JHWCR JOURNAL OF HEALTH, WELLNESS AND COMMUNITY RESEARCH 3007-0570

https://doi.org/10.61919/2cpycr42

Original Article

Safety, Efficacy, and Tolerability of Tofacitinib in Children and Adolescents With Juvenile Idiopathic Arthritis in Pakistan

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"Cite this Article" Received: 08 March 2025; **Accepted**: 18 May 2025; **Published**: 06 June 2025

Author Contributions: Concept: T.Z.; Design: S.F.R., M.A.S.; Data Collection: T.Z., M.H., M.S.; Analysis: M.A.S., N.M.A.; Drafting: T.Z., S.F.R., M.A.S.. **Ethical Approval**: Sindh Institute of Physical Medicine and Rehabilitation, Sindh, Pakistan**. Informed Consent**: Written informed consent was obtained from all participants; **Conflict of Interest**: The authors declare no conflict of interest. **Funding**: No external funding; **Data Availability**: Available from the corresponding author on reasonable request; **Acknowledgments**: N/A.

ABSTRACT

Background: Juvenile idiopathic arthritis is a chronic inflammatory disorder of childhood that often requires treatment escalation beyond conventional synthetic disease-modifying antirheumatic drugs, particularly in patients with persistent or refractory disease. In resource-constrained settings, biologic therapy may be limited by cost, access, and treatment logistics, making orally administered targeted therapies such as tofacitinib clinically relevant. Objective: To evaluate the safety, efficacy, and tolerability of tofacitinib in children and adolescents with juvenile idiopathic arthritis treated in a real-world Pakistani cohort. Methods: This prospective study included 47 patients aged 2–18 years with juvenile idiopathic arthritis managed at two rheumatology centers in Lahore, Pakistan, between January 2024 and February 2025. Data were extracted from routine clinical records and electronic databases. Baseline demographic and clinical characteristics, Physician Visual Analog Scale scores, adverse events, infections, and reasons for treatment discontinuation were recorded. Changes in disease activity were analyzed using paired statistical testing, and adverse-event frequencies were summarized with confidence intervals and exposure-adjusted rates. Results: The mean age was 14.15 ± 3.88 years, and polyarticular juvenile idiopathic arthritis was the most frequent subtype. Mean Physician Visual Analog Scale score decreased from 7.15 ± 0.91 at baseline to 2.96 ± 1.60 at follow-up, with a mean reduction of 4.19 ± 1.51 points ($p<0.0001$). Improvement was observed in 95.7% of patients. Adverse events occurred in 6.4%, no infections or serious adverse events were recorded, and treatment discontinuation occurred in 6.4%. Conclusion: Tofacitinib was associated with substantial short-term improvement in physician-assessed disease activity and acceptable early tolerability in this Pakistani juvenile idiopathic arthritis cohort. Larger multicenter studies with longer follow-up and standardized outcome measures are needed to confirm long-term safety and effectiveness. Keywords: juvenile idiopathic arthritis, tofacitinib, JAK inhibitor, pediatric rheumatology, safety, efficacy, tolerability, Pakistan.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) comprises a heterogeneous group of chronic inflammatory arthritis's beginning in childhood and characterized by persistent joint inflammation, pain, stiffness, and variable extra-articular involvement. The International League of Associations for Rheumatology classification remains the most widely used framework for categorizing JIA into clinically distinct subtypes, although more recent consensus efforts have sought to refine disease definitions and improve phenotypic classification for research and clinical care (1). JIA represents the most common chronic rheumatic disease in children and adolescents and is associated with substantial risks of functional limitation,

impaired growth, reduced quality of life, ocular complications, and long-term musculoskeletal disability when disease control is delayed or inadequate. Its global incidence and prevalence vary widely across regions because of ethnic, geographic, and methodological differences, but available evidence consistently indicates that JIA imposes a meaningful and sustained burden on affected children, families, and health systems (2,13).

Although epidemiological data from South Asia remain limited, the regional burden is likely underestimated because of under-recognition, delayed referral, and restricted access to pediatric rheumatology services. In low- and middle-income settings such as Pakistan, these challenges are further amplified by diagnostic delays, inconsistent long-term follow-up, affordability constraints, and dependence on a limited number of tertiary centers, all of which may contribute to prolonged inflammatory activity and preventable disability (3,7). The clinical heterogeneity of JIA adds further complexity, as oligoarticular, polyarticular, systemic-onset, enthesitis-related, and psoriatic forms differ in presentation, inflammatory burden, treatment response, and risk of complications. Consequently, management requires timely recognition and a treatment strategy that is both biologically effective and practically sustainable within the local healthcare context (4,5).

