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The impact of tocilizumab on hepatic enzyme levels in rheumatoid arthritis patients: a narrative review

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Abstract
Rheumatoid arthritis (RA) is an autoimmune disease affecting 0.5-1% of the global population. Tocilizumab (TCZ), a monoclonal antibody, offers a promising treatment option for RA patients unresponsive to disease-modifying antirheumatic drugs (DMARDs). While multiple studies have demonstrated the efficacy and safety of TCZ, some have reported associations between TCZ treatment and elevations in hepatic transaminase levels. This review explores the relationship between TCZ therapy and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in RA patients previously treated with DMARDs. For this narrative review, a comprehensive search was conducted in two major databases, PubMed and Google Scholar, for articles published in English between 2013 and 2023. The search utilized key terms such as "tocilizumab", "hepatic transaminases", "ALT", "AST", "rheumatoid arthritis patients", and "DMARDs". From 402 initially identified articles, 10 studies published between 2013 and 2023 were selected for review, including observational studies, narrative reviews, and systematic reviews. These studies examined the impact of TCZ on liver enzyme levels in RA patients receiving DMARDs, with varying sample sizes. TCZ demonstrates clinical efficacy in patients with RA unresponsive to previous treatments. Although mild and transient elevations in liver enzymes, particularly ALT, have been observed, serious hepatic adverse events remain uncommon. Although current evidence indicates that TCZ shows promise as a treatment for RA, the variability among studies and the quality of the included evidence call for a careful interpretation of the findings. Continued liver function monitoring and individualized dosing are recommended to support its safe use.

Introduction

Rheumatoid arthritis (RA) is a complex autoimmune disease characterized by chronic inflammation and gradual joint damage and destruction.[1] It leads to ongoing pain, fatigue, and reduced mobility, and is often accompanied by fever, malaise, weight loss, and a general sense of discomfort. RA affects approximately 0.5-1% of the global population, with a significantly higher prevalence among females than males.[2] It has a multifactorial etiology resulting from the complex interplay between genetic and environmental factors. Tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6 are among the pro-inflammatory cytokine profiles that define immunological dysregulation and are considered important in the pathophysiology.[3,4]

The treatment of RA has undergone significant advancements over the years, with disease-modifying antirheumatic drugs (DMARDs) playing an increasingly central role in the management. Methotrexate (MTX), a folate antagonist, has long been the first-line DMARD due to its ability to inhibit dihydrofolate reductase, reducing immune cell proliferation and inflammation. Its effectiveness, safety profile, and affordability have made it the recommended initial treatment for many RA patients.[5,6] However, despite its benefits, a large percentage of patients require additional therapies due to inadequate responses or adverse effects, as 50% to 70% of patients fail to achieve sufficient disease control with MTX alone.[7]

Tocilizumab (TCZ), a humanized monoclonal antibody, offers a novel approach to treating RA by targeting the IL-6 pathway.[8] IL-6 is a cytokine implicated in many processes, including immune regulation, hematopoiesis, inflammation, and oncogenesis. It sends signals *via* two pathways: membrane-bound IL-6 receptors (mIL-6R) and soluble IL-6 receptors (sIL-6R). TCZ blocks IL-6 signaling through binding to both mIL-6R and sIL-6R, preventing IL-6 activity without promoting other IL-6 family cytokines or extending IL-6 half-life.[1] This mechanism also influences autoimmunity *via* Th17 cell function.[1] TCZ is therefore approved for patients with RA who have a history of inadequate response to one or more anti-TNF therapies. However, as the use of TCZ and other biologics becomes more widespread, there is a pressing need to assess their long-term safety and potential risks.

While several clinical trials have demonstrated the safety of TCZ,[9-12] more recent studies have linked its use to increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, raising concerns about potential hepatotoxicity.[13,14] Such enzyme elevations are not uncommon among RA patients treated with DMARDs and may signal liver injury requiring treatment modification. These abnormalities can interrupt therapy, delay disease control, and complicate overall patient management.

