

Safety Profile of Tofacitinib in a Single-Center Real-World Cohort: A Comprehensive Analysis of Adverse Events and Associated Risk Factors

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Review began 10/06/2026

Review ended 10/14/2026

Published 10/18/2026

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DOI: 10.7759/cureus.118124

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Abstract

Background and aim

Tofacitinib, an oral Janus kinase (JAK) inhibitor, has significantly changed the treatment landscape of inflammatory arthritis. Real-world safety data on tofacitinib regarding serious infections, major adverse cardiovascular events (MACE), and malignancies are less common. This study aimed to describe the incidence of significant adverse events (AEs) and identify baseline and treatment-related factors associated with these outcomes in a routine clinical setting.

Methods

This was a single-center observational study conducted at the Department of Rheumatology, Divisha Arthritis and Medical Center, Bengaluru, India. The study included 1,000 adult patients with inflammatory arthritides who received tofacitinib and had documented safety follow-up. Patients who received tofacitinib for various types of arthritis from January 2022 to January 2024 (two years) were observed. Patients were selected using consecutive sampling based on predefined eligibility criteria. Safety endpoints included tuberculosis (TB), MACE, stroke, herpes zoster (HZ), cytopenia, GI issues, and malignancy. Fisher's exact test was used for univariate screening, and multivariable logistic regression was used to identify independent predictors and calculate adjusted ORs (aORs).

Results

The most frequently observed AEs were TB (21 (2.1%)), HZ (15 (1.5%)), GI issues (13 (1.3%)), and cytopenia (10 (1.0%)). Cardiovascular events were rare, with three strokes (0.3%) and two MACE events (0.2%); notably, no malignancies were reported in the dataset. Significant independent risk factors for TB included prior TB risk (aOR, 38.2), prior tumor necrosis factor inhibitor use (aOR, 3.1), and prior steroid use (aOR, 2.8). Smoking was significantly associated with MACE ($p = 0.0463$). The small number of stroke events precluded reliable multivariable assessment of factors associated with stroke.

Conclusions

The safety profile was consistent with known JAK inhibitor mechanisms, but the high TB incidence in this endemic region emphasizes the need for a layered risk assessment. Rigorous screening for latent TB, aggressive management of metabolic risks such as diabetes, and cardiovascular risk stratification are essential to optimize the benefit-risk balance of tofacitinib.

Categories: Pharmacology, Rheumatology, Pulmonology

Keywords: adverse events, herpes zoster, inflammatory arthritis, janus kinase (jak) inhibitor, major adverse cardiovascular events (mace), risk factors, safety, tofacitinib, tuberculosis

Introduction

Rheumatoid arthritis (RA) and other inflammatory arthritides are chronic, progressive autoimmune diseases characterized by inflammatory synovitis, joint destruction, and significant comorbidities that often lead to a lower quality of life and increased mortality [1-3]. The therapeutic landscape has evolved from conventional synthetic disease-modifying antirheumatic drugs to biologic DMARDs (bDMARDs) and, more recently, targeted synthetic DMARDs [1,4,5]. Tofacitinib, a potent oral small-molecule inhibitor of the Janus kinase (JAK) family (specifically JAK1 and JAK3), was the first in its class approved for treating RA, psoriatic arthritis, and ankylosing spondylitis [5-8]. By modulating the JAK-STAT signaling pathway, tofacitinib inhibits the action of various proinflammatory cytokines, including interleukins and interferons, which are central to the pathogenesis of these conditions [2,6,9].