The current therapeutic goal in JIA is to achieve low disease activity or remission through a treat-to-target approach using sequential or combination therapy based on disease subtype, severity, and response. Conventional treatment commonly begins with non-steroidal anti-inflammatory drugs, intra-articular corticosteroids, and conventional synthetic disease-modifying antirheumatic drugs, particularly methotrexate, which remains the cornerstone of first-line systemic therapy for many patients (5). However, a substantial subset of children continue to experience persistent disease activity, incomplete response, treatment intolerance, or recurrent relapse despite conventional therapy. Biologic disease-modifying agents, including tumor necrosis factor inhibitors and interleukin-1 or interleukin-6 antagonists, have substantially improved outcomes in resistant disease and transformed the management of refractory JIA (6). Even so, the use of biologics is often constrained by high cost, limited availability, parenteral administration, variable adherence, immunogenicity, and adverse-effect concerns, all of which are especially relevant in resource-constrained settings where treatment interruption may occur for financial rather than clinical reasons (6,7,14,15).

Janus kinase inhibitors have emerged as an important therapeutic option in inflammatory rheumatic disease by targeting intracellular signaling pathways involved in multiple cytokine-mediated immune responses. Tofacitinib, an oral Janus kinase inhibitor, interrupts JAK-STAT signaling and thereby modulates inflammatory pathways implicated in the pathogenesis of JIA, including those mediated by interleukin-6, interferons, and related cytokine networks (8,9). Clinical and pharmacokinetic data suggest that pediatric exposure profiles are comparable to those seen in adults, and phase 3 evidence has demonstrated meaningful efficacy in polyarticular-course JIA, including improvements in patient-reported and clinician-assessed outcomes (10). Emerging real-world data from South Asia also indicate that tofacitinib may offer a practical and comparatively affordable alternative for children with refractory disease, particularly where access to biologic therapies is inconsistent or unsustainable (11). These features make tofacitinib especially relevant in settings where oral administration, reduced treatment logistics, and cost considerations may influence adherence and treatment continuity.

Despite this promise, the pediatric evidence base for tofacitinib remains incomplete. Published studies have reported favorable short- to medium-term efficacy, but the available literature is still limited by relatively small samples, short follow-up durations, concentration on selected JIA phenotypes, incomplete representation of diverse populations, and insufficient reporting of long-term safety, functional outcomes, and patient-centered measures (8,10-12). Existing data from South Asia are sparse, and no robust Pakistani real-world cohort has adequately characterized the safety, efficacy, and tolerability of tofacitinib in children and adolescents with JIA across different subtypes. This gap is clinically important because treatment access, background immunosuppressive exposure, nutritional

status, infection risk, and healthcare utilization patterns may differ substantially from those in high-income settings, potentially influencing both therapeutic response and adverse-event profiles.

The present study was therefore undertaken to evaluate the safety, efficacy, and tolerability of tofacitinib in children and adolescents with JIA treated in two rheumatology centers in Lahore, Pakistan. Specifically, the study aimed to assess short-term change in physician-assessed disease activity, document adverse events and treatment discontinuation, and describe treatment experience across JIA subtypes in a real-world clinical setting. It was hypothesized that tofacitinib would be associated with clinically meaningful improvement in disease activity together with an acceptable short-term tolerability profile in this Pakistani pediatric cohort (1-12).

MATERIALS AND METHODS

This prospective study was conducted to evaluate the safety, efficacy, and tolerability of tofacitinib in children and adolescents diagnosed with juvenile idiopathic arthritis and managed at the Rheumatology outpatient services of National Hospital and Medical Centre and Arthritis Care Foundation, Lahore, Pakistan, between January 2024 and February 2025. The study was based on routinely maintained clinical records and the shared electronic database of the participating centers, from which eligible cases were identified and analyzed using a predefined data extraction framework. The cohort approach was selected to characterize real-world treatment outcomes in a setting where standardized longitudinal JIA registries remain limited and where treatment decisions are made as part of routine specialist care rather than protocol-driven intervention.

All children and adolescents aged 2 to 18 years with a diagnosis of JIA according to the International League of Associations for Rheumatology classification criteria were considered eligible, irrespective of subtype, provided they had been prescribed tofacitinib during the study period and had at least 3 months of follow-up after treatment initiation (1). To ensure interpretability of both baseline status and treatment response, only patients with sufficiently complete records were included, specifically those with documented demographic information, JIA subtype, treatment history, and Physician Visual Analog Scale assessments at treatment initiation and at follow-up. Patients were excluded if they had another concurrent autoimmune or autoinflammatory disorder that could confound disease activity assessment, including systemic lupus erythematosus, inflammatory bowel disease, or vasculitis, or if follow-up was shorter than 3 months or the record lacked essential baseline or follow-up disease activity data. Because the study used routinely collected clinical data from a defined treatment population, all eligible patients meeting the selection criteria during the study interval were included in the analytic cohort.

