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Screening for Hepatitis B Virus Prior to Initiating Tocilizumab and Tofacitinib in Patients With Rheumatic Diseases: A Cross-sectional Study

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ABSTRACT. ***Objective.*** Hepatitis B virus (HBV) can reactivate among rheumatology patients initiating tocilizumab (TCZ) or tofacitinib (TOF). HBV screening is recommended by the Centers for Disease Control and Prevention (CDC), the American Association for the Study of Liver Diseases (AASLD), and the Canadian Rheumatology Association, but it is not explicitly recommended by the American College of Rheumatology.

Methods. We conducted a cross-sectional study to characterize HBV screening practices for adult rheumatology patients initiating TCZ or TOF before December 31, 2018, in the Greater Boston area. We classified appropriate HBV screening patterns prior to TCZ or TOF (i.e., HBV surface antigen [HBsAg], total core antibody [anti-HBcAb], and surface antibody [HBsAb]) as follows: complete (all 3 tested), partial (any 1 or 2 tests), or none. We determined the frequency of inappropriate HBV testing (HBV e-antigen, anti-HBcAb IgM, or HBV DNA without a positive HBsAg or total anti-HBcAb) and used multivariable regression to assess factors associated with complete HBV screening.

Results. Among 678 subjects initiating TCZ, 194 (29%) completed appropriate HBV screening, 307 (45%) had partial screening, and 177 (26%) had none. Among 391 subjects initiating TOF, 94 (24%) completed appropriate HBV screening, 195 (50%) had partial screening, and 102 (26%) had none. Inappropriate testing was performed in 22% of subjects. Race was associated with complete HBV screening (White vs non-White: OR 0.74, 95% CI 0.57–0.95), whereas prior immunosuppression was not (conventional synthetic disease-modifying antirheumatic drugs [DMARDs]: OR 1.05, 95% CI 0.72–1.55; biologic DMARDs: OR 0.73, 95% CI 0.48–1.12).

Conclusion. Patients initiating TCZ or TOF are infrequently screened for HBV despite recommendations from the AASLD and CDC.

Key Indexing Terms: hepatitis B virus, Janus kinase inhibitors, latent infection, monoclonal antibodies, rheumatoid arthritis, vasculitis

Reactivation of the hepatitis B virus (HBV) is characterized by increased HBV replication, which can cause acute liver failure and death among people taking immunosuppressive drug therapy.[1] Individuals with past HBV infection have persistent HBV DNA in hepatocytes even without circulating HBV surface antigen (HBsAg) or a detectable serum HBV DNA. They remain at risk of HBV reactivation when treated with immunosuppressive drug therapy, despite having HBV surface antibody (HBsAb).[2] For adults with past or active HBV infection, HBV reactivation risk varies based on the immunosuppressive drug and the HBV serologic profile. HBV reactivation occurs in > 25% of people with active HBV infection (HBsAg-positive) undergoing chemotherapy for cancer.[2,3] In people with past HBV infection (HBsAg-negative with anti-HBV core antibody [anti-HBcAb]),

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HBV reactivation occurs in 3–41% with rituximab (RTX) and up to 5% with tumor necrosis factor-α inhibitors (TNFi).[4] HBV reactivation can be prevented with antiviral therapy; patients who are treated prophylactically have fewer episodes of hepatitis, liver failure, and interruptions in immunosuppression.[3]

Despite the risk of serious illness and the opportunity for prevention, many people are not screened for HBV prior to initiating immunosuppressive drug therapy.[5] Guidelines from the Centers for Disease Control and Prevention (CDC) and the American Association for the Study of Liver Diseases (AASLD) recommend screening for HBsAg, anti-HBcAb, and HBsAb prior to initiation of immunosuppressive drug therapy, "including chemotherapy, immunosuppression related to organ transplantation, and immunosuppression for rheumatological or gastroenterologic disorders."[6,7] The Canadian Rheumatology Association (CRA) also recommends HBV screening prior to biologic therapy.[8] In contrast, the American College of Rheumatology (ACR) guidelines for management of rheumatoid arthritis (RA) do not explicitly recommend HBV screening prior to immunosuppression, although they provide guidance on HBV DNA monitoring for those with diagnosed HBV.[9]

Without uniform recommendations for HBV screening, clinical practice may vary by the specific type of immunosuppressive drug and the perceived risks of HBV reactivation. HBV screening practices have been previously described for TNFi and RTX,[10,11,12] but practices may differ with more recently approved agents, such as interleukin (IL)-6 receptor antagonists and oral Janus kinase (JAK) inhibitors. Previous reports suggest that the IL-6 receptor antagonist tocilizumab (TCZ) has an equivalent HBV reactivation risk to other biologic agents (i.e., up to 5% in past HBV infections).[13,14] HBV reactivation has also been observed in postmarketing studies of the oral JAK inhibitor tofacitinib (TOF), which remains the first-line JAK inhibitor of choice in the treatment of RA.[14] These 2 medication classes are being used with increasing frequency as first-line agents for an expanding number of indications in rheumatic diseases and other disorders, but HBV screening practices are not well described. We previously reported the prevalence of resolved and active HBV infection in this population.[15] In this analysis, we sought to characterize HBV screening among people initiating TCZ or TOF for rheumatic indications and to assess factors associated with complete HBV screening in a large academic US healthcare system.