While pivotal clinical trials demonstrated tofacitinib's efficacy and established a safety profile during nearly

How to cite this article

Rao V, N T, Vernekar A, et al. (October 18, 2026) Safety Profile of Tofacitinib in a Single-Center Real-World Cohort: A Comprehensive Analysis of Adverse Events and Associated Risk Factors. Cureus 18(10): e118124. DOI 10.7759/cureus.118124

a decade of clinical development, subsequent postmarketing requirements led to the ORAL Surveillance study [10,11]. This trial specifically targeted an older population (aged ≥ 50 years) with at least one cardiovascular risk factor [11–13]. Results from ORAL Surveillance revealed a higher risk of major adverse cardiovascular events (MACE) and malignancies with tofacitinib compared with tumor necrosis factor inhibitors (TNFis), leading regulatory bodies such as the Food and Drug Administration and European Medicines Agency to issue boxed warnings for the entire JAK inhibitor class [12,14]. Further post hoc analyses identified age ≥ 65 years and long-term smoking as critical drivers of these excess risks [10,12,15].

Despite these findings, the controlled environment of randomized controlled trials often excludes complex patients with multiple comorbidities, limiting the external validity of their results in routine clinical practice [11]. Real-world evidence (RWE) is therefore essential to characterize the long-term safety and treatment persistence of tofacitinib in diverse, unselected patient populations [10,11]. Existing RWE on tofacitinib has generally supported a safety profile consistent with bDMARDs, although an increased risk of herpes zoster (HZ) has emerged as a distinct class-related concern [11]. However, large-scale studies focusing on regional risks, such as tuberculosis (TB) in endemic areas, or the role of metabolic comorbidities in cerebrovascular events remain critical for refining risk-stratification strategies [3].

This study aimed to evaluate the safety and clinical outcomes of tofacitinib in a large, real-world cohort of 1,000 patients with inflammatory arthritides. Specifically, it focused on identifying independent predictors of serious adverse events (AEs), including risk factors for TB occurrence and metabolic drivers of cerebrovascular risk. By examining period-dependent risk patterns in a substantial patient population, this research sought to contribute vital data on the need for pretreatment screening for latent TB and the importance of managing cardiovascular comorbidities during tofacitinib therapy.

Materials And Methods

Aim, design, and setting of the study

This was a single-center, retrospective observational cohort study conducted at the Department of Rheumatology, Divisha Arthritis and Medical Center, Bengaluru, India. Medical records of 1,000 eligible adult patients with inflammatory arthritides who received tofacitinib and had documented safety follow-up were reviewed. Patients were identified through consecutive sampling. The study aimed to characterize the occurrence of AEs and explore associations between these events and baseline clinical and treatment-related characteristics using existing medical records from routine clinical practice. The study cohort was defined according to the eligibility criteria, observation period, and availability of treatment and follow-up records. Although this design enabled the assessment of real-world safety outcomes, including uncommon events, the completeness and accuracy of AE documentation could not be independently verified, and unrecorded events may have been missed. The observational design and absence of a comparator group also limited causal inference; therefore, the findings are interpreted as descriptive patterns and exploratory associations rather than as evidence of causality or definitive time-dependent risk.

Primary objective

The primary objective of this study was to describe the frequency and distribution of selected AEs among adult patients with inflammatory arthritides receiving tofacitinib in a real-world clinical setting.

Secondary objectives

The secondary objectives were (1) to examine the associations between selected baseline demographic, clinical, and treatment-related factors and the occurrence of specific AEs, particularly TB, MACE, stroke, HZ, cytopenia, and GI AEs; (2) to evaluate adjusted associations between selected clinical risk factors and specific AEs using multivariable logistic regression, where appropriate based on the available data and event counts; and (3) to descriptively compare the distribution of selected AEs between patients with treatment durations of ≤ 24 months and > 24 months.

Participants and study population

The study included 1,000 adult patients with inflammatory arthritides. Patients were eligible for inclusion if they had a confirmed diagnosis of inflammatory arthritis according to established classification criteria, documented exposure to tofacitinib for any duration, available baseline demographic and clinical data, and documented follow-up for safety assessment. Patients with incomplete baseline safety data or those who missed follow-up immediately after treatment initiation, thereby precluding safety assessment, were excluded.

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the ACE Independent Ethics Committee. Patient data were de-identified to maintain confidentiality.

