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Risk of hepatitis B reactivation in rheumatic patients receiving tocilizumab treatment

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MAIN POINTS

- No HBV reactivation was observed during tocilizumab therapy, one HBsAg-positive patient achieved HBsAg seroclearance under antiviral treatment.
- In HBsAg-negative/anti-HBc-positive patients, vigilant monitoring without routine antiviral prophylaxis may be sufficient, as no reactivation occurred in this group.
- These findings suggest that tocilizumab may have a low risk of HBV reactivation, though larger prospective studies are needed for confirmation.

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ABSTRACT

Aim: This study aimed to investigate the relationship between tocilizumab, a biological agent widely used for treating rheumatic diseases, and hepatitis B virus reactivation (HBVr).

Materials and Methods: The electronic records of all patients who received tocilizumab in our rheumatology outpatient clinic between July 2018 and August 2024 were retrospectively reviewed. Demographic data, baseline and followup HBV serological markers, liver biochemistry, and antiviral prophylaxis details were extracted and analyzed.

Results: A total of 54 patients were included (76.2 % female; mean age 57.5 ± 14.3 years). While HBsAg, anti-HBc IgGG and anti-HBs were requested for all patients before treatment, HBsAg was positive in 1 of 54 patients (1.9%) and anti-HBc IgG was positive in 26 (48.1%). While antiviral treatment was initiated in 10 (18.5%) of the patients, 9 were HBsAg negative, 1 was HBsAg positive, and 1 was anti-HBc Ig G positive. No patient experienced HBV reactivation during treatment; however, one HBsAg-positive patient achieved HBsAg seroclearance. The mean follow-up period was 50.5 ± 22.9 months.

Conclusion: No patient experienced HBV reactivation during tocilizumab therapy, and a single HBsAgpositive participant on prophylactic tenofovir achieved HBsAg seroclearance. These realworld data suggest that HBsAgnegative/antiHBcpositive individuals may be managed with vigilant biochemical and serological monitoring rather than routine antiviral prophylaxis during tocilizumab treatment. Nevertheless, the retrospective singlecentre design and modest sample size limit the strength and generalizability of these findings; larger prospective studies are required for definitive guidance.

Keywords: Rheumatological disease, Tocilizumab, Hepatitis B virus reactivation

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INTRODUCTION

Interleukin-6 (IL-6) is a crucial factor in the regulation of the immune system and is significantly involved in the development of inflammation, infections, and autoimmune disorders. In addition to its proinflammatory effects, IL-6 supports antiviral immunity by enhancing type I interferon signaling and promoting virus-specific $CD8^+$ T-cell responses. Tocilizumab (TCZ) is a monoclonal antibody designed to block the IL-6 receptor, thereby targeting the effects of IL-6. It is employed in the management of several rheumatic conditions, including rheumatoid arthritis, juvenile idiopathic arthritis, and giant cell arteritis [1,2]. IL-6 signaling modulates HBV replication in a context-dependent manner In vitro, IL6 can suppress the formation of covalently closed circular DNA (cccDNA) and reduce HBV transcripts via signal transducer and activator of transcription 3 (STAT3) activation [3]. Conversely, chronic IL6/STAT3 overactivation has been linked to hepatocarcinogenesis in human hepatitis B virus models [4]. This dual role raises the question of whether pharmacological IL6 blockade with tocilizumab could lift a natural brake on HBV replication and precipitate reactivation.

The suppressive effect of IL-6 on HBV replication suggests that tocilizumab treatment may increase the risk of reactivation, especially in latent HBV carriers [5,6]. Several factors affect the risk of HBV reactivation in patients receiving TCZ

treatment. Among these factors, being an HBV carrier, treatment duration, and immune response play an important role [7]. The long-term use of biological therapies for treating rheumatic diseases is a concern for physicians, especially in terms of the risk of HBV infection reactivation [8]. In addition, careful monitoring and early initiation of antiviral therapy are important to prevent HBV reactivation (HBVr) under tocilizumab therapy.

Although several small series from Asia and Western Europe suggest that the risk of HBV reactivation (HBVr) under tocilizumab therapy is lower than with TNF-α inhibitors, most cohorts include fewer than 30 antiHBcpositive patients and seldom report followup beyond 2 years. Moreover, data from countries with intermediate HBV endemicity, such as Türkiye, are scarce.