METHODS

We conducted a retrospective cross-sectional study of all adult patients who initiated TCZ or TOF prior to December 31, 2018, while engaged in rheumatology care within the Mass General Brigham (MGB) health system in the Greater Boston area. We studied clinical practices at 2 quaternary care hospitals, 3 community hospitals, and their affiliated outpatient clinics.

We identified eligible patients using the Research Patient Data Registry (RPDR), a comprehensive, centralized clinical care database of electronic data. This study was exempt from institutional board approval by the MGB Human Research Committee due to the retrospective use of information from healthcare operations and medical records (protocol #2019P000836); informed consent was waived.

TCZ and TOF were approved for use in the US on January 11, 2010, and November 6, 2012, respectively. We queried the RPDR database to identify all adult patients who received at least 1 medication order or prescription for TCZ or TOF from the time of their approved use until December 31, 2018. We included patients aged > 18 years with at least 1 outpatient rheumatology encounter in the MGB health system 90 days prior to or 30 days following the initiation of TCZ or TOF. We stratified patients based on their history of receiving conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biologic DMARDs (bDMARDs), or neither (i.e., prior to TCZ or TOF).

We classified appropriate HBV screening patterns into 3 mutually exclusive categories: complete (HBsAg, total anti-HBcAb, and HBsAb), partial (any 1 or 2 of these tests), or none (0 of these tests). We classified inappropriate HBV testing as either HBV e-antigen (HBeAg), anti-HBcAb IgM, or HBV DNA without a positive HBsAg or total anti-HBcAb. For both TCZ and TOF, we determined the frequency of inappropriate HBV testing among subjects in each category of appropriate HBV screening (complete, partial, and none).

We used the RPDR to extract demographic information, medical encounters, laboratory data, and medications for all subjects between January 1, 1995, and December 31, 2018. To determine the primary indication for TCZ and TOF, we identified the most commonly coded principal diagnosis for any rheumatology encounter in the RPDR dataset for each patient. We used accepted International Classification of Diseases, 9th revision (ICD-9) and ICD-10 codes for RA (ICD-9 714, except 714.3; ICD-10 M05–M07), psoriatic arthritis (ICD-9 696; ICD-10 L40), vasculitis (ICD-9 446.5; ICD-10 M31.5), and other arthritis (ICD-9 713, 714.3, 715–719; ICD-10 M08, M12–M25). For subjects whose charted diagnosis differed from common rheumatic indications, we conducted a manual chart review to confirm the primary indication for drug therapy.

We determined the date of HBV laboratory testing in reference to the date of the earliest prescription for TCZ or TOF. We classified subjects as having completed HBV screening if testing occurred any time before or up to 30 days following the date of the first TCZ or TOF prescription. We extracted the site of care and the prescribing clinician for TCZ and TOF. For a randomly selected 5% of patients, we used chart review to confirm that the RPDR search strategy produced a relevant study population and that laboratory data captured in RPDR accurately reflected the information available to rheumatology clinicians initiating TCZ and TOF.

We report continuous variables as means and SDs and categorical variables as frequencies and percentages. We used chi-square tests to compare the proportion of subjects with complete, incomplete, absent, and inappropriate HBV screening among those receiving TCZ or TOF. We used multivariable logistic regression to determine factors associated with complete appropriate HBV screening. We accounted for provider-level and site-level clustering using generalized estimating equations (GEEs). We adjusted for covariates thought to be relevant a priori, including sex, drug (TCZ or TOF), race, and prior receipt of bDMARD or csDMARD therapy. In these analyses, subjects who received both TCZ and TOF were categorized by the drug they received first. We used a P value < 0.05 as the predefined threshold of statistical significance. We used SAS 9.4 (SAS Institute) using the GENMOD procedure for GEEs.

RESULTS

We identified 913 subjects initiating TCZ and 630 subjects initiating TOF at MGB before December 31, 2018 (Figure 1). After excluding subjects aged < 18 years (TCZ, n = 2; TOF, n = 3) and those without outpatient rheumatology encounters (TCZ, n = 233; TOF, n = 236), the final study population included 678 subjects initiating TCZ and 391 subjects initiating TOF.