Processes and safety endpoints

Each safety endpoint was derived from binary variables recorded in the center's electronic medical record

system. The safety endpoints evaluated included the following: (1) TB, defined as the occurrence of active TB during therapy; (2) MACE, defined as major cardiac events documented in clinical records; (3) stroke, defined as confirmed ischemic or hemorrhagic cerebrovascular events documented by neuroimaging and clinical assessment; (4) HZ, defined as clinically diagnosed localized or disseminated infections confirmed by laboratory testing; (5) cytopenia, defined as clinically significant reductions in blood counts observed on at least two consecutive measurements, including anemia (hemoglobin 8% or poor glycemic control).

Statistical analysis

Categorical variables and AEs were summarized using frequencies and percentages. The frequency of each AE was expressed as the number of patients experiencing the event divided by the total evaluable population and reported as n/N (%). Exploratory comparisons of categorical variables between patients with and without the relevant AE were performed using Fisher's exact test, particularly when expected cell counts were small. Corresponding two-sided exact p-values are reported.

Overall AE frequencies are presented descriptively as n/N (%). ORs were not calculated because the analysis summarizes event frequencies in the overall cohort rather than comparing the odds of an event between groups.

Potential predictors of AEs were explored using a two-stage analytical approach. In the first stage, baseline and treatment-related variables were evaluated using univariate analyses with Fisher's exact test. Variables with $p < 0.20$ were considered candidates for multivariable logistic regression, together with prespecified clinically relevant confounders, where appropriate for the specific outcome and available event counts. Multivariable logistic regression models used a binary AE outcome, a binomial distribution, and a logit link. Adjusted ORs (aORs) with 95% CIs were reported when the available data permitted reliable estimation. For the TB model, age and sex were included as adjustment variables, together with predictors meeting the prespecified screening criterion.

Crude ORs were used to describe the unadjusted associations between individual risk factors and TB occurrence, whereas aORs from multivariable logistic regression were used to estimate associations after accounting for selected covariates. ORs were interpreted as measures of association rather than direct measures of absolute risk. Given the relatively small number of TB events, the precision and stability of the adjusted estimates were considered when interpreting the findings. The corresponding 95% CIs were reported to indicate the uncertainty around the estimates.

Because only three stroke events were observed, multivariable logistic regression was not considered reliable for this outcome owing to the risk of unstable estimates. Stroke findings were therefore summarized descriptively, and no aORs were reported for stroke. Ischemic heart disease and uncontrolled diabetes mellitus were examined as potential clinical factors in relation to stroke; any crude estimates were interpreted cautiously because of the very small number of events.

Crude ORs from univariate comparisons and aORs from multivariable regression were distinguished from descriptive event proportions. All tests were two-sided, and $p < 0.05$ was considered statistically significant. Because Fisher's exact test was used for univariate categorical comparisons, exact p-values are reported rather than t , χ^2 , or F statistics. Numerical test statistics were reported only when generated by the relevant statistical procedure. Analyses were performed using IBM SPSS Statistics for Windows, version 29.0 (released 2022; IBM Corp., Armonk, NY, USA) and Python 3.0.

Results

The study cohort comprised 1,000 patients with a mean tofacitinib exposure of 11.61 months (median, 9.0 months). Analysis of AEs revealed distinct patterns according to treatment duration, categorized as early-onset, cumulative, and steady-state risks.

Early-onset and transition risks

Complications such as TB reactivation, acne, and menstrual abnormalities predominantly occurred within the first 24 months of therapy. The incidence of TB was higher in the short-to-medium-term group (≤ 24 months), at 19 (2.14%), than in the long-term exposure group (> 24 months), at 2 (1.79%). Similarly, acne (46 (5.18%) vs. 3 (2.68%)) and menstrual irregularities (39 (4.39%) vs. 3 (2.68%)) were nearly twice as frequent in the first two years, suggesting that these AEs may be more common during the initial treatment phase or dose-titration period.

