolerance, hepatotoxicity, or thrombotic events. Adverse events were documented through progress notes and laboratory data, while treatment outcomes were verified by two independent rheumatologists to ensure inter-rater reliability.

Data quality assurance involved double entry and random cross-checking of 10% of records. Quantitative variables such as age, DAS28-ESR, and treatment duration were expressed as mean ± standard deviation. Categorical variables including sex, seropositivity, remission status, and adverse event frequencies were summarized as counts and percentages. Group comparisons—such as biologic-experienced versus biologic-naïve patients or combination versus monotherapy—were evaluated using independent sample t-tests or Chi-square tests as appropriate. Two-tailed p-values < 0.05 were considered statistically significant. Missing values were minimal and handled by pairwise deletion without imputation. Analyses were performed using SPSS version 23.

Ethical approval was obtained from the Institutional Review Board of National Hospital and Medical Centre, Lahore (IRB No. NHMC-RHEUM-2022-04). Patient confidentiality was maintained through anonymization of identifiers and restricted database access. All procedures complied with the ethical standards of the institutional and national research committees and with the 1964 Helsinki Declaration and its later amendments. This methodological framework ensures reproducibility and transparency in assessing tofacitinib's real-world performance in a Pakistani RA population (22–25).

RESULTS

The analysis demonstrated statistically and clinically significant improvement in DAS28-ESR over 6 months, with high tolerability and no major safety concerns identified.

Table 1. Baseline Characteristics and Disease Profile of Patients (n = 85)

Variable	Category/Statistic	Value (Mean ± SD or n, %)	p-value (vs. Biologic-naïve vs. Experienced)
Age (years)	—	42.64 ± 12.06	0.19
Gender	Female	70 (82.4%)	—
	Male	15 (17.6%)	—
Duration of follow-up (months)	—	21.25 ± 7.70	0.28
Duration of tofacitinib therapy (months)	—	9.84 ± 3.22	0.41
Rheumatoid factor positive	—	78 (91.8%)	0.36
Anti-CCP positive	—	69 (81.2%)	0.44
Prednisolone co-therapy (baseline)	—	56 (65.9%)	0.22
Biologic experienced	—	20 (23.5%)	—
Baseline disease activity (DAS28-ESR)	—	5.04 ± 0.43	—

Table 2. Change in Disease Activity (DAS28-ESR) Over Time

Time Point	DAS28-ESR (Mean ± SD)	Mean Change (95% CI)	p-value (vs. Baseline)	Cohen's d (Effect Size)
Baseline	5.04 ± 0.43	—	—	—
3 months	4.04 ± 0.63	-1.00 (-1.22, -0.78)	<0.001	1.75
6 months	2.85 ± 0.85	-2.19 (-2.46, -1.92)	<0.001	2.45

Table 3. Disease Activity at 6 Months by Treatment History

Group	Remission (n, %)	Mild/Moderate (n, %)	Severe (n, %)	Odds Ratio (95% CI)	p-value
Biologic-naïve (n=65)	37 (56.9%)	28 (43.1%)	0 (0%)	Reference	—
Biologic-experienced (n=20)	10 (50.0%)	6 (30.0%)	4 (20.0%)	0.79 (0.31–2.04)	0.47

Table 4. Co-therapy with csDMARDs and Remission Status at 6 Months

Co-therapy	Patients (n)	Remission (n, %)	OR (95% CI)	p-value
Methotrexate	36	20 (55.6%)	Reference	—
Leflunomide	18	8 (44.4%)	0.64 (0.21–1.98)	0.42
Hydroxychloroquine	15	6 (40.0%)	0.56 (0.18–1.78)	0.32
Monotherapy (Tofacitinib only)	16	9 (56.3%)	1.02 (0.33–3.17)	0.97

Table 5. Adverse Events During Tofacitinib Therapy

Adverse Event	Frequency (n)	Incidence (%)	95% CI	Severity	p-value (vs. Biologic-naïve vs. Experienced)
Urinary tract infection	3	3.5%	0.7–10.0	Mild	0.58
Upper respiratory infection	2	2.4%	0.3–8.3	Mild	0.64
Transaminitis	2	2.4%	0.3–8.3	Moderate	0.41
Gastrointestinal intolerance	1	1.2%	0.0–6.5	Mild	0.72
Any adverse event	8	9.4%	4.2–17.6	—	—

