

Original Article

## Tuberculosis with tofacitinib: Analysis of adverse drug reaction reporting trends in the World Health Organisation global drug safety database

Sreya Mazumder<sup>1</sup>, Suparna Chatterjee<sup>1</sup>, Shreya Kotal<sup>1</sup>

<sup>1</sup>Department of Pharmacology, Institute of Postgraduate Medical Education and Research, Kolkata, West Bengal, India.

**\*Corresponding author:**

Suparna Chatterjee,  
Department of Pharmacology,  
Institute of Postgraduate  
Medical Education and  
Research, Kolkata, West Bengal,  
India.

drsuptchat@gmail.com

Received: 05 February 2025  
Accepted: 01 June 2025  
Epub Ahead of Print: 25 August 2025  
Published:

DOI  
10.25259/IJPP\_67\_2025

Quick Response Code:



### ABSTRACT

**Objectives:** Tofacitinib, a first-generation Janus Kinase (JAK) inhibitor, was approved in 2012 by the United States Food and Drug Administration for various arthritic disorders. However, it is used for several other indications as well. Tuberculosis (TB) is a listed serious adverse drug reaction of tofacitinib. This study evaluated the global reporting pattern of TB with tofacitinib use in the World Health Organisation global drug safety database (VigiBase).

**Materials and Methods:** We performed a Vigilyze search on 21 January 2025 using the following search criteria: Drug-tofacitinib (active ingredient) and Reaction-TB (Preferred Term). The following outcome data were analysed-total number of reports, reporting countries, dechallenge and rechallenge information, seriousness and fatalities. Information component (IC value) and lower bound (IC<sub>025</sub>) were noted for signal detection.

**Results:** A total of 234 individual case safety reports with TB as an adverse reaction were noted worldwide, and only four were from India. About 68% were healthcare professional reporters. About 45.3% of the patients were in the 45–64 years age-group with female preponderance (67.9%). There were 228 serious cases with four fatalities. The most common co-administered drug was methotrexate (11.5%). The IC value was 2.3, and IC<sub>025</sub> was 2.2, indicating that it could be considered statistically as a 'signal'.

**Conclusion:** This study highlights the importance of screening and close monitoring of patients on tofacitinib to ensure the early detection of TB. It also re-emphasises the need for routine screening for TB before initiating therapy, especially in countries like India, where the prevalence of TB is high.

**Keywords:** Adverse drug reactions, Janus Kinase inhibitor(s), Safety, Tofacitinib, Tuberculosis

### INTRODUCTION

Janus Kinase (JAK) inhibitors have revolutionised the landscape for the treatment of autoimmune disorders over the past decade. While ruxolitinib was the first JAK inhibitor to receive approval in November 2011 for myelofibrosis, polycythemia vera and steroid-resistant Graft-versus-Host Disease, a multitude of biologic drugs with a similar mechanism of action have since been approved and marketed for various arthritic disorders.<sup>[1]</sup>

Tofacitinib, approved by the United States Food and Drug Administration (US-FDA) in 2012 and the Central Drugs Standard Control Organisation (CDSCO) in 2016, is a first-generation JAK inhibitor marketed across the globe for moderate to severe cases of rheumatoid arthritis, psoriatic arthritis and ulcerative colitis.<sup>[2]</sup> Tofacitinib is a small-molecule oral JAK inhibitor, indicated in suboptimal responders or those intolerant to other biologics.<sup>[2]</sup> It has various off-label uses as well.

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-Share Alike 4.0 License, which allows others to remix, transform, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.  
©2025 Published by Scientific Scholar on behalf of Indian Journal of Physiology and Pharmacology

A preferential inhibitor of JAK3 and JAK1, Tofacitinib, downregulates several cytokines to modulate the immune responses in autoimmune conditions. Real-world data have proven its efficacy in patients who were previously treated with other biologics.

With the increasing use of tofacitinib, several cases of bacterial, invasive fungal and viral have been reported. Amongst these, tuberculosis (TB) was reported as a serious adverse drug reaction (ADR) of tofacitinib.<sup>[3]</sup> US-FDA recommended testing for latent TB before therapy initiation.