Therefore, this singlecentre retrospective study aims to provide longterm, realworld evidence on HBVr in tocilizumab treated rheumatic patients from an intermediate prevalence region, including the clinical course of an HBsAgpositive individual who achieved seroclearance.

MATERIALS AND METHODS

Study design and patient selection

This retrospective, single-center cohort study was conducted in the Rheumatology Outpatient Clinic of Recep Tayyip Erdoğan University Training and Research Hospital. All adults (≥ 18 years) who received at least three consecutive doses of tocilizumab for a rheumatic disease between July 1, 2018, and August 31, 2024 were screened. Tocilizumab was prescribed according to the established American College of Rheumatology/European League Against Rheumatism criteria for rheumatoid arthritis, adult-onset Still's disease, and other inflammatory arthritides.

Inclusion criteria

1. Age ≥ 18 years.
2. Receipt of tocilizumab for ≥ 3 months.
3. Complete baseline HBV serology (HBsAg, antiHBs, and antiHBc) within six months before therapy was available.

The exclusion criteria (Figure 1)

1. Tocilizumab exposure < 3 months.
2. Active malignancy or chemotherapy in the previous 12 months.
3. Positive for HCVRNA.
4. Missing baseline HBV tests or < 6 months of follow-up data.

HBV reactivation within the first two dosing cycles of tocilizumab has rarely been reported. Most published series indicate that events occur after ≥ 12 weeks of continuous exposure when cumulative immunomodulation becomes clinically relevant [9]. Therefore, patients who received < 3 months of TCZ were excluded to ensure a uniform exposure window in which reactivation could plausibly occur and to guarantee at least one scheduled HBVDNA assessment.

Because this was an exploratory real-world analysis, all eligible patients during the study window were included without an a priori sample size calculation.

Antiviral prophylaxis was initiated at the discretion of the treating physician (gastroenterology or infectious diseases specialist). In practice, all HBsAg-positive patients received prophylaxis, whereas HBsAg-negative/anti-HBc-positive patients received either prophylaxis or close monitoring. This approach reflects real-world variability and is broadly consistent with recommendations of international guidelines [8].

Data collection

Demographic variables (age, sex), primary rheumatic diagnosis, comorbidities, prior immunosuppressive therapy, tocilizumab initiation date, and longitudinal laboratory data (HBV serology, HBV DNA, liver enzymes) were retrieved from the hospital's electronic medical record system (Akgun®, version 25.4.) using a standardized casereport form. Two independent investigators crosschecked all entries for accuracy.

Serum HBVDNA was quantified at baseline, at months 3 and 6, and every six months thereafter. An unscheduled test was also performed whenever alanine aminotransferase (ALT) exceeded 2 × the upper limit of normal or when clinical hepatitis was suspected. This schedule followed the national HBV reactivation surveillance guidelines. Figure 1 shows the flow chart of the study participants.

The study protocol was approved by the Recep Tayyip Erdoğan University Ethics Committee (Approval No. 2024/219) and conformed to the principles of the Declaration of Helsinki.

Definitions and explanations

Within six months before initiating tocilizumab therapy, patients underwent HBV screening, including tests for HBsAg and anti-HBc. Individuals with HBsAg positivity for more than six months were classified as having chronic hepatitis B. Those who tested negative for HBsAg but positive for anti-HBc were considered to have a resolved HBV infection [10]. During patient follow-up, HBV reactivation was identified either by the emergence of detectable HBV DNA in those who initially had undetectable levels, indicating a significant rise—typically tenfold—or by a new onset of HBsAg positivity in individuals who were previously negative [9]. Hepatitis is characterized by a rise in serum alanine aminotransferase