Cumulative long-term risks

In contrast, infectious risks, such as HZ and skin and soft tissue infections, demonstrated a possible association with longer treatment duration. The frequency of HZ increased from 11 (1.24%) in patients with ≤ 24 months of exposure to four (3.57%) in those treated for > 24 months. Skin and soft tissue infections also showed an upward trend, with five (4.46%) cases in the long-term group vs. 27 (3.04%) in the short-to-

medium-term group, indicating that the risk of certain infections may be associated with longer JAK inhibitor exposure.

Steady-state physiological effects

Metabolic and physical changes, specifically weight gain and hair fall, were reported at similar frequencies across both treatment-duration groups. Hair fall was reported in 114 (12.84%) patients in the short-to-medium-term group and 15 (13.39%) in the long-term group, while weight gain occurred in 86 (9.68%) and 12 (10.71%) patients, respectively. These findings suggest that the frequencies of these AEs were similar across the two treatment-duration groups.

Dosing and discontinuation

AEs were disproportionately associated with the twice-daily (BD) regimen, which accounted for 768 (76.8%) of all reported AEs. A total of 162 patients (16.2%) discontinued treatment because of AEs, with a mean time to discontinuation of 12.6 months. Serious events, including MACE (n = 2), stroke (n = 3), and deep vein thrombosis (DVT; n = 1), were rare, while no cases of malignancy or pulmonary embolism were observed during the study period. The distribution of selected AEs according to treatment duration is summarized in Table 1.

AE	≤24 months, n (%)	>24 months, n (%)
HZ	11 (1.24%)	4 (3.57%)
Skin and soft tissue infection	27 (3.04%)	5 (4.46%)
Weight gain	86 (9.68%)	12 (10.71%)
Hair fall	114 (12.84%)	15 (13.39%)
TB	19 (2.14%)	2 (1.79%)
Fatigue	55 (6.19%)	6 (5.36%)
Acne	46 (5.18%)	3 (2.68%)
Menstrual abnormalities	39 (4.39%)	3 (2.68%)

TABLE 1: Risk profile comparison: long-term vs. short-term.

AE, adverse event; HZ, herpes zoster; TB, tuberculosis

Overall safety profile

Among the 1,000 patients treated with tofacitinib in this single-center cohort, the frequencies of seven selected safety outcomes were assessed. Table 2 summarizes the number of patients with each recorded event and the corresponding proportion of the total cohort. TB was the most frequently recorded event, followed by HZ, GI issues, and cytopenia. These descriptive findings characterize the observed frequencies of safety events in the study population.

Safety event	Events, n	Total, N	Patients with event, n (%)
TB	21	1,000	21 (2.1%)
MACE	2	1,000	2 (0.2%)
Stroke	3	1,000	3 (0.3%)
HZ	15	1,000	15 (1.5%)
Cytopenia	10	1,000	10 (1.0%)
GI issues	13	1,000	13 (1.3%)
Malignancy	0	1,000	0 (0.0%)

TABLE 2: Frequency and proportion of key AEs among patients receiving tofacitinib (N = 1,000).

AE, adverse event; HZ, herpes zoster; MACE, major adverse cardiovascular events; TB, tuberculosis

The most frequently observed AEs were TB, occurring in 21 patients (2.1%); HZ, in 15 (1.5%); GI issues, in 13 (1.3%); and cytopenia, in 10 (1.0%). Cardiovascular events were uncommon, with stroke reported in three patients (0.3%) and MACE in two (0.2%). No malignancies were recorded in the study dataset during the observation period. These findings represent descriptive event proportions and should not be interpreted as comparative odds or estimates of the causal risk attributable to tofacitinib.

Factors associated with TB

TB occurred in 21 of the 1,000 patients (2.1%). Exploratory univariate analyses were performed to evaluate associations between TB and demographic, clinical, and treatment-related factors. Crude ORs, 95% CIs, and corresponding p-values are presented in Table 3. Prior steroid use and prior TNFI exposure showed statistically significant associations with TB. The association between baseline TB risk factors and TB occurrence was also evaluated.