Data were extracted using a standardized proforma to improve consistency and reproducibility of abstraction across records. The extracted variables included age at tofacitinib initiation, sex, JIA subtype, duration of disease where documented, prior biologic exposure, concomitant conventional synthetic disease-modifying antirheumatic drug use, corticosteroid exposure, tofacitinib start date, treatment duration, and duration of follow-up. Baseline and follow-up disease activity was assessed using the Physician Visual Analog Scale, which was used in this study as the principal available clinician-based indicator of inflammatory activity because full composite disease activity measures, including JADAS and JIA-ACR response components, were not consistently available across records. Additional variables included erythrocyte sedimentation rate and C-reactive protein where available, patient- or parent-reported side effects, infections, clinically documented adverse events, and reasons for treatment discontinuation. Follow-up data were recorded from routine visits scheduled at approximately 1 month, 3 months, 6 months, and 12 months where available, with the last documented visit used for the principal pre-post efficacy analysis.

The primary outcomes were safety, efficacy, and tolerability. Safety was operationalized as the occurrence of adverse events, serious adverse events, infections, and clinically recorded laboratory abnormalities

temporally associated with tofacitinib exposure. Efficacy was defined as change in Physician Visual Analog Scale score from baseline to the last available follow-up visit, with reduction in score indicating improvement in disease activity. Tolerability was assessed by permanent discontinuation of tofacitinib attributable to intolerance, adverse events, or perceived lack of effectiveness. Secondary descriptive outcomes included available information on pain and physical functioning reported by patients or parents during follow-up encounters. All variables were extracted in anonymized form and entered into a secure database for analysis.

Several procedural steps were used to reduce bias and strengthen data integrity. Eligibility criteria were applied uniformly across both centers before analysis. A single standardized abstraction template was used to reduce information heterogeneity and to ensure that outcome definitions were applied consistently. Records with missing key baseline or follow-up Physician Visual Analog Scale values were excluded to minimize outcome misclassification in the primary efficacy analysis. To reduce selective interpretation, outcomes were defined before formal statistical analysis, and subgroup comparisons by JIA subtype were treated as exploratory because of small cell sizes. Potential confounding related to concurrent methotrexate, leflunomide, sulfasalazine, corticosteroid use, and prior biologic exposure was addressed descriptively through detailed baseline reporting and subgroup characterization, recognizing that the modest sample size limited the stability of multivariable adjustment. Because treatment allocation was determined by routine clinical care rather than randomization, findings were interpreted as real-world associations rather than causal treatment effects.

The sample size was originally estimated on the basis of the anticipated proportion of patients experiencing adverse events, which was designated as the principal safety outcome. Using an expected adverse-event frequency of 30%, a 95% confidence level, and a precision margin of 10%, the minimum calculated sample was approximately 81 participants, which was increased to 90 to allow for incomplete follow-up. However, the number of eligible patients who received tofacitinib during the defined study period was 47, and therefore the full accessible cohort was included. This whole-cohort inclusion strategy maximized the use of available real-world pediatric data while acknowledging that precision for subgroup and rare-event analyses would remain limited.

Data were analyzed using SPSS version 26.0. Continuous variables were summarized as mean with standard deviation or median with interquartile range according to distributional properties, while categorical variables were presented as frequencies and percentages. Normality of continuous variables was assessed using the Shapiro-Wilk test. The primary efficacy comparison between baseline and last follow-up Physician Visual Analog Scale values was performed using the paired t-test for normally distributed paired data and the Wilcoxon signed-rank test where non-parametric evaluation was more appropriate. Exact binomial 95% confidence intervals were calculated for key proportions, including adverse events, infections, and treatment discontinuation. Incidence rates for adverse events and infections were computed per 100 patient-months based on cumulative treatment exposure. Baseline characteristics, efficacy estimates, and safety outcomes were also explored across JIA subtypes using the Kruskal-Wallis test for continuous non-parametric comparisons and chi-square or Fisher's exact test for categorical variables, as appropriate. Missing data were minimal and were handled by listwise deletion after confirming that the pattern of missingness was random and did not materially affect the analytic sample. A two-sided p-value of less than 0.05 was considered statistically significant. Given the exploratory nature of subtype analyses and the limited number of outcomes, no formal adjustment for multiple comparisons was applied.

The study was approved by the Institutional Review Board/Ethics Committee of National Hospital and Medical Centre, Lahore, Pakistan, and was conducted in accordance with the ethical principles of the Declaration of Helsinki. Patient confidentiality was maintained throughout the study by anonymizing all extracted records and restricting access to the study database to the research team only. Data handling

procedures were standardized across centers, and all entries were reviewed for internal consistency before analysis to support reproducibility, traceability, and analytical reliability.