There is a paucity of studies analysing the reporting trends of TB with tofacitinib use, hence this study was undertaken.

### Objectives

The objectives of this observational study were to evaluate the drug safety reports of TB with tofacitinib in the World Health Organisation (WHO) global spontaneous reporting database (VigiBase) and to estimate the disproportionality metrics of the 'Individual Case Safety Reports' (ICSR).

## MATERIALS AND METHODS

### Data source and search criteria

VigiBase<sup>®</sup> with is the WHO global drug safety database of reported potential adverse events of medicinal products, developed and maintained by the Uppsala monitoring centre (UMC), which contains ICSRs from more than 180 countries to evaluate the global reporting pattern of TB with tofacitinib.<sup>[4]</sup>

On 21 January 2025, a Vigilyze search was conducted using.

The following search criteria: Drug-tofacitinib (active ingredient) and Reaction-Tuberculosis, Medical Dictionary for Drug Regulatory Activities (MedDRA) preferred term, to analyse all the associated ICSR in the database for the time period 1<sup>st</sup> January 2014 to 20<sup>th</sup> January 2025. The filters selected for the dataset included geographical scope-global, therapeutic scope-drugs, duplicate scope-de-duplicated and reporting date to be the VigiBase Initial Date, with the MedDRA language set to be English.

Each ICSR had anonymous data about the country of origin, reporting date and types of reporter. Patient data included age and gender, while drug information included the active ingredient, indication for therapy, start and end dates of therapy, dosage regimen and route of administration. The ICSR also included information about the reactions or events-reported terms, MedDRA classification terms, date of onset, end date, seriousness of the reaction and final outcome.

### Disproportionality analysis

The Vigilyze data mining disproportionality analysis tool helped analyse the safety profile of Tofacitinib.

For signal detection, the 'proportional reporting ratio' (PRR),<sup>[5]</sup> 'reporting odds ratio' (ROR) and its 95% confidence interval (CI) were noted.<sup>[5]</sup>

In addition, as per WHO UMC criteria the 'information component' (IC), a Bayesian indicator for disproportionate reporting compares observed and expected values to find drug-adverse effect combinations which have been reported more often than expected.<sup>[6]</sup> We also reported the IC<sub>025</sub>, which is the lower end of the 95% credibility interval for the IC. A positive IC<sub>025</sub> value (>0) is the threshold used in statistical signal detection in VigiBase<sup>®</sup>.<sup>[7]</sup>

According to the WHO caveat, these are reporting rates and do not necessarily imply causation. Since the information comes from varied sources, the probability of the suspected adverse effect being drug-related may not be uniform in all cases. The information does not represent the opinion of the UMC or the WHO.<sup>[8]</sup>

## RESULTS

A total of 234 ICSR with TB (both primary and reactivated) as adverse reactions were noted worldwide, and only four were from India. Table 1 depicts the patients profile. Almost 78% of these reports were contributed by the United States of America, while only 7% of the reports were from Asian nations. Table 1 depicts the patients profile.

About 45.3% of the patients belonged to the age group of 45–64 years, 22.2% in the 65–74 years age group. Female preponderance (67.9%) was noted. These reports originated from physicians, pharmacists, other health professionals, as well as consumers of the medicine. About 68% of the reporters were healthcare professionals.

Almost half of the reported ICSRs date back to 2018 (17.9%) and 2019 (27.4%), with only 17 reports each in 2023 and 2024. Since the turn of the decade, TB reports with tofacitinib has declined, probably due to an increased emphasis on screening for latent infections before therapy and monitoring for opportunistic infections in those receiving therapy.

Rheumatoid arthritis was the most commonly reported indication for tofacitinib use. Table 2 depicts the drug details. However, the distinct lack of completeness in ADR reporting makes it difficult to analyse whether off-label uses outweigh the labelled use in most countries.

The most common co-administered drug was methotrexate (11.5%), followed by prednisolone (4.7%). Etanercept and adalimumab were identified as suspect or interacting active ingredients in six and five cases, respectively. The median

daily dose of tofacitinib was 11 mg, while the median time to onset was 30 weeks (although the range varied from as low as 15 days to as high as 8 years).