Factor (comparison)	TB cases with factor, n	Crude OR (95% CI)	Crude p-value*	aOR (95% CI)**
Age >50 vs. ≤50 years	12	1.71 (0.71-4.09)	0.269	-
Male vs. female	8/21 male cases	1.58 (0.65-3.86)	0.329	-
Smoking: yes vs. no	1	1.91 (0.25-14.78)	0.428	-
Prior steroid use: yes vs. no	8	3.67 (1.49-9.02)	0.007	2.8 (1.1-7.2)
Concomitant steroid use: yes vs. no	1	0.73 (0.10-5.51)	1.000	-
Concurrent DMARD use: yes vs. no	16	1.26 (0.46-3.48)	0.808	-
Prior TNFI use: yes vs. no	7	4.60 (1.81-11.67)	0.003	3.1 (1.2-8.4)

TABLE 3: Crude and adjusted associations between selected factors and TB during tofacitinib treatment.

* Crude ORs and p-values were obtained from univariate comparisons of patients with and without TB. Fisher’s exact test was used for categorical comparisons.

** aORs were obtained from multivariable logistic regression when the event count and available data permitted estimation. The adjustment variables included in the final model should be specified.

aOR, adjusted OR; DMARD, disease-modifying antirheumatic drug; TB, tuberculosis; TNFI, tumor necrosis factor inhibitor

Multivariable logistic regression analysis identified prior steroid use, prior TNFI exposure, and baseline TB risk factors as potential independent predictors of TB occurrence after adjustment for the covariates specified in the model. Prior steroid use (aOR, 2.8; 95% CI, 1.1-7.2), prior TNFI exposure (aOR, 3.1; 95% CI, 1.2-8.4), and baseline TB risk factors (aOR, 38.2; 95% CI, 12.4-110.5) were associated with higher odds of TB.

These findings should be interpreted cautiously because of the relatively small number of TB events. The results represent associations and do not establish causality.

For each key safety endpoint, exploratory analyses were performed to examine the associations between selected baseline or treatment-related factors and the occurrence of the AE.

MACE

MACE was rare in this cohort, occurring in only two patients (0.2%; 95% CI, 0.001-0.008). The small number of events limited the statistical power to detect associations with most risk factors (Table 4).

Factor	MACE ADR	p-value
Age >50	1	1.0
Sex (male/female)	2/0	0.1409
Smoking	1	0.0463
Prior steroid use	1	0.686
Concomitant steroid use	0	1.0
Tofacitinib with concurrent DMARDs	2	0.9198
Prior TNFI use	0	1.0
Prior TB risk factors	0	1.0

TABLE 4: Factors associated with MACE (n = 2 events).
ADR, adverse drug reaction; DMARDs, disease-modifying antirheumatic drugs; MACE, major adverse cardiovascular events; TB, tuberculosis; TNFI, tumor necrosis factor inhibitor

Both MACE events occurred in male patients, although this sex distribution did not reach statistical significance (p = 0.1409). Smoking was the only factor significantly associated with MACE occurrence (p = 0.0463), with one of the two MACE cases occurring in a smoker. However, given the very small number of events, this association should be interpreted cautiously and requires validation in larger cohorts. One of the two patients was older than 50 years, and neither had prior TNFI exposure or TB risk factors. One patient had a history of prior steroid use. Both MACE cases occurred in patients receiving combination therapy with conventional DMARDs.

Because of the low event count (n = 2), a full multivariable model was not considered appropriate. However, univariate analysis identified a statistically significant association between smoking and MACE (p = 0.0463). Both events occurred in male patients, although this finding did not reach statistical significance (p = 0.1409).

Stroke

Stroke occurred in three patients (0.3%; 95% CI, 0.001-0.009). Analysis of traditional stroke risk factors revealed no statistically significant associations with the factors routinely collected in the cohort (Table 5).

Factor	Stroke cases, n	p-value
Age >50 years	2	0.8367
Sex (male/female)	1/2	1.000
Smoking	0	1.000
Prior corticosteroid use	0	1.000
Concomitant corticosteroid use	0	1.000
Concomitant conventional DMARD use	3	0.6566
Prior TNFI use	0	1.000
Prior TB risk factors	0	1.000

TABLE 5: Factors associated with stroke occurrence (n = 3 events).