RESULTS

A total of 47 children and adolescents with juvenile idiopathic arthritis who received tofacitinib and met the eligibility criteria were included in the final analysis. The cohort had a mean age of 14.15 ± 3.88 years, with a median age of 15 years, and females comprised 59.6% of the study population. Polyarticular juvenile idiopathic arthritis was the predominant subtype, accounting for 55.3% of cases, whereas systemic-onset juvenile idiopathic arthritis and enthesitis-related arthritis each represented 21.3%, and psoriatic juvenile idiopathic arthritis accounted for 2.1%. Most patients were receiving concomitant conventional synthetic disease-modifying antirheumatic drugs, most commonly methotrexate in 53.2% and leflunomide in 23.4%, while 12.8% received tofacitinib without a concomitant csDMARD. Previous biologic exposure was documented in 34.0% of patients, most frequently etanercept in 23.4%, whereas 66.0% had not previously received biologic therapy. The mean follow-up duration was 3.26 ± 1.01 months, while the mean cumulative tofacitinib exposure was 18.3 ± 9.67 months, indicating that many patients had been receiving treatment before the defined analytic follow-up window captured in the present dataset. At the last recorded visit, 70.2% of patients were no longer receiving corticosteroids, 23.4% remained on 5–10 mg, and 6.4% were receiving less than 5 mg.

Table 1. Baseline Demographic and Clinical Characteristics of the Study Cohort (n=47)

Characteristic	Value
Age, mean ± SD (years)	14.15 ± 3.88
Age, median (IQR) (years)	15 (12–18)
Female sex, n (%)	28 (59.6)
Male sex, n (%)	19 (40.4)
Polyarticular JIA, n (%)	26 (55.3)
Systemic-onset JIA, n (%)	10 (21.3)
Enthesitis-related arthritis, n (%)	10 (21.3)
Psoriatic JIA, n (%)	1 (2.1)
Uveitis present, n (%)	1 (2.1)
Methotrexate use, n (%)	25 (53.2)
Leflunomide use, n (%)	11 (23.4)
Sulfasalazine use, n (%)	3 (6.4)
Cyclosporine use, n (%)	2 (4.3)
No concomitant csDMARD, n (%)	6 (12.8)
Previous biologic exposure, n (%)	16 (34.0)
No previous biologic exposure, n (%)	31 (66.0)
Duration of follow-up, mean ± SD (months)	3.26 ± 1.01
Duration of follow-up, median (IQR) (months)	3 (2–4)
Tofacitinib exposure, mean ± SD (months)	18.3 ± 9.67
Tofacitinib exposure, median (IQR) (months)	18 (11.5–24)
No steroids at last visit, n (%)	33 (70.2)
Steroids 5–10 mg at last visit, n (%)	11 (23.4)
Steroids <5 mg at last visit, n (%)	3 (6.4)

With respect to efficacy, physician-assessed disease activity improved substantially over the observation period. The mean Physician Visual Analog Scale score decreased from 7.15 ± 0.91 at baseline to 2.96 ± 1.60 at the last available follow-up, corresponding to a mean reduction of 4.19 ± 1.51 points. This mean paired reduction yielded an approximate 95% confidence interval of 3.75 to 4.63 points and a large standardized paired effect size (Cohen's dz ≈ 2.77), supporting a strong within-patient improvement signal. The paired t-test demonstrated highly significant improvement ($t=18.99$, $p<0.0001$), and the Wilcoxon signed-rank test confirmed the same direction and strength of association (statistic=1.0, $p<0.0001$). Overall, 45 of 47 patients, corresponding to 95.7% (95% CI 85.2%–99.5%), showed a positive reduction in Physician Visual Analog Scale score. These findings indicate marked short-term improvement in clinician-assessed disease activity in the analyzed cohort.

Table 2. Primary Efficacy Outcomes Based on Physician Visual Analog Scale (n=47)

Outcome	Mean ± SD / n (%)	Median (IQR)	Inferential Statistic	95% CI	Effect Size
Baseline PVAS	7.15 ± 0.91	7 (7–8)	—	—	—
Last-visit PVAS	2.96 ± 1.60	3 (2–4)	—	—	—
Change in PVAS (dPVAS)	4.19 ± 1.51	4 (4–5)	Paired t=18.99; p<0.0001	3.75 to 4.63	Cohen's dz=2.77
Change in PVAS (non-parametric confirmation)	—	—	Wilcoxon statistic=1.0; p<0.0001	—	—
Patients with improvement (dPVAS >0)	45 (95.7)	—	—	85.2% to 99.5%	—

Safety and tolerability outcomes were favorable within the available follow-up period. Three patients experienced any adverse event, giving an overall adverse-event frequency of 6.4% with a 95% confidence interval of 1.3% to 17.5% and an incidence rate of 0.35 events per 100 patient-months based on 860 total patient-months of exposure. Two patients discontinued treatment because of intolerance and one because of perceived inefficacy. No infections, serious adverse events, or clinically documented laboratory abnormalities were reported during the analytic period. Although these findings support acceptable short-term tolerability in the present cohort, they should be interpreted conservatively because the study was not powered to detect rare events and the follow-up interval was relatively brief for long-latency safety outcomes.