There were 228 serious cases with four fatalities. In addition, two of these experienced life-threatening situation, and 22 required initial or prolonged hospitalisation. Globally, cases have been reported from 19 different countries. Table 3 shows the global viewpoints. Tofacitinib was the sole suspect drug in a 92.7%, ICSRs, (217 cases). The drug was withdrawn in 95 patients, in 63 cases, there was no dosage change, 11 cases were dechallenge positive.

From an Indian perspective, only four cases have been reported in the past 10 years, the first report dates back to June 2021. This involved a 79-year-old male who took tofacitinib for a period of 8 years from March 2013 to February 2021. The dosage regimen, the indication, as well as the outcome remain unknown, but the drug was withdrawn. As per the ICSR, this was a case of TB disease recurrence.

The second report in November 2023 is that of a 65-year-old female, who was prescribed a 5mg daily dose of tofacitinib for rheumatoid arthritis. The drug was withdrawn. The median time to onset was unavailable, but the patient was recovering at the time of initial reporting to the VigiBase.

The two latest reports in June 2024 were from the younger population, both 35-year-old males who were prescribed tofacitinib for seronegative rheumatoid arthritis. Dechallenge information was unavailable, but both patients were recovering at the time of reporting.

Worldwide, the IC value was 2.3 and  $IC_{025}$  was 2.2, indicating that it could be considered statistically as a 'signal'.

The lower limit of the credibility interval for both PRR and ROR was 4.6. Table 4 shows the results of disproportionality analysis.

Figure 1 depicts the yearly trend of the IC value over the search duration.

The yearly trend of the IC value for the search duration suggests that the criterion for signal detection was not

fulfilled in the initial years of 2014, 2015 and 2016. However, with the rapid rise of Tofacitinib usage, the IC value has ranged between 2.3 and 2.5 in the past 6 years.

## DISCUSSION

As per WHO UMC criteria, a safety "signal" was generated between TB and tofacitinib.<sup>[9]</sup> A devastating disease in all aspects, the burden of TB depends not only on the active cases but also on those harbouring latent infection.

A higher risk of opportunistic infections has been traditionally noted in patients with autoimmune disorders, mostly due to their therapies.<sup>[10]</sup> Studies have shown that in the case of anti-tumour necrosis factor therapies, organisms causing granulomatous inflammation are mainly implicated.<sup>[11]</sup> A similar trend has been observed with tofacitinib.

A 2012 study conducted at USA concluded that tofacitinib administration led to increased bacterial replication in a mouse model of chronic paucibacillary TB, suggesting the drug had the propensity to reactivate latent TB infections in humans.<sup>[12]</sup>

According to a case report published in 2023 a 54-year-old rheumatoid arthritis patient from Uttar Pradesh, India, developed reactivation of latent TB following 6 weeks of tofacitinib therapy.<sup>[3]</sup>

A synthetic disease-modifying agent, tofacitinib, is a specific and selective inhibitor of pro-inflammatory receptor signalling mechanisms.<sup>[13]</sup> Certain cytokines are implicated in the pathogenesis of varied autoimmune diseases, which utilise the JAK/STAT pathway for their effects, making them a suitable target for JAK inhibitors.<sup>[14]</sup> Critical for immunoregulation, genetic polymorphisms of type I cytokine receptors confer susceptibility towards psoriasis, rheumatoid arthritis, ankylosing spondylitis and inflammatory bowel disease.<sup>[15]</sup>

Tofacitinib mechanistically inhibits the activity of JAK1 and JAK3 and, to a small extent, JAK2 and Tyrosine kinase 2