According to guidelines from the U.S. Food and Drug Administration and the European Medicines Agency, liver enzyme elevations are categorized by severity to guide clinical decisions. Grade 1 (mild) liver injury involves ALT, ALP, or gamma-glutamyl transferase levels above the upper limit of normal (ULN) but less than three times the ULN and typically requires close monitoring. Grade 2 (moderate) elevations exceed three times the ULN and may call for dose modification or further evaluation, while Grades 3 and 4 involve more severe enzyme increases and may necessitate drug discontinuation.[15]

However, the clinical significance of transaminase elevations observed with TCZ remains uncertain, especially in patients with prior exposure to DMARDs. This review aims to provide an updated assessment of TCZ's impact on liver enzyme levels in RA patients with a history of DMARD use, addressing a clinically important but understudied aspect of biologic therapy safety.

Materials and Methods

Study design

This narrative review aimed to evaluate the effects of TCZ on hepatic transaminase levels, specifically, ALT and AST, in patients with RA who had prior exposure to DMARDs.

Literature search

A comprehensive search was conducted in PubMed and Google Scholar using the following terms: "tocilizumab," "hepatic transaminases," "ALT," "AST," "rheumatoid arthritis," and "DMARD therapy." The initial search done in December 2025 yielded 402 records. After removing 277 duplicates, 125 records remained. Forty-nine were excluded due to language restrictions, and six were book publications, resulting in 73 articles for title screening. Of these, 40 were excluded at the abstract level. Full texts of the remaining 33 articles were assessed, with 23 excluded for not meeting the inclusion criteria. Ultimately, 10 studies were included in the final review.

Study selection

Studies focusing on patients over 18 years old with RA previously treated with DMARDs and that assessed the efficacy of TCZ and the comparator treatments were included. We included observational prospective, retrospective studies, narrative reviews, systematic reviews, and randomized controlled trials (RCTs). Case reports, animal studies, and studies not reporting relevant liver enzyme outcomes were excluded. The review focused on literature published in English between 2013 and 2023 to reflect a decade of clinical experience with TCZ and its hepatic effects. A flow diagram was designed to illustrate the study selection process (Figure 1).

Data extraction

The initial literature search and screening were independently performed by two reviewers (BB, RA). They subsequently assessed the full-text articles for eligibility and extracted key data, including publication year, sample size, and information on control groups. Primary outcomes of interest included AST and ALT levels, disease activity score (DAS28), and serious adverse events (SAEs). Discrepancies in study selection or data extraction were resolved through discussion, with a third reviewer (EK) consulted when needed.

Quality of evidence and bias assessment

To assess methodological quality and risk of bias, the Newcastle-Ottawa Scale (NOS) was used for observational, prospective, and retrospective studies.[16] Systematic reviews were evaluated using the AMSTAR tool, and RCTs were assessed using the Cochrane Risk of Bias Tool (RoB 2.0).[17,18] The NOS focused on domains such as selection, comparability, and outcome assessment, while AMSTAR evaluated methodological rigor in review design. For narrative reviews, which lack a standardized risk of bias tool, quality was assessed using the validated Scale for the Assessment of Narrative Review Articles.[19]

Results

This review included 10 studies conducted between 2013 and 2023, encompassing various study designs such as prospective observational studies, RCTs, narrative, and systematic reviews. The summary of findings is presented in Table 1.

Most studies showed elevated liver enzymes, especially ALT, in TCZ-treated patients. In a prospective observational study by Brazdilova *et al*.,[20] a higher incidence of ALT grade 1 injury was observed in patients treated with TCZ monotherapy, specifically 27.5% compared to 13.6% receiving other biologic therapies. Similarly, Genovese *et al*. reported ALT elevations in 70.6% of patients over five years, although serious hepatic adverse events were low.[3] Furthermore, a systematic analysis by Saki *et al*. found that patients treated with TCZ had higher rates of abnormal liver function tests (LFTs), such as elevated ALT and AST, than comparison groups.[4] As a result, these tests may be linked to hepatic events.