DMARD, disease-modifying antirheumatic drug; TB, tuberculosis; TNFI, tumor necrosis factor inhibitor

Three stroke events (3/1,000; 0.3%) were documented among the 1,000 patients during the study period. Exploratory analyses of routinely collected demographic and treatment-related factors revealed no statistically significant associations with stroke occurrence (Table 5). Two of the three patients were older than 50 years, and the cases comprised one male and two females. None of the patients had a history of smoking, prior corticosteroid use, or previous TNFI exposure. All three patients were receiving concomitant conventional DMARDs. A descriptive assessment of cardiovascular comorbidities identified ischemic heart disease and uncontrolled diabetes mellitus among patients who experienced stroke. However, given the small number of events, these observations were considered exploratory, and the available data were insufficient to support reliable multivariable logistic regression analysis. Accordingly, aORs and corresponding CIs were not reported. Overall, stroke was uncommon in this cohort, and no definitive conclusions regarding its independent predictors could be drawn from the limited number of events. Larger studies are required to evaluate potential associations between cardiovascular comorbidities and stroke during tofacitinib therapy.

HZ

HZ was the second most frequently recorded AE after TB, occurring in 15 patients (1.5%; 95% CI, 0.009–0.025). Analysis of potential risk factors revealed no statistically significant associations (Table 6).

Factor	HZ ADR	p-value
Age >50	7	1.0
Sex (male/female)	5/10	0.876
Smoking	2	0.0696
Prior steroid use	4	0.3515
Concomitant steroid use	0	0.6249
Tofacitinib with concurrent DMARDs	14	0.1145
Prior TNFI use	2	1.0
Prior TB risk factors	1	0.8573

TABLE 6: Factors associated with HZ (n = 15 events).

ADR, adverse drug reaction; DMARDs, disease-modifying antirheumatic drugs; HZ, herpes zoster; TB, tuberculosis; TNFI, tumor necrosis factor inhibitor

Of the patients with HZ, seven were older than 50 years ($p = 1.0$). More female patients experienced HZ than male patients (10 vs. 5), but this difference was not statistically significant ($p = 0.876$). Smoking showed a

possible association with HZ (p = 0.0696), with two of the 15 cases occurring in smokers; however, this association did not reach statistical significance. Prior steroid use was present in four of the 15 cases (p = 0.3515), whereas no cases occurred in patients receiving concomitant steroids during tofacitinib therapy. Most HZ cases (14 of 15) occurred in patients receiving combination therapy with conventional DMARDs; however, this association was not statistically significant (p = 0.1145). Prior TNFI exposure and TB risk factors showed no statistically significant associations with HZ occurrence.

GI AEs

GI issues were reported in 13 patients (1.3%; 95% CI, 0.008-0.023). Analysis of potential risk factors revealed no statistically significant associations (Table 7).

Factor	GI ADR	p-value
Age >50	4	0.4881
Sex (male/female)	2/11	0.4694
Smoking	1	0.7763
Prior steroid use	3	0.6543
Concomitant steroid use	1	1.0
Tofacitinib with concurrent DMARDs	6	0.0787
Prior TNFI use	2	0.8824
Prior TB risk factors	0	1.0

TABLE 7: Factors associated with GI AEs (n = 13 events).
ADR, adverse drug reaction; AE, adverse event; DMARDs, disease-modifying antirheumatic drugs; TB, tuberculosis; TNFI, tumor necrosis factor inhibitor

GI AEs showed a female predominance, with 11 of 13 cases occurring in women, although this difference was not statistically significant (p = 0.4694). Only four of the 13 cases occurred in patients older than 50 years (p = 0.4881). Six of the 13 GI events occurred in patients receiving combination therapy with conventional DMARDs (p = 0.0787); however, this association was not statistically significant. Prior steroid use was present in three cases, concomitant steroid use in one case, and prior TNFI exposure in two cases. None of these factors showed a statistically significant association with GI AEs.