Table 3. Safety and Tolerability Outcomes (n=47)

Outcome	n (%)	95% CI	Rate per 100 Patient-Months	p-value
Any adverse event	3 (6.4)	1.3%–17.5%	0.35	—
Intolerance	2 (4.3)	0.5%–14.5%	—	—
Inefficacy leading to event/discontinuation	1 (2.1)	0.1%–11.3%	—	—
Infections	0 (0.0)	0.0%–7.6%	0.00	—
Treatment discontinuation	3 (6.4)	1.3%–17.5%	—	—
Discontinuation due to intolerance	2 (4.3)	0.5%–14.5%	—	—
Discontinuation due to inefficacy	1 (2.1)	0.1%–11.3%	—	—

Exploratory subtype analysis showed that the magnitude of improvement was numerically greatest in polyarticular juvenile idiopathic arthritis, where the mean reduction in Physician Visual Analog Scale score was 4.65 ± 1.16 points, compared with 3.60 ± 1.78 points in systemic-onset disease and 3.60 ± 1.84 points in enthesitis-related arthritis. The single psoriatic juvenile idiopathic arthritis case improved by 4.00 points. Approximate 95% confidence intervals around mean reduction were 4.18 to 5.12 for polyarticular disease, 2.33 to 4.87 for systemic-onset disease, and 2.28 to 4.92 for enthesitis-related arthritis, indicating that the point estimates favored numerically greater response in the polyarticular subgroup, although interval overlap was substantial. The Kruskal-Wallis test did not demonstrate a statistically significant difference in change scores across the multi-patient subtypes (statistic=4.67, p=0.097), indicating that apparent between-subtype variation should be considered exploratory rather than confirmatory.

Table 4. Efficacy Outcomes by JIA Subtype

Outcome	Polyarticular (n=26)	SoJIA (n=10)	ERA (n=10)	Psoriatic (n=1)	p-value
Baseline PVAS, mean ± SD	7.31 ± 0.79	7.20 ± 0.79	6.70 ± 1.25	7.00	—
Last-visit PVAS, mean ± SD	2.65 ± 1.32	3.60 ± 1.96	3.10 ± 1.91	3.00	—
Change in PVAS, mean ± SD	4.65 ± 1.16	3.60 ± 1.78	3.60 ± 1.84	4.00	0.097*
Approx. 95% CI for mean dPVAS	4.18 to 5.12	2.33 to 4.87	2.28 to 4.92	Not estimable	—

*Kruskal-Wallis test across Polyarticular, SoJIA, and ERA; psoriatic JIA excluded from inferential testing because n=1.

The distribution of adverse events across subtypes was sparse and showed no statistically significant between-group difference. One adverse event occurred in each of the polyarticular, systemic-onset, and enthesitis-related arthritis groups, corresponding to frequencies of 3.8%, 10.0%, and 10.0%, respectively, whereas no adverse event was recorded in the psoriatic subgroup. Adverse-event rates per 100 patient-months were 0.20 in polyarticular disease, 0.50 in systemic-onset disease, and 0.67 in enthesitis-related

arthritis, suggesting a numerically higher event burden in the latter two subtypes despite similar absolute event counts because of lower cumulative exposure time. However, the chi-square comparison was not significant (p=0.853), and these differences should not be overinterpreted given the very small number of events.

Table 5. Safety and Tolerability Outcomes by JIA Subtype

Outcome	Polyarticular (n=26)	SoJIA (n=10)	ERA (n=10)	Psoriatic (n=1)	p-value
Any adverse event, n (%)	1 (3.8)	1 (10.0)	1 (10.0)	0 (0.0)	0.853†
Infections, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	—
Treatment discontinuation, n (%)	1 (3.8)	1 (10.0)	1 (10.0)	0 (0.0)	0.853†
Total patient-months	499	199	150	12	—
AE rate per 100 patient-months	0.20	0.50	0.67	0.00	—
Infection rate per 100 patient-months	0.00	0.00	0.00	0.00	—

†Chi-square test across Polyarticular, SoJIA, and ERA; psoriatic JIA excluded from inferential testing because n=1.

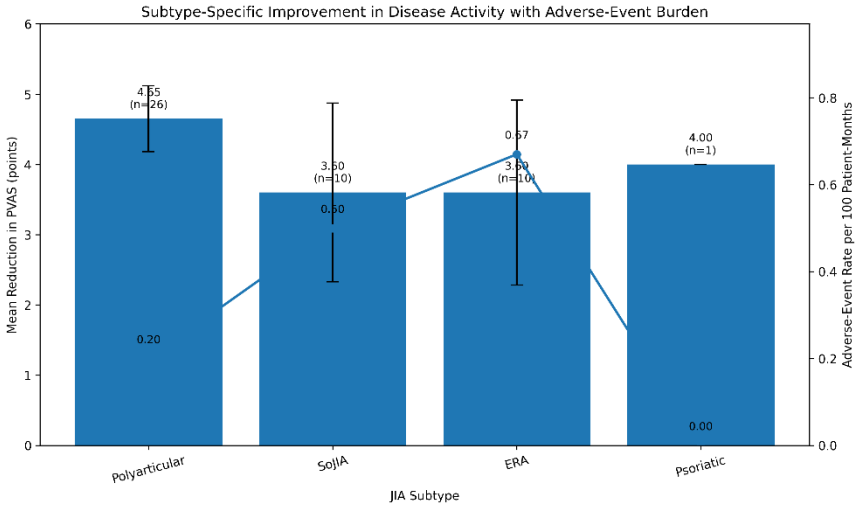

Figure 1 Subtype-Specific Improvement in Disease Activity with Adverse-Event Burden