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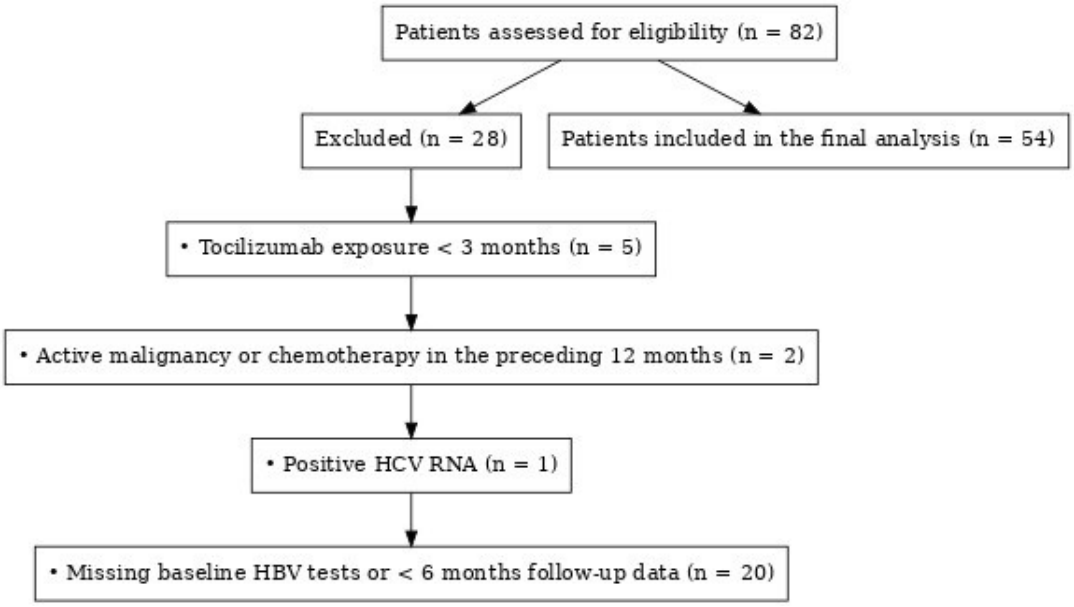

Figure 1. Flow chart of the study participants.

Table 1. Demographic and clinical characteristics of the patients included.

Variables		p
Male / Female, n (%)	12 (22.2) / 42 (77.8)	
Age, mean ± SD	57.52 ± 14.34	0.376
Male	54.25 ± 16.01	
Female	58.45 ± 13.90	
Rheumatological disease, n (%)		
Rheumatoid arthritis	49 (90.7)	
Adult Still's disease	2 (3.7)	
Temporal arteritis	1 (1.9)	
Polyarteritis Nodosa	1 (1.9)	
FMF	1 (1.9)	
Chronic diseases, n (%)		
HT	36 (66.7)	
DM	5 (9.3)	
CKD	2 (3.7)	
COPD	1 (1.9)	

FMF: Familial Mediterranean fever, HT: Hypertension, DM: Diabetes mellitus, CKD: Chronic kidney disease; COPD, chronic obstructive pulmonary disease.

(ALT) levels to three times or more above the normal upper limit, defined as ALT levels of 45 U/L [11]. HBV-related hepatitis was identified by the presence of liver inflammation accompanied by an increase in HBV DNA levels [12].

Blood immune and viral replication markers in hepatitis B

HBV-related markers in the blood, such as HBsAg, anti-HBs, and anti-HBc, were analyzed using the Roche Cobas e6001 system (Roche Diagnostics, Mannheim, Germany) using the electrochemiluminescence immunoassay technique. Serum HBV DNA was quantified through real-time PCR using the Rotor-Gene Q platform (QIAGEN, Hilden, Germany), with a detection threshold of 12 IU/mL. Standard biochemical tests were performed using a Cobas 8000 Modular Analyzer (Roche Diagnostics, Germany).

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 22 for Windows. The distribution of continuous variables was assessed using histograms, Q-Q plots, and normality tests (Shapiro-Wilk or Kolmogorov-Smirnov), depending on the number of variables. Continuous variables following a normal distribution are presented as mean ± standard deviation. The independent t-test was utilized to compare the two groups.

RESULTS

The study included 54 patients, of whom 76.2% were females, and the mean age was 57.52 ± 14.34 years. No significant difference was found in age between genders (p = 0.376). Patients most commonly received TCZ treatment due to RA (90.7%). The average follow-up duration was 50.5 ± 22.9 months, with high blood pressure (66.7%) and type 2 diabetes (9.3%) being the most prevalent comorbid conditions (Table 1).