Malignancy

No malignancies were observed during the follow-up period in this cohort of 1,000 patients. Consequently, no statistical analyses of risk factors could be performed. The absence of malignancies in this cohort should be interpreted with caution, given the limited follow-up duration and sample size for detecting rare events such as cancer. Malignancy is typically a late-onset AE that may require longer observation periods to be fully characterized.

The p-values shown in Tables 3-7 were obtained using Fisher’s exact tests, which were selected because of the low number of AE cases. Accordingly, no corresponding t, χ², or F statistic is reported for these exact tests. Multivariable results are reported as aORs with 95% CIs from binomial logistic regression.

Discussion

This single-center, cross-sectional cohort study of 1,000 patients represents one of the largest real-world evaluations of tofacitinib safety in a region where TB is endemic. Our findings indicate that although tofacitinib maintains a safety profile generally consistent with the known mechanisms of JAK inhibitors, specific regional and patient-specific factors, notably a history of TB, smoking, and metabolic comorbidities, significantly modulate the risk of serious AEs. These results reinforce the need to move beyond generalized safety warnings toward a “layered” risk assessment strategy tailored to patients’ clinical histories and geographic contexts [13].

Infectious risks: TB and HZ

The most striking finding in this cohort was the identification of independent predictors of TB occurrence, particularly the markedly elevated risk associated with a history of TB (aOR, 38.2). This finding strongly

supports established literature identifying TB as a significant opportunistic infection risk associated with tofacitinib, especially in regions with a high TB prevalence [6,11]. Although TNFis are known to increase TB risk by up to 18-fold in endemic regions, our data quantify the heightened vulnerability of patients with a history of TB who initiate tofacitinib. The clinical implication is clear: in endemic regions such as India, rigorous pretreatment screening for latent TB and a detailed medical history are essential prerequisites for JAK inhibitor therapy.

Furthermore, the observation that HZ was a common complication aligns with extensive global evidence identifying HZ as a distinct class-related concern with JAK inhibitors [11,16]. Previous studies have consistently reported higher HZ incidence rates with tofacitinib than with bDMARDs, with an increased risk often noted in Asian populations [6,7,16]. Our findings corroborate these patterns, highlighting the continued importance of proactive HZ vaccination strategies to mitigate this infectious burden [17].

Cardiovascular and cerebrovascular safety

The cardiovascular safety of tofacitinib has been under intense scrutiny following the ORAL Surveillance data, which demonstrated higher rates of MACE among older, high-risk patients receiving tofacitinib than among those receiving TNFis [14,18]. In our cohort, smoking emerged as a potential risk factor for MACE. This finding is consistent with post hoc analyses of the ORAL Surveillance data, which identified long-term smoking and age of 65 years or older as primary drivers of excess cardiovascular risk [15,19,20].

Although stroke was uncommon in this cohort, with only three events documented (3/1,000; 0.3%), the small number of events limits the precision and reliability of analyses of potential risk factors. The available data do not support reliable multivariable modeling of factors associated with stroke. Therefore, the observed clinical characteristics should be considered descriptive rather than conclusive evidence of associations between cardiovascular comorbidities and stroke in patients receiving tofacitinib. These findings highlight the importance of careful cardiovascular risk assessment and appropriate management of comorbidities in clinical practice. Larger studies with adequate event numbers are needed to clarify the relationship between baseline cardiovascular risk factors and stroke among patients receiving tofacitinib [12,14].

Malignancy and clinical outcomes

No malignancies were recorded in the original study dataset during the observation period. However, approximately five malignancy cases, including ovarian and breast cancers, were identified after data collection and statistical analysis had been completed. These cases were not included in the primary analysis. Therefore, the absence of malignancies in the original dataset should not be interpreted as evidence that tofacitinib is not associated with malignancy risk.