This figure demonstrates a clinically informative divergence between efficacy magnitude and event burden across juvenile idiopathic arthritis subtypes. Polyarticular disease showed the largest mean reduction in Physician Visual Analog Scale score at 4.65 points with an approximate 95% confidence interval of 4.18 to 5.12, whereas systemic-onset and enthesitis-related arthritis each showed mean reductions of 3.60 points, with wider approximate confidence intervals of 2.33 to 4.87 and 2.28 to 4.92, respectively. Despite similar absolute adverse-event counts of one event each in these three multi-patient subgroups, the adverse-event rate per 100 patient-months increased from 0.20 in polyarticular disease to 0.50 in systemic-onset disease and 0.67 in enthesitis-related arthritis because cumulative exposure time declined from 499 to 199 and 150 patient-months, respectively. The combined display therefore suggests that polyarticular juvenile idiopathic arthritis had the most favorable observed efficacy-to-event profile in this cohort, while systemic-onset and enthesitis-related arthritis showed comparable symptomatic improvement but a numerically less favorable exposure-adjusted safety gradient, a pattern that is hypothesis-generating rather than definitive because subgroup differences were not statistically significant in formal testing.

DISCUSSION

This study provides real-world evidence on the use of tofacitinib in Pakistani children and adolescents with juvenile idiopathic arthritis and addresses an important regional gap in the literature, where data on Janus kinase inhibitor use in pediatric rheumatology remain limited. The cohort reflected a clinically relevant case mix dominated by polyarticular disease, with additional representation from systemic-onset and enthesitis-related arthritis, and demonstrated a substantial reduction in physician-assessed

disease activity over follow-up. The mean Physician Visual Analog Scale score decreased by 4.19 points, and 95.7% of patients showed improvement, suggesting that tofacitinib was associated with meaningful short-term clinical benefit in this treatment-experienced population. These findings are broadly consistent with trial and post-trial evidence demonstrating clinically important responses to tofacitinib in polyarticular-course juvenile idiopathic arthritis, as well as with emerging observational reports from South Asia supporting its practical utility in refractory disease and resource-constrained clinical settings (10-12).

The observed treatment effect is notable because many patients in this cohort had prior exposure to conventional synthetic disease-modifying antirheumatic drugs and more than one-third had previously used biologic therapy, indicating that tofacitinib was often introduced in a context of incomplete response, treatment escalation, or access-related treatment transition. In such settings, the oral route of administration may confer particular advantages by reducing treatment logistics, improving family acceptability, and lowering barriers associated with parenteral biologic therapy. This is especially relevant in low- and middle-income countries, where continuity of advanced therapy may be interrupted by affordability, limited drug availability, or travel burdens related to tertiary-center care. The present findings therefore support the view that tofacitinib may represent a clinically useful and operationally feasible option for children with persistent disease activity when conventional therapy is insufficient and sustained biologic use is difficult to maintain (6-8,11,14,15).

Subtype-level findings should be interpreted cautiously but remain clinically informative. The greatest numerical improvement in Physician Visual Analog Scale score was observed in polyarticular juvenile idiopathic arthritis, while systemic-onset and enthesitis-related arthritis also showed clear improvement, though with wider uncertainty because of smaller subgroup sizes. Formal comparison across the major multi-patient subtypes did not reach statistical significance, indicating that the study was not able to confirm true between-subtype differences in response. Even so, the consistency of directional improvement across subtypes is encouraging and aligns with the broader biologic plausibility of Janus kinase inhibition in inflammatory disorders characterized by multi-cytokine immune activation. Published evidence has been strongest for polyarticular-course disease, but accumulating case-based and observational data suggest potential value in systemic-onset and other refractory phenotypes, particularly when standard biologic pathways are inaccessible, unaffordable, or previously unsuccessful (8,10-12,17).