Before treatment, HBsAg, anti-HBc IgGG and anti-HBs tests were requested for all patients. HBsAg and anti-HBc IgG were positive in 1 (1.9%) and 26 (48.1%) of 54 patients, respectively. Antiviral treatment was initiated in 10 (18.5%) of the patients, 6 with entecavir, 3 with tenofovir disoproxil, and 1 with tenofovir alafenamide. Of those who received treatment, nine were HBsAg negative and anti-HBc IgG positive, while 1 was HBsAg positive. While HBVr did not occur in any patient during the treatment, HB Ag seroclearance occurred in the HBs Ag-positive patient.

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Patient with HBsAg seroclearance

A 47-year-old male patient has been followed up since 2007 due to adult Still's disease. The patient, who had no known chronic disease other than adult Still's disease and had previously received corticosteroid and methotrexate treatments, was started on tocilizumab treatment in 2020 and simultaneously on tenofovir alafenamide treatment. Before treatment, the patient was HBsAg positive, anti-HBe positive, and had a HBV DNA level of 1622 IU/ml. In the 43rd month of treatment, the patient was negative for HBsAg and HBV DNA.

DISCUSSION

Hepatitis B infection is an important health problem in society, and the risk of reactivation, especially among hepatitis B virus carriers, poses a significant safety concern. In addition, chronic hepatitis B infection causes serious complications, such as hepatocellular cancer (HCC) and cirrhosis, causing significant morbidity and mortality. HBV reactivation (HBVr) occurs when the immune response to the virus is retriggered. Conditions of immunosuppression, including the use of anti-tumor necrosis factor (TNF)-α inhibitors, tocilizumab (TCZ), corticosteroids, and other immunosuppressive treatments for rheumatological disorders, can lead to viral reactivation due to their detrimental effects on the immune system's ability to control HBV replication [6,7,13].

In the study conducted by Hong X. et al., the risk of HBVr was found to be low in patients with rheumatoid arthritis who were HBsAg negative/HBV core antibody positive and used TCZ, and it was stated that antiviral treatment was a safe option for prophylaxis [14]. In the study conducted by Rodríguez-Tajes S et al., in 44 HBsAg-negative/anti-HBc-positive patients with COVID-19 treated with TCZ, 61% of the patients received prophylactic entecavir, and HBV DNA positivity was detected in only one patient [15]. Another study reported that anti-HBs had a protective effect in patients with rheumatism treated with TCZ [16]. Studies have also emphasized the importance of early antiviral treatment initiation in preventing HBVr under TCZ treatment [17,18]. In our study, HBVr was not observed during tocilizumab treatment, which is similar to the findings in the literature. However, HBV serology performed before treatment and antiviral treatment initiation significantly reduced the risk of reactivation.

A potentially fatal case of HBV exacerbation has been reported in a patient with rheumatoid arthritis who was HBsAg positive following TCZ treatment [19]. HBVr is quite high in HBs-positive patients with TCZ. HBVr begins in the early stages of treatment with TCZ, and reactivation is almost negligible after the initiation of antiviral prophylaxis [20]. In our study, it was observed that hepatitis B could be controlled with antiviral treatment in patients positive for HBsAg. For example, in a 47-year-old adult patient with Adult Still's disease, tenofovir alafenamide treatment, initiated together with tocilizumab treatment, was found to be effective in providing HBV DNA and HBsAg seroclearance.

Numerous cytokines, such as IL-6, play a role in HBV infection progression. Abnormal IL-6 production has been observed in chronic inflammatory conditions such as hepatitis B and rheumatoid arthritis. IL-6 is a key factor in HBV replication and hepatitis B progression. It has been associated with both hepatitis B advancement and HBV entry and replication processes within the host. The risk of HBVr under TCZ treatment has been a controversial issue. While some studies suggest that IL-6 has a suppressive effect on HBV replication, TCZ may eliminate this suppressive effect and cause reactivation [21,22].