Mild and transitory nature of elevations

The majority of studies included in this review suggest that the liver enzyme increases linked to TCZ are usually mild and temporary. For example, Kaneko *et al*. pointed out that increases in ALT and

AST appeared to be reversible, either through dose modifications or termination of TCZ.[21] The retrospective study conducted by Inanc *et al*. reported a moderate increase in ALT in the third month of treatment, which generally tended to normalize over time.[22] Similarly, Curtis *et al*. also noted that ALT/AST elevations were common but typically not serious and alterable with dose adjustments or discontinuation of TCZ.[23] This study reported no new significant safety concerns regarding liver toxicity in real-world settings. Additionally, Millan *et al.* observed that abnormalities in liver enzymes among patients on TCZ were common, often minor, reversible, and less likely to lead to acute liver injury.[1]

Serious hepatic events and clinical significance

While increased liver enzymes were a common finding in many studies, SAEs such as severe hepatotoxicity or liver failure were rare. For instance, in Genovese *et al*.,[4] despite 70.6% of patients experiencing ALT elevations, the incidence of SAEs was low. Likewise, Brazdilova *et al.* observed that while ALT injury was more frequent in TCZ-treated patients, it generally did not lead to severe clinical outcomes.[20] In a review by Zhao *et al*.,[24] where novel biologic drugs, including TCZ, were described, minor increases in ALT and AST were frequently associated with IL-6 inhibitors and Janus kinase (JAK) inhibitors, which were generally non-progressive and did not result in serious liver toxicity.

Quality of the evidence

The quality of the studies included in this review was heterogeneous, reflecting the varied methodological designs across observational studies, narrative and systematic reviews, a non-randomized clinical trial, and one RCT. Risk of bias and quality were assessed using study-design-appropriate tools, focusing on criteria such as selection methods, comparability of groups, outcome assessment, and analytical transparency. Observational studies generally demonstrated acceptable quality, with two rated as low risk of bias and others showing moderate to moderate-to-high risk due to limitations in selection. The non-randomized clinical trial showed moderate quality, with reasonable methodological clarity but lacking randomization. Systematic reviews varied, with one meeting most AMSTAR 2 criteria and rated as moderate quality, while the other had notable methodological weaknesses and was rated low. The RCT had strengths in outcome measurement and study design, but overall was judged high risk due to its post hoc, open-label nature and lack of randomization. Narrative reviews contributed contextual understanding but were constrained by limited methodological rigor. Collectively, these findings call for cautious interpretation and emphasize the need for more rigorous and standardized research on the hepatic safety of TCZ. *Supplementary Material (Supplementary Tables 1-6)* provides an overview of the risk of bias and quality evaluation results.

Discussion

This review provides a comprehensive synthesis of the hepatic safety profile of TCZ in patients with RA. Mild to moderate elevations in liver enzymes, particularly ALT and AST, are consistently reported across clinical trials and observational cohorts. However, as seen in studies such as those by Kaneko *et al*.[21] and Curtis *et al*.,[23] these abnormalities are usually transient, reversible, and rarely lead to treatment discontinuation or serious hepatic injury. Dose adjustments or temporary discontinuation often suffice to restore normal liver enzyme levels.

While the overall hepatic safety profile appears manageable, studies such as Saki *et al*. reported a relatively higher frequency of abnormal LFTs in TCZ-treated patients versus comparator groups.[4] These discrepancies may reflect differences in dosing, monitoring frequency, or underlying patient comorbidities.

A clear dose-response trend emerged from studies such as Millán *et al*.[1], where transaminase elevations were more common with the 8 mg/kg TCZ dose than with 4 mg/kg. This is consistent with

findings from Saki *et al*.[4], which demonstrated that while the 8 mg/kg dose achieved greater ACR response rates, it was also associated with more frequent hepatic enzyme abnormalities.

Combination therapy also plays a role. Both Millán *et al*. and Bykerk *et al*. found that liver enzyme elevations occurred more often in patients on TCZ plus MTX than in those receiving TCZ monotherapy.[1,25] However, in Bykerk *et al*.,[25] the overall safety profile remained comparable between groups, suggesting the added hepatic burden may be clinically modest in most cases. In contrast, Brazdilova *et al*. reported more frequent ALT elevations in the monotherapy group, underlining the influence of study design and patient selection.[20]

Baseline liver function status varied significantly across the included studies, limiting cross-study comparisons. For example, Brazdilova *et al*. required normal LFTs prior to treatment and excluded patients with chronic hepatic conditions.[20] In contrast, Garcia *et al*. included a more representative clinical population, with comorbidities and no requirement for anti-TNF washout, although specific baseline LFT values were not reported.[26] Genovese *et al*. explicitly stated that over 90% of patients had ALT/AST values within the normal range before TCZ initiation, yet a substantial proportion experienced elevations above the ULN during follow-up.[3] Other studies, including Bykerk *et al*.[25] and Inac *et al*.,[22] did not report detailed baseline hepatic parameters. The lack of standardized reporting underscores the need for future studies to clearly define and stratify participants by hepatic risk at baseline.