The short-term safety and tolerability profile in the present cohort was favorable, with adverse events documented in only 6.4% of patients, no serious infections, no serious adverse events, and no clinically recorded laboratory abnormalities during the analyzed follow-up period. Treatment discontinuation occurred in three patients and was attributable to intolerance in two and inefficacy in one, suggesting acceptable early treatment persistence in most cases. These findings compare favorably with reports from controlled studies and long-term extension datasets in which mild infections, laboratory abnormalities, and treatment discontinuations are more common over longer durations of exposure (12,17,18). However, this apparent safety advantage should not be overstated. The follow-up interval captured in the analytic dataset was relatively short, the sample size was modest, and the study was not designed to reliably detect rare but clinically important outcomes such as opportunistic infection, herpes zoster, cytopenia, thromboembolic complications, or other delayed adverse effects. Accordingly, the present results support short-term tolerability rather than definitive long-term safety.

An important interpretive consideration is the potential influence of concomitant and prior therapy. More than half of the patients were receiving methotrexate, nearly one-quarter were receiving leflunomide, and a subset remained on corticosteroids at the last visit. In addition, one-third had prior biologic exposure. These background treatments may have influenced both efficacy and adverse-event patterns, and because treatment allocation was determined by routine clinical judgment rather than randomization, residual confounding by indication cannot be excluded. The observed improvement

therefore cannot be attributed to tofacitinib alone with complete certainty. Instead, the findings should be understood as reflecting the effectiveness of tofacitinib-containing real-world treatment regimens in specialist practice. This distinction is important, particularly for readers evaluating comparative effectiveness against biologic agents or conventional regimens, because the present study was observational and descriptive rather than controlled or causal in design (5-7,10,12).

The use of the Physician Visual Analog Scale as the primary efficacy indicator was a pragmatic response to limitations in real-world record completeness, but it also constrains interpretation. Composite disease activity indices such as JADAS, formal JIA-ACR response criteria, functional outcomes such as CHAQ-DI, patient-reported pain trajectories, and sustained remission measures were not consistently available. As a result, the study captures clinician-assessed improvement but cannot fully characterize multidimensional response, quality-of-life change, or disease control durability. Similarly, the absence of uniformly available laboratory monitoring data limits the ability to comment on asymptomatic abnormalities, including dyslipidemia and hepatic enzyme elevation, which have been described in the broader tofacitinib literature (8,10,12,18). These data limitations do not invalidate the observed clinical signal, but they do narrow the scope of inference and highlight the need for better structured pediatric rheumatology follow-up systems in routine practice.

This study nonetheless has several strengths. It contributes original data from a population that is underrepresented in the pediatric rheumatology literature, it reflects actual prescribing and monitoring conditions in a South Asian tertiary-care environment, and it includes clinically relevant subtype-level description rather than limiting analysis to a single juvenile idiopathic arthritis phenotype. In a field where most published data come from high-income settings or controlled trial populations, such real-world evidence is important for contextualizing treatment feasibility and informing local practice. The study also highlights the role of affordability in treatment pathways, an issue that is often underemphasized in efficacy-focused discussions but is central to therapeutic continuity in many healthcare systems (11,14,15).

At the same time, the limitations are substantial and should be openly acknowledged. The sample size was considerably smaller than the originally estimated target, which reduced precision and limited the interpretability of subgroup analyses. The study was conducted across two centers in one city, which restricts generalizability to the wider Pakistani pediatric population and to other South Asian healthcare environments with different referral structures and treatment access patterns. The observational design, short analytic follow-up, incomplete availability of standardized composite outcome measures, and lack of multivariable adjustment all limit causal inference. In addition, the single psoriatic juvenile idiopathic arthritis case does not permit any meaningful subtype-specific conclusion. These factors position the current study best as an informative early real-world cohort rather than a definitive comparative evaluation.

Taken together, the present findings suggest that tofacitinib may offer clinically meaningful short-term improvement with acceptable early tolerability in children and adolescents with juvenile idiopathic arthritis managed in a resource-limited Pakistani setting. The results are particularly relevant for contexts in which biologic therapy is difficult to sustain because of cost, access, or treatment logistics. Future work should build on these observations through larger multicenter prospective cohorts and, where feasible, comparative studies incorporating standardized disease activity indices, functional outcomes, laboratory monitoring, infection surveillance, and longer-term follow-up. Such work would help clarify subtype-specific response, strengthen safety estimates, and support development of context-appropriate treatment pathways for juvenile idiopathic arthritis in low- and middle-income countries (8,10-12,17,18).

CONCLUSION

In this real-world cohort of Pakistani children and adolescents with juvenile idiopathic arthritis, tofacitinib was associated with substantial short-term improvement in physician-assessed disease activity and a favorable early tolerability profile, with most patients demonstrating clinical improvement and few documented adverse events or discontinuations. These findings support the potential role of tofacitinib as a practical therapeutic option in resource-constrained settings where biologic therapy may be difficult to access or maintain, although the observational design, modest sample size, concomitant background therapy, and limited follow-up mean that conclusions regarding comparative effectiveness and long-term safety should remain cautious. Larger multicenter studies using standardized composite outcomes, patient-reported measures, and structured laboratory surveillance are needed to confirm these findings and better define the place of tofacitinib in the management of juvenile idiopathic arthritis across diverse pediatric populations.