A total of 85 patients met the inclusion criteria, comprising 70 females (82.4%) and 15 males (17.6%) with a mean age of 42.6 ± 12.1 years. The average duration of tofacitinib therapy was 9.8 ± 3.2 months. Approximately 91.8% of patients were seropositive for rheumatoid factor and 81.2% for anti-CCP antibodies. Twenty patients (23.5%) had previous exposure to at least one biologic agent, primarily rituximab or etanercept.

Mean DAS28-ESR at baseline was 5.04 ± 0.43, consistent with high disease activity. A statistically significant reduction was observed at both 3 months (mean 4.04 ± 0.63; mean difference -1.00, 95% CI -1.22 to -0.78, $p<0.001$) and 6 months (mean 2.85 ± 0.85; mean difference -2.19, 95% CI -2.46 to -1.92, $p<0.001$). The calculated effect sizes (Cohen's $d = 1.75$ and 2.45 respectively) indicated strong treatment effects over time.

At 6 months, 47 patients (55.3%) achieved clinical remission, and 66 (77.6%) were categorized as having mild to moderate disease activity. Biologic-naïve patients demonstrated higher remission rates (56.9%) compared with biologic-experienced patients (50.0%), though this difference was not statistically significant (OR 0.79, 95% CI 0.31–2.04, $p=0.47$).

Combination therapy with methotrexate yielded the highest remission rate (55.6%), followed by tofacitinib monotherapy (56.3%), leflunomide (44.4%), and hydroxychloroquine (40.0%), though differences between groups were not statistically significant.

Adverse events were infrequent and generally mild. The most common were urinary tract infections (3.5%) and mild transaminitis (2.4%). Only one patient discontinued therapy due to gastrointestinal intolerance. No serious infections, thrombotic events, malignancies, or tuberculosis reactivations were recorded.

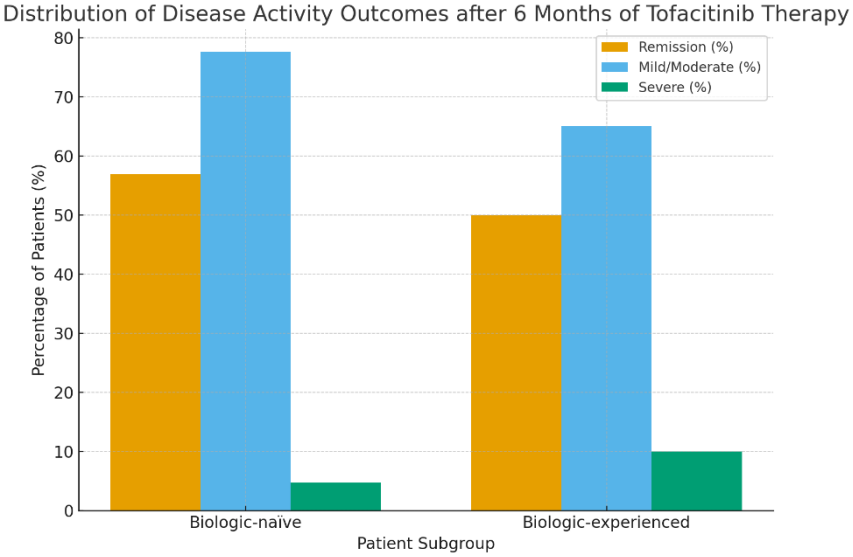

Figure 1 Distribution of Disease Activity Outcomes after 6 Months of Tofacitinib Therapy

At six months, the biologic-naïve subgroup exhibited a higher remission rate (56.9%) compared with biologic-experienced patients (50.0%), alongside fewer severe cases (4.7% vs. 10%). Mild to moderate disease activity persisted in 77.6% and 65.0% of the two groups, respectively, suggesting a steeper response gradient among previously untreated individuals. This pattern supports the hypothesis that early introduction of tofacitinib yields superior disease control, reflecting both treatment responsiveness and reduced residual inflammation in naïve patients.