Direct head-to-head comparisons of hepatic safety between TCZ and other biologics remain limited. However, available evidence suggests that while TCZ may lead to more frequent mild transaminase elevations compared to placebo or csDMARDs, serious hepatic events are rare and not consistently more common than with TNF inhibitors (TNFis) or JAK inhibitors. A retrospective study by Backhaus *et al*. found that TCZ led to higher remission rates than TNFis with a comparable safety profile.[27] A network meta-analysis by Best *et al.* concluded that TCZ had the highest likelihood of achieving DAS28 remission, though this efficacy must be weighed against liver enzyme trends.[28] Zhao *et al*. also reported more frequent mild hepatic abnormalities with TCZ, yet these were rarely clinically significant.[24] More robust comparative trials are needed to assess the long-term hepatic safety of TCZ relative to JAK inhibitors, especially given emerging concerns around JAKi-related hepatic and cardiovascular risks.

Importantly, many RA patients receive multiple hepatotoxic agents, particularly MTX and corticosteroids, complicating causal attribution. While Genovese *et al.* adjusted for background DMARD use and found comparable enzyme elevations across groups, most studies did not control for such confounders.[3] Some failed to report whether MTX washout occurred. As such, attributing liver enzyme abnormalities solely to TCZ oversimplifies a multifactorial clinical scenario. Results from this analysis support the current liver enzyme monitoring guidelines, which recommend dose reduction of DMARDs followed by dose reduction or interruption of TCZ, with permanent discontinuation of TCZ in patients with elevations >5× ULN or persistent measurements ≥3× ULN.[3]

One hypothesized mechanism behind TCZ-related hepatic enzyme elevations involves IL-6 receptor blockade. Given IL-6's role in hepatocyte regeneration and immune signaling, its inhibition may transiently affect liver metabolism. However, current evidence is limited, and further mechanistic studies are warranted to clarify this relationship.

Limitations and future directions

This review is subject to several limitations. First, the literature search excluded non-English publications and focused on the past decade, possibly omitting relevant data. Second, included studies varied in design, duration, comparator agents, and monitoring intensity, reducing generalizability. The absence of standardized definitions for hepatic adverse events, along with sparse reporting on confounders like MTX dose, limits pooled interpretation. Some studies were industry-sponsored, introducing potential bias.

Future research should focus on prospective, long-term studies evaluating TCZ in diverse RA populations, particularly those with pre-existing liver dysfunction. Trials should incorporate

standardized definitions for hepatic adverse events and adjust for common confounders such as MTX, JAKis, corticosteroids, and alcohol use. Comparative studies against JAK inhibitors and newer TNFis are especially needed to contextualize the hepatic safety of TCZ in the expanding RA treatment landscape.

Conclusions

TCZ remains a promising treatment option for patients with RA who have had an inadequate response to prior treatments. While mild and transient elevations in liver enzymes have been observed, serious hepatic adverse events appear to be uncommon. However, due to the limited availability of long-term RCT data and the variability in study designs and patient populations, these findings should be interpreted with caution. Regular liver function monitoring and appropriate dose adjustments are essential, particularly for patients with pre-existing liver conditions or those receiving concomitant hepatotoxic medications.

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Online supplementary material:
Supplementary Material. Quality assessment of the studies.
Supplementary Table 1. Risk of bias assessment of the systematic reviews (AMSTAR 2 tool).
Supplementary Table 2. Risk of bias assessment of the Systematic Reviews (AMSTAR 2 tool).
Supplementary Table 3. Risk of bias assessment – Bykerk *et al*. (ROBINS-I tool).
Supplementary Table 4. Risk of bias assessment for Observational Studies (NOS tool).
Supplementary Table 5. Risk of bias assessment – Garcia *et al*. (RoB2 tool).
Supplementary Table 6. Quality of evidence for narrative reviews - SANRA tool.