REFERENCES

1. Chen K, Zeng H, Togizbayev G, Martini A, Zeng H. New classification criteria for juvenile idiopathic arthritis. Int J Rheum Dis. 2023;26(10):1889-1892. doi:10.1111/1756-185X.14813.

2. McHugh J. Global prevalence of JIA, JSLE and club foot. Nat Rev Rheumatol. 2020;16(8):408. doi:10.1038/s41584-020-0465-6.

3. Tanya M, Teh KL, Das L, Hoh SF, Gao X, Arkachaisri T. Juvenile idiopathic arthritis in Southeast Asia: the Singapore experience over two decades. Clin Rheumatol. 2020;39(11):3455-3464. doi:10.1007/s10067-020-05081-9.

4. Ren T, Guan JH, Li Y. Evolution of treatment options for juvenile idiopathic arthritis. Front Pharmacol. 2022;13:891703. doi:10.3389/fphar.2022.891703.

5. Giancane G, Consolaro A, Lanni S, Davì S, Schiappapietra B, Ravelli A. Juvenile idiopathic arthritis: diagnosis and treatment. Rheumatol Ther. 2016;3(2):187-207. doi:10.1007/s40744-016-0040-4.

6. Civino A, Diomeda F, Burrone M, Natoli V, Ravelli A. Update on biologic therapy in juvenile idiopathic arthritis: a five-year narrative review. Biologics. 2025;19:425-441. doi:10.2147/BTT.S486359.

7. Palman J, Shoop-Worrall S, Hyrich K, McDonagh JE. Update on the epidemiology, risk factors and disease outcomes of juvenile idiopathic arthritis. Best Pract Res Clin Rheumatol. 2018;32(2):206-222. doi:10.1016/j.berh.2018.10.004.

8. Melki I, Frémond ML. JAK inhibition in juvenile idiopathic arthritis (JIA): better understanding of a promising therapy for refractory cases. J Clin Med. 2023;12(14):4695. doi:10.3390/jcm12144695.

9. Padda IS, Bhatt R, Parmar M. Tofacitinib. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026.

10. Brunner HI, Ruperto N, Synoverska O, Ting TV, Mendoza CA, Spindler AJ, et al. Tofacitinib for the treatment of juvenile idiopathic arthritis: patient-reported outcomes in a phase 3, randomized, double-blind, placebo-controlled withdrawal trial. Arthritis Care Res (Hoboken). 2022;74(8):1340-1350. doi:10.1002/acr.24590.

11. Iman MN, Islam MR, Rabbani MG, Akther N, Ahsan A, Das S, et al. Treatment of refractory polyarticular course juvenile idiopathic arthritis with tofacitinib: extended experience from Bangladesh. PLoS One. 2025;20(1):e0312174. doi:10.1371/journal.pone.0312174.

12. Jones NT, Keller CL, Abadie RB, Bratton MB, Henderson EJ, Moore P, et al. Safety and effectiveness of tofacitinib in treating polyarticular course juvenile idiopathic arthritis. Cureus. 2023;15(10):e48258. doi:10.7759/cureus.48258.

13. Thierry S, Fautrel B, Lemelle I, Guillemin F. Prevalence and incidence of juvenile idiopathic arthritis: a systematic review. Joint Bone Spine. 2014;81(2):112-117. doi:10.1016/j.jbspin.2013.09.003.

14. Souto A, Maneiro JR, Salgado E. Rate of discontinuation and drug survival of biologic therapies in rheumatoid arthritis: a systematic review and meta-analysis of drug registries and health care databases. Rheumatology (Oxford). 2016;55(3):523-534. doi:10.1093/rheumatology/kev343.

15. Ramiro S, Landewé R, van der Heijde D, van Vollenhoven RF, Dougados M, Emery P, et al. Discontinuation rates of biologics in patients with rheumatoid arthritis: are they related to the introduction of biosimilars? RMD Open. 2015;1(1):e000155. doi:10.1136/rmdopen-2015-000155.

16. Ly K, Beck KM, Smith MP, Orbai AM, Liao W. Tofacitinib in the management of active psoriatic arthritis: patient selection and perspectives. Psoriasis (Auckl). 2019;9:97-107. doi:10.2147/PTT.S161453.

17. Zhu X, Li X, Han X, Chen H, Zhang F, Gao M, et al. Tofacitinib treatment of systemic juvenile idiopathic arthritis: a case report and literature review. Front Pediatr. 2025;13:1482762. doi:10.3389/fped.2025.1482762.

18. Wollenhaupt J, Lee EB, Curtis JR, Silverfield J, Terry K, Soma K, et al. Safety and efficacy of tofacitinib for up to 9.5 years in the treatment of rheumatoid arthritis: final results of a global, open-label, long-term extension study. Arthritis Res Ther. 2019;21(1):89. doi:10.1186/s13075-019-1866-2.