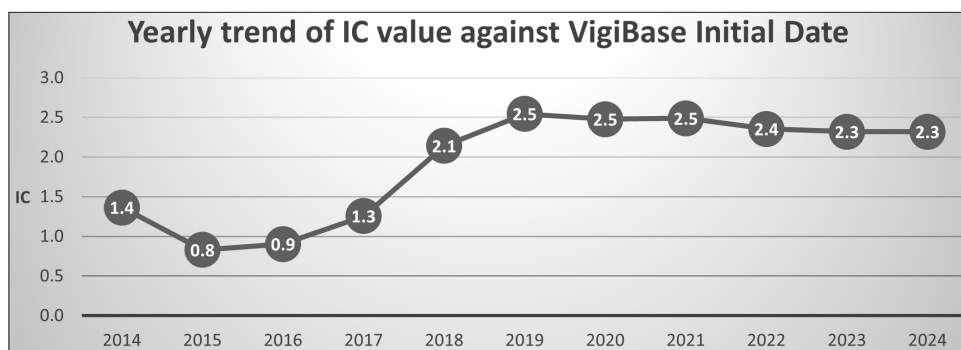


Figure 1: Yearly trend of the information component value. Measure of X axis: Years.

(TYK2). As a result,  $\gamma$ c cytokines such as interleukin (IL)-4, IL-7, IL-2, IL-9, IL-15 and IL-21, which are mediated through JAK3, are blocked by tofacitinib.<sup>[13]</sup> In addition, inhibition of JAK1 blocks gp130 family cytokines such as IL-11 and IL-6,

as well as type II cytokine receptor family, which includes IL-10, interferon (IFN)- $\alpha/\beta$  and IFN- $\gamma$ .

Inhibition of JAK2 results in blockade of  $\beta$ c family of cytokines such as granulocyte-macrophage colony-stimulating factor, erythropoietin, IFN- $\gamma$ , IL-3 and IL-5. It also interferes with pathogenic Th17 cells generation that is dependent on IL-23, and Th1 cells differentiation, which produce IFN- $\gamma$ . Inhibition of intracellular signalling of IL-12, IFN- $\gamma$  and similar other cytokines, which play a crucial role in the development of pathogen-specific memory T cells, contributes to the augmented risk of TB and other invasive infections in patients receiving tofacitinib.<sup>[16]</sup>

Genetic predisposition to serious TB infections has been previously documented in individuals with Mendelian susceptibility to mycobacterial diseases due to germline mutations in seven autosomal and two X-linked genes, including those encoding IL-12, IFN- $\gamma$  and STAT1 pathways.<sup>[17]</sup> Tofacitinib's suppression of both innate and active immune response, hence, is responsible for the development of TB-a fact which could have disastrous consequences on the public health of countries like India, which have a very high prevalence of TB.<sup>[18]</sup>

A three-pronged approach is necessary to tackle this growing concern. The patients must be made aware of the possible infectious complications of tofacitinib therapy and the signs and symptoms that they should look out for, to ensure early reporting of any such events. More importantly, the onus lies on the treating physician to screen for latent TB before tofacitinib administration and stringent supervision of the patient's clinical status post-therapy initiation. Although mandated by the US-FDA, screening for latent TB is not a routine practice in India, which, along with inadequate follow-up, plays a significant role in under-reporting of TB as an adverse reaction.

Finally, regulatory authorities must ensure that the marketing authorisation holders mention TB as an opportunistic infection on their packaging label. Strengthening the post-marketing surveillance system is the need of the hour in our country. Risk benefit analysis and risk minimisation strategies must be adopted.

This was the first study to systematically evaluate worldwide reporting trends of TB with tofacitinib. However, reporting patterns from various countries were not uniform, and the quality of reports were highly variable. In most ICSRs, distinctions were

**Table 1:** A qualitative analysis of ICSRs-patient profile.

	n (%)	Data availability n (%)
Sex		221 (94.4)
Male	62 (26.5)	
Female	159 (67.9)	
Age (years)		207 (88.4)
18–44	29 (12.4)	
45–64	106 (45.3)	
65–74	52 (22.2)	
$\geq 75$	20 (8.5)	
Region reporting		234 (100)
Americas	205 (87.6)	
Europe	11 (4.7)	
Asia	17 (7.3)	
Oceania	0	
Africa	1 (0.4)	