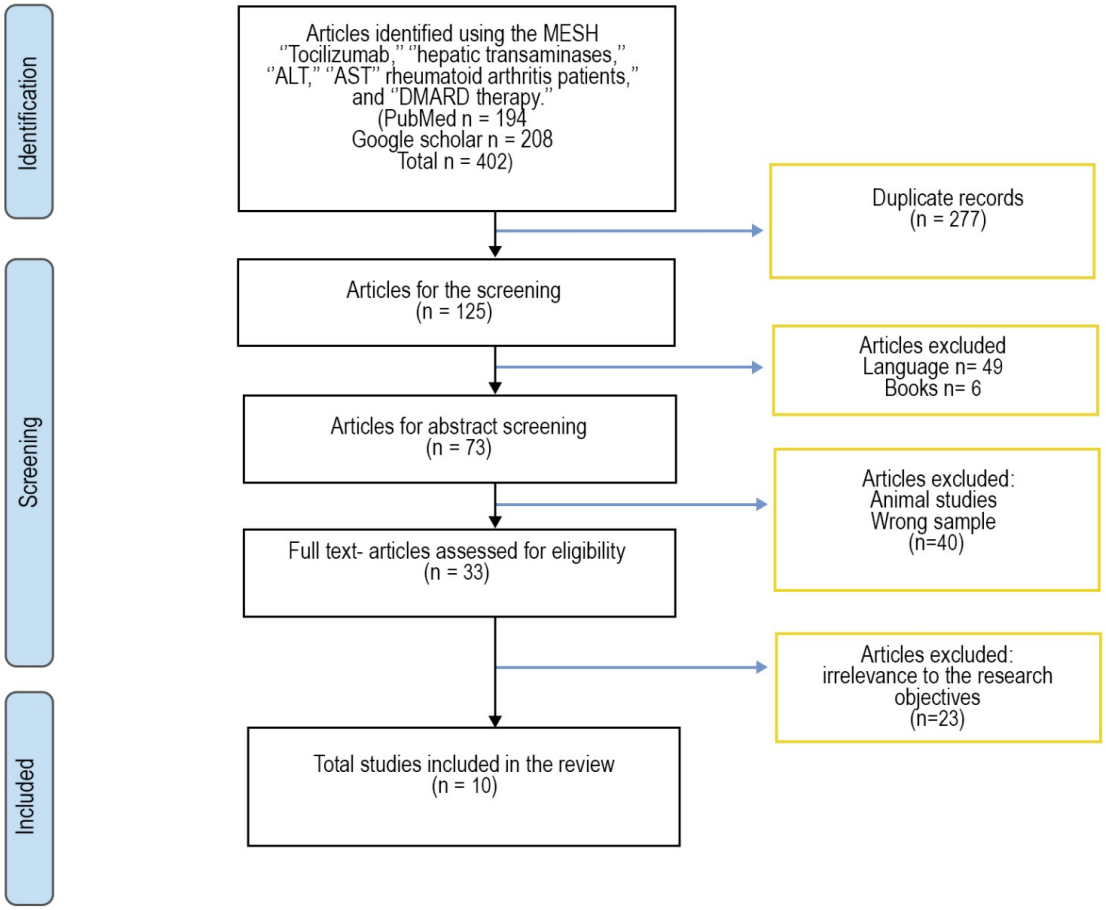

Figure 1. Flow diagram of the study selection process.