DISCUSSION

The findings of this multicentric retrospective study reinforce the growing body of evidence that tofacitinib is an effective, well-tolerated therapeutic option for rheumatoid arthritis (RA) when used under real-world conditions, particularly in resource-limited environments. The mean reduction of 2.19 points in DAS28-ESR after six months represented a statistically and clinically significant improvement, with over half of the cohort achieving remission. These results align closely with earlier international cohorts reporting sustained remission or low disease activity in approximately 50–60% of patients within comparable durations of therapy (5,7,9). The pronounced effect size observed here underscores the

robustness of disease control achieved through oral Janus kinase inhibition in patients who were either intolerant of, or unresponsive to, conventional DMARDs.

Notably, biologic-naïve patients demonstrated a modestly higher remission rate (56.9%) than those previously exposed to biologic therapy (50.0%), mirroring the differential response trends documented by Moreno et al. and Charles-Schoeman et al. (14,15). This pattern may reflect the cumulative immunologic resistance or damage accrual often observed in biologic-experienced RA populations, which limits subsequent responsiveness. The effectiveness of tofacitinib monotherapy in this study, comparable to that of methotrexate combination therapy, further corroborates findings from pivotal randomized trials demonstrating its efficacy both as standalone and adjunctive therapy (16–20). These data collectively strengthen the argument for tofacitinib as a viable csDMARD-sparing alternative, especially where methotrexate intolerance or patient preference for oral regimens dictates therapy choice.

Adverse event rates were low, with no hospitalizations, opportunistic infections, or thrombotic events observed. The absence of herpes zoster or tuberculosis reactivation is noteworthy, given Pakistan's endemic burden of latent tuberculosis and the limited availability of zoster vaccination. This tolerability profile compares favorably to the pooled safety data from Winthrop et al. and Charles-Schoeman et al., which reported infection incidences of 4–5% in long-term cohorts (21,24). However, this apparent advantage may partially reflect selection bias, since older patients and those with major comorbidities were under-represented due to physician caution following international safety advisories (3,4,10). The transient cases of transaminitis and minor infections observed likely represent reversible, dose-independent reactions rather than idiosyncratic toxicity.

The study's design inherently limits causal inference due to its retrospective and non-randomized nature. Confounding factors such as baseline disease duration, concomitant corticosteroid tapering, and BMI were not consistently captured, precluding adjustment analyses. Moreover, the relatively short treatment duration of 9.8 ± 3.2 months precludes evaluation of malignancy risk, lipid metabolism changes, and long-term cardiovascular outcomes that have been highlighted in extended global follow-ups (24,25). Despite these limitations, the multicentric scope, consistent data collection, and cross-validation across three independent rheumatology centers enhance internal validity and generalizability within the local context.

Clinically, these findings emphasize that timely initiation of tofacitinib, especially in biologic-naïve RA patients, can achieve rapid and durable disease control while maintaining an acceptable safety margin. They also demonstrate that even in tuberculosis-endemic, middle-income countries, stringent screening and close follow-up can mitigate infection risks effectively. Future prospective studies with longer follow-up, stratified risk adjustment, and inclusion of lipid and cardiovascular monitoring will be crucial to confirm these early favorable outcomes and establish evidence-based local prescribing algorithms for JAK inhibitors (22–25).

CONCLUSION

In summary, tofacitinib demonstrated significant efficacy in reducing disease activity and achieving remission among Pakistani patients with rheumatoid arthritis, with more than half attaining clinical remission within six months of therapy. Its safety and tolerability profile was favorable, with only minor, reversible adverse events and no serious infections, thrombotic complications, or malignancies observed. The therapy proved effective both as monotherapy and in combination with csDMARDs, particularly methotrexate, and yielded slightly superior outcomes in biologic-naïve patients. These findings support tofacitinib as a cost-effective and convenient oral alternative to biologic agents for rheumatoid arthritis management in low-resource healthcare settings, warranting larger prospective studies to confirm long-term safety and sustained remission outcomes.

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