ICSRs: Individual case safety reports

**Table 2:** A qualitative analysis of ICSRs-drug details.

	n (%)	Data availability n (%)
Indication		101 (43.1)
Rheumatoid arthritis	86 (36.8)	
Ulcerative colitis	6 (2.6)	
Psoriatic arthropathy	7 (3.0)	
Alopecia	2 (0.8)	
Daily dosage (mg)		216 (92.3)
5	86 (39.8)	
11	130 (60.1)	
Co-administered drugs		207 (88.46)
Methotrexate	27 (11.5)	
Prednisone	11 (4.7)	
Folic acid	7 (3.0)	
Etanercept	6 (2.6)	
Hydroxychloroquine	6 (2.6)	

ICSRs: Individual case safety reports

**Table 3:** A quantitative analysis of ICSRs from a global viewpoint.

N <sub>country</sub>	N <sub>singlesusp</sub>	N <sub>dechall</sub>	N <sub>rechall</sub>	N <sub>serious</sub>	N <sub>fatal</sub>
19	217	11	0	228	4

N<sub>country</sub>: No. of countries reporting, N<sub>singlesusp</sub>: No. of individual case safety reports (ICSRs) with tofacitinib being the single suspect drug, N<sub>dechall</sub>: No. of ICSRs where tofacitinib was withdrawn (dechallenged) after onset of tuberculosis, N<sub>rechall</sub>: No. of ICSRs where a rechallenge was performed with tofacitinib, N<sub>serious</sub>: No. of ICSRs in which the adverse event was classified as serious, N<sub>fatal</sub>: No. of ICSRs in which the outcome of the adverse event was fatal

**Table 4:** Filter-based disproportionality analysis of tuberculosis with active ingredient tofacitinib.

$N_{\text{observed}}$	$N_{\text{expected}}$	$N_{\text{drug}}$	$N_{\text{reaction}}$	$IC_{0.25}$	IC	$PRR_{0.25}$	PRR	$ROR_{0.25}$	ROR
234	46	139682	10364	2.2	2.3	4.6	5.2	4.6	5.2

$N_{\text{observed}}$ : No. of actual ICSRs in which a specific drug-adverse event combination is reported,  $N_{\text{expected}}$ : No. of expected ICSRs for a specific drug-adverse event combination assuming there is no association between drug and event,  $N_{\text{drug}}$ : No. of ICSRs in which tofacitinib is mentioned as suspected (either alone or with other drugs), regardless of adverse event reported,  $N_{\text{reaction}}$ : No. of ICSRs in which tuberculosis has been reported as an adverse event, irrespective of drug involved, IC: Information component,  $IC_{0.25}$ : Lower limit of a 95% credibility interval for the IC, PRR: Proportional reporting ratio,  $PRR_{0.25}$ : Lower limit of a 95% credibility interval for the PRR, ROR: Reporting odds ratio,  $ROR_{0.25}$ : Lower limit of a 95% credibility interval for the ROR

not made between pulmonary and extra-pulmonary TB. The fact that a statistical signal does not necessarily implicate causation is the other limitation of the study.

## CONCLUSION

This study highlights the importance of screening and close monitoring of patients on tofacitinib to ensure the early detection of TB. It also re-emphasises the need for routine screening for TB before initiating therapy especially in countries like India where the prevalence of TB is high.

Health care providers should be encouraged to report such serious adverse events. Additional evidence is necessary to compare the risk of tofacitinib with that of other biologics and immunosuppressive agents in development of opportunistic infections in different population groups.

**Acknowledgement:** National Coordination Centre for Pharmacovigilance Programme of India, Indian Pharmacopoeia Commission.

**Ethical approval:** The research/study was approved by the Institutional Review Board at Jawaharlal Nehru Medical College and Hospital, Aligarh Muslim University, Aligarh (UP), number IECJNMC/536, dated 02nd November 2021.

**Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent.

**Financial support and sponsorship:** Nil.

**Conflicts of interest:** There are no conflicts of interest.

**Use of artificial intelligence (AI)-assisted technology for manuscript preparation:** The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

## REFERENCES

- Rothlin CV, Gutkind JS. Immunosuppressants, immunomodulation, and tolerance. In: Brunton LL, Knollmann BC, editors. Goodman and Gilman's: The pharmacological basis of therapeutics. 14<sup>th</sup> ed. New York, NY: McGraw-Hill Education; 2023. Available from: <https://www.accesspharmacy.mhmedical.com/content.aspx?aid=1193234400> [Last accessed on 2025 Jan 31].
2018. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/203214s018lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203214s018lbl.pdf) [Last accessed on 2024 Jan 15].
- Johri N, Varshney S, Gandha S, Maurya A, Mittal P. Reactivation of latent tuberculosis infection following initiation of tofacitinib therapy for rheumatoid arthritis: A case report. *J Orthop Rep* 2023;2:100196.
- Lindquist M. VigiBase, the WHO global ICSR database system: Basic facts. *Drug Inform J* 2008;42:409-19.
- Rothman KJ, Lanes S, Sacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. *Pharmacoepidemiol Drug Saf* 2004;13:519-23.
- Chrétien B, Jourdan JP, Davis A, Fedrizzi S, Bureau R, Sassier M, *et al.* Disproportionality analysis in VigiBase as a drug repositioning method for the discovery of potentially useful drugs in Alzheimer's disease. *Br J Clin Pharmacol* 2021;87:2830-7.
- The UMC measures of disproportionate reporting; 2016. Available from: [https://who/umc.org/media/164041/measures-of-disproportionate-reporting\\_2016.pdf](https://who/umc.org/media/164041/measures-of-disproportionate-reporting_2016.pdf) [Last accessed on 2025 Jan 18].
- UMC caveat. Available from: [https://who/umc.org/media/yzpznmdv/umc\\_caveat.pdf](https://who/umc.org/media/yzpznmdv/umc_caveat.pdf) [Last accessed on 2025 Jan 31].
- What is a signal? Available from: <https://who/umc.org/signal/work/what/is/a/signal> [Last accessed on 2024 Jan 17].
- Zhang Z, Deng W, Wu Q, Sun L. Tuberculosis, hepatitis B and herpes zoster in tofacitinib-treated patients with rheumatoid arthritis. *Immunotherapy* 2019;11:321-33.
- Wallis RS, Broder MS, Wong JY, Hanson ME, Beenhouwer DO. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. *Clin Infect Dis* 2004;38:1261-5.
- Maiga M, Lun S, Guo H, Winglee K, Ammerman NC, Bishai WR. Risk of tuberculosis reactivation with tofacitinib (CP-690550). *J Infect Dis* 2012;205:1705-8.
- Kucharz EJ, Stajszyk M, Kotulska-Kucharz A, Batko B, Brzosko M, Jeka S, *et al.* Tofacitinib in the treatment of patients with rheumatoid arthritis: Position statement of experts of the polish society for rheumatology. *Reumatologia* 2018;56:203-11.
- Banerjee S, Biehl A, Gadina M, Hasni S, Schwartz DM. JAK-STAT signaling as a target for inflammatory and autoimmune diseases: Current and future prospects. *Drugs* 2017;77:521-46.
- O'Shea JJ, Kontzias A, Yamaoka K, Tanaka Y, Laurence A. Janus kinase inhibitors in autoimmune diseases. *Ann Rheum Dis* 2013;72 Suppl 2:ii11-5.
- Taxonera C, Olivares D, Alba C. Real-world effectiveness and safety of tofacitinib in patients with ulcerative colitis: Systematic review with meta-analysis. *Inflamm Bowel Dis* 2022;28:32-40.
- Abel L, El-Baghdadi J, Bousfiha AA, Casanova JL, Schurr E. Human genetics of tuberculosis: A long and winding road. *Philos Trans R Soc B Biol Sci* 2014;369:20130428.

18. Global tuberculosis report 2023. World health organization. Available from: <https://iris.who.int/bitstream/handle/10665/373828/9789240083851/eng.pdf?sequence=1> [Last accessed on 2024 Jan 15].

**How to cite this article:** Mazumder S, Chatterjee S, Kotal S. Tuberculosis with tofacitinib: Analysis of adverse drug reaction reporting trends in the World Health Organisation global drug safety database. *Indian J Physiol Pharmacol.* doi: 10.25259/IJPP\_67\_2025