While in vitro data suggest that IL-6 may suppress HBV replication [3], leading to concerns that tocilizumab could theoretically unleash viral activity, our real-world findings do not support this in the context of diligent screening and monitoring. This discrepancy highlights the complexity of the role of IL-6 in HBV pathogenesis, which may differ significantly between in vitro models and complex in vivo human systems, especially when rheumatic disease activity and concomitant therapies simultaneously modulate other immune pathways. On the other hand, some studies have emphasized that HBVr can be prevented by initiating antiviral treatment and that such patients should be closely monitored during the treatment process [23,24]. Although HBVr was not observed in all patients in our study, it was concluded that HBV serological tests should be performed before treatment and antiviral treatment should be initiated. This is an important clinical strategy, especially for patients with HBV.

No HBV reactivation was observed in anti-HBc–positive patients receiving tocilizumab following CAR T-cell therapy, provided that regular HBV DNA monitoring was performed [25]. Isolated clinical observations suggest that IL6 receptor blockade may also benefit patients with postacute sequelae of severe acute respiratory syndrome coronavirus 2 (SARSCoV2) infection ("longCOVID"). In a recent case report, a woman with rheumatoid arthritis and persistent SARSCoV2 antigenemia experienced marked symptomatic and virological improvement after a short course of nirmatrelvir–ritonavir followed by tocilizumab therapy, without any evidence of HBV reactivation or hepatic flare [26]. These observations, together with our 50 month rheumatology cohort, indicate that IL-6 antagonism does not inherently trigger HBVr when evidence based screening and surveillance protocols are applied. Importantly, our study extends the mechanistic overview by Kishimoto & Kang (2022) by providing longterm, realworld data from an intermediate endemic region and by reporting—to our knowledge—the first instance of HBsAg seroclearance under combined tenofovir alafenamide and tocilizumab therapy.

The spontaneous loss of HBsAg in immunocompetent adults occurs at an estimated rate of 0.5%–1% per patient-year [27]. Although spontaneous seroclearance rates may

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be slightly higher in HBeAg-negative individuals than in HBeAg-positive individuals, our patient's baseline HBeAg negativity coupled with an HBV DNA of 1622 IU/ml still indicated active infection requiring intervention. In contrast, long-term nucleos(t)ide analog (NA) therapy, such as tenofovir, accelerates seroclearance, with cumulative rates of 5%–12% after 3–5 years [28]. Our patient, who received tenofovir alafenamide concomitantly with tocilizumab, became negative for HBsAg after 43 months. This timeline is more consistent with NA-induced rather than spontaneous clearance. Therefore, while the case is clinically interesting, its significance should not be overemphasized, and causality cannot be proven from a single observation. Other factors—such as immune reconstitution once rheumatic disease activity was controlled—may also have contributed to this outcome.

From a healtheconomic perspective, modeling studies indicate that routine nucleos(t)ideanalog prophylaxis is costeffective only in HBsAgpositive patients or in antiHBcpositive individuals exposed to highrisk regimens, whereas close biochemical and virological surveillance is more costefficient than indefinite antiviral therapy in lowrisk antiHBcpositive/antiHBspositive patients [29, 30].

Limitations

This retrospective, singlecentre study enrolled a modest cohort (n = 54) without a parallel control group; therefore, the observed absence of reactivation cannot be causally attributed to tocilizumab exposure alone. The sample size limits statistical power, and the singlecentre setting may reduce generalizability. Potential information and referral biases inherent to ERRs also remain. Larger, prospective, multicenter studies with matched controls are needed to confirm these findings.

CONCLUSION

While no patient using tocilizumab developed hepatitis B reactivation, one patient who was positive for HBs Ag and receiving antiviral treatment developed HBs Ag seroclearance. Although these findings predict that patients with hepatitis B who do not receive antiviral treatment can be followed with careful monitoring after tocilizumab treatment, studies with larger samples are needed to reach definitive conclusions.

Ethics Committee Approval: The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Recep Tayyip Erdoğan University Local Ethics Committee (date: 15.08.2024, no: 2024/219).

Informed Consent: Since this was a retrospective study, informed consent was not obtained.

Peer-review: Externally peer-reviewed.

Conflict of Interest: All authors have no competing financial or nonfinancial interests related to this work.

Author Contributions: BK: Investigation, Writing Supervision, and Methodology. OC: Conceptualization and Writing. SD: Formal analysis and project administration.

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