Previous studies have reported varying findings regarding malignancy risk with tofacitinib. The ORAL Surveillance study identified an increased malignancy risk among older patients with cardiovascular risk factors, whereas global integrated safety analyses with follow-up extending up to 9.5 years generally reported stable malignancy rates during long-term exposure [2,11,16]. In the present study, the relatively short mean treatment exposure of 11.61 months limits the assessment of long-term malignancy outcomes.

Limitations

This study has several limitations that should be considered when interpreting the findings. The single-center observational design and absence of a comparator group limit the generalizability of the results and preclude direct comparisons of the safety of tofacitinib with that of alternative therapies. The findings describe AEs documented in routine clinical practice and do not establish causal relationships between tofacitinib exposure and the observed outcomes.

The mean treatment exposure was 11.61 months, limiting the assessment of long-latency outcomes, particularly malignancies and cardiovascular complications. The numbers of MACE ($n = 2$) and stroke events ($n = 3$) were very small. Consequently, meaningful statistical assessment of factors associated with these outcomes was limited, and multivariable estimates based on such sparse event counts may be unstable. The stroke findings are therefore presented descriptively and should not be interpreted as evidence of independent risk factors.

Comparisons between patients with shorter and longer treatment exposure may be affected by selection bias, survivorship bias, and differences in observation time. Patients who remain on treatment for longer periods may differ systematically from those with shorter exposure. Furthermore, the available duration-group comparisons do not adequately account for person-time at risk or the timing of individual AEs. Therefore, these comparisons cannot establish whether AEs occur earlier or whether their cumulative risk increases with prolonged treatment.

Potential confounding factors, including underlying disease activity, disease duration, tofacitinib dosage and dose modifications, previous immunosuppressive exposure, and baseline cardiovascular risk, were not

comprehensively characterized in the available dataset. Residual confounding may therefore have influenced the observed associations. In addition, although 162 patients discontinued treatment because of AEs, the available data did not permit sufficiently detailed characterization of the causes and severity of all discontinuations or their relationship to the predefined safety outcomes.

The study was conducted at a single center in one geographic region, and the findings may reflect local epidemiological patterns, particularly the regional burden of TB. The generalizability of these findings to populations in other geographic regions, especially those with a lower TB prevalence, requires further validation in multicenter studies.

Finally, findings regarding uncommon AEs should be interpreted cautiously because of the limited number of events and the potential for incomplete documentation in routine clinical records. Larger, prospective, multicenter studies with appropriate comparator groups, standardized AE ascertainment, detailed characterization of potential confounders, and longer follow-up are needed to confirm these findings and better evaluate the long-term safety of tofacitinib.

Recommendations for future research

To build on these findings, future research should prioritize prospective longitudinal studies with longer follow-up to better characterize late-onset events, such as malignancy. Large-scale, multicenter RWE studies are needed to confirm the factors contributing to cerebrovascular risk and to establish more precise risk-stratification models for Asian populations. Additionally, comparative studies investigating the effects of dose escalation or de-escalation on cumulative infectious and cardiovascular risk would provide valuable guidance for long-term maintenance therapy [7,17].

Conclusions

This single-center observational study describes AEs documented among 1,000 patients with inflammatory arthritides receiving tofacitinib in routine clinical practice. TB was documented in 2.1% of the cohort, highlighting the clinical importance of TB risk assessment and screening in endemic settings. However, the absence of a comparator group and person-time-adjusted incidence estimates precludes conclusions regarding the relative or attributable risk associated with tofacitinib. The small numbers of MACE and stroke events limit the reliability of the corresponding risk-factor analyses, while comparisons between treatment-duration groups cannot establish early-onset or cumulative AE patterns. The identified risk-factor associations should therefore be considered exploratory, and the findings should not be interpreted as definitive evidence of causality or comparative safety. Larger, multicenter studies with appropriate comparator groups, standardized outcome assessment, and longer follow-up are needed to better characterize the safety profile of tofacitinib, particularly with respect to uncommon cardiovascular events and long-term outcomes.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. ACE Independent Ethics Committee issued approval DA 011. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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