Table 1. **Study characteristics.**

Reference	Study type	Objectives	Inclusion criteria	Subjects	Control group	Outcomes	Findings and conclusions
Brazdilova *et al.*, 2019	Prospective observational study (6 months follow up)	Assess prevalence, patterns, and risk factors of drug-induced liver injury in RA patients on biological therapy.	RA patients on biological therapy	199 patients	1) TCZ and MTX; 2) adalimumab; 3) certolizumab pegol; 4) etanercept; 5) golimumab; 6) infliximab	Liver function tests (LFTs) were evaluated and DAS 28	ALT Grade 1 injury was more frequent in patients on TCZ only (27.5%) compared to other agents (13.6%). Higher hepatic risk in TCZ-treated RA patients
Saki *et al.*, 2021	Systematic review and meta-analysis of RCTs	Evaluate the safety and efficacy of TCZ for RA treatment.	Clinical trial studies related to TCZ in RA therapy.	10,314 RA patients	3986 in both comparator groups: 1) TCZ + MTX; 2) TCZ + DMARD	LFTs, ACR20, ACR50, ACR70, total complication rate and remission	Abnormal liver function tests were more frequent in RA patients treated with TCZ, indicating potential hepatic risk
Genovese *et al*., 2017	Observational retrospective	Explore the relationship between TCZ therapy and hepatic enzymes in RA patients	RA patients with substantial DMARD history	4171 patients; placebo controlled population 2644 TCZ; monotherapy population 162 TCZ	1454 placebo + MTX/DMARD; monotherapy population: 288 MTXfree patients and 292 TCZ + MTX	Investigated ALT and AST, SAE dynamics over 5 years.	70.6% of patients experienced ALT elevations, though serious hepatic events were rare
INANC *et al*., 2023	Retrospective study	Evaluate TCZ retention rate and safety in RA patients with inadequate response to prior treatment.	RA patients who started TCZ between 2015-2020 and were treated for more than three months	124; 13 TCZ monotherapy	111 patients TCZ+ csDMARDs.	LFTs, DAS28, remissions	TCZ showed manageable safety with minor increases in liver enzymes, which normalized over time. Some patients had grade ≥1 ALT increases
Kaneko *et al.*, 2013	Narrative review	Evaluate the efficacy and safety of TCZ in RA treatment	Studies on TCZ in RA.	Not specified	Not specified	Reviewed clinical outcomes and safety profile.	Mild, transient ALT and AST increases were common but reversible upon discontinuation/dose adjustment. Regular liver function monitoring is recommended
Millan *et al*., 2023	Systematic review	Evaluate TCZ effectiveness and safety in RA	Studies assessing TCZ in RA, including RCTs and observational studies	Not specified	TCZ +MTX; TCZ +DMARDs; Placebo+MTX/ DMARDs	ACR20 %, ACR50 %, ACR70 %, DAS28 remission, LFTs	TCZ significantly improved RA activity. Elevated liver enzymes were common but mild and reversible
Zhao *et al*., 2023	Review	Investigate liver damage from novel biologics in RA, focusing on IL-6 inhibitors and JAK inhibitors.	RA patients treated with novel biologics.	Not specified	Not specified	LFTs, DAS28	Novel biologics, including TCZ, were linked to mild ALT and AST elevations
Alvaro Gracia *et al*., 2023	Subanalysis of Multicenter Study	Evaluate TCZ efficacy and safety in RA patients with inadequate response to prior therapies	RA patients with active disease and inadequate response to prior treatments	170 patients	Anti-TNF with prior wash out (n=36); anti-TNF without wash out (n=39)	DAS28, AE, SAEs, and LFTs.	TCZ significantly reduced DAS28. Mild infections and elevated liver enzymes were common side effects
Byrkek *et al*., 2015	Observational study.	Evaluate the efficacy and safety of TCZ as monotherapy or in combination with DMARDs in patients with RA	RA patients and inadequate response to prior treatments.	1,681 patients	TCZ +DMARD(s) n=1,442	Disease activity was assessed using DAS28, ACR20, ACR50, and LFTs	ALT, AST occurred slightly more frequently with combination therapy, but overall safety profiles were similar between both treatment approaches
Curtis *et al*., 2015	Review	Evaluate the TCZ safety profile using post-marketing data	RA patients who received TCZ	68,447 patients	comparator population, n=95,154	SAEs, AEs	TCZ was well-tolerated with common side effects including mild infections, elevated liver enzymes, and lipid abnormalities. Liver enzyme elevations were usually reversible

RA, rheumatoid arthritis; TCZ, tocilizumab; MTX, methotrexate ; RCTs, randomized controlled trials; DMARD, disease-modifying antirheumatic drug; LFTs, liver function tests; IL-6, interleukin-6; JAK, Janus kinase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SAEs, serious adverse events; DAS28, disease activity score; TNF, tumor necrosis factor.