Mean age was 61 (SD 16) years (TCZ) and 60 (SD 13) years (TOF), and the majority of patients were female and non-Hispanic White (Table 1). Nearly all subjects (89%) were followed in our health system for at least a year prior to their

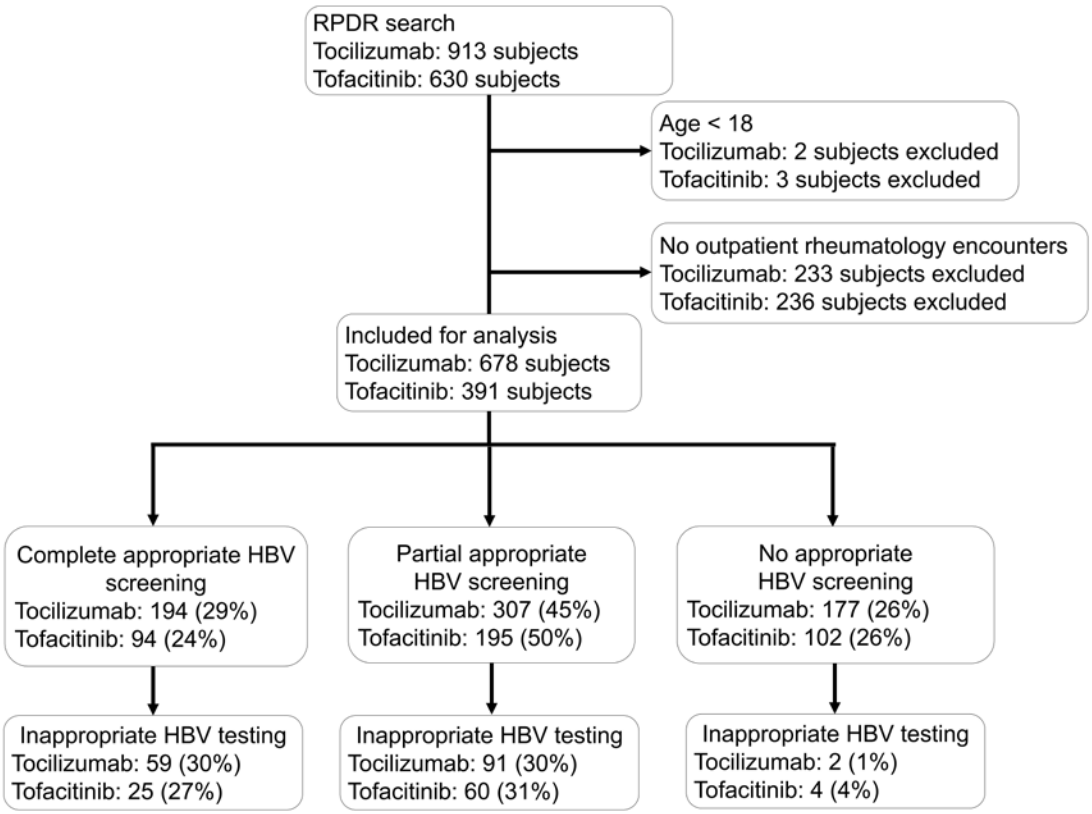

Figure 1. Flowchart of HBV screening among patients treated with TCZ and TOF. RPDR query identified all patients receiving TCZ and TOF from the time of their approval to December 31, 2018. The cohort for this analysis included adult patients with outpatient rheumatology encounters within 90 days before or 30 days after their first TCZ or TOF prescription. Complete appropriate screening includes all 3 of HBV surface antigen, HBV surface antibody, and total anti-HBV core antibody; partial appropriate screening includes any 1 or 2 of these tests; no appropriate screening includes 0 of these tests. Inappropriate HBV testing includes HBV e-antigen, anti-HBV core IgM, or HBV DNA without a positive HBV surface antigen or total anti-HBV core antibody. HBV: hepatitis B virus; RPDR: Research Patient Data Registry; TCZ: tocilizumab; TOF: tofacitinib.

first prescription of TCZ or TOF. The most common indication was RA (TCZ 362 [53%]; TOF 301 [77%]). Most subjects were previously treated with csDMARDs or bDMARDs; 152 (22%) of those initiated on TCZ and 16 (4%) on TOF had received no prior treatment with csDMARDs or bDMARDs.

Of the 678 subjects initiating TCZ, 194 (29%) underwent complete appropriate HBV screening, 307 (45%) underwent partial appropriate HBV screening, and 177 (26%) had no appropriate HBV screening (Figure 1). Of the 152 subjects who received TCZ without a prior history of csDMARD or bDMARD therapy, 51 (33%) underwent complete appropriate HBV screening, 47 (31%) underwent partial appropriate HBV screening, and 54 (36%) had no appropriate HBV screening. Of the remaining 526 subjects who received TCZ with a history of csDMARD and/or bDMARD therapy, 143 (27%) had complete appropriate HBV screening, 260 (49%) had partial appropriate HBV screening, and 123 (23%) had no appropriate HBV screening. Compared to subjects without prior immunosuppression, those with a history of csDMARD and/or bDMARD use were no more likely to undergo complete appropriate HBV screening ($P = 0.31$), but they more frequently had partial appropriate HBV screening ($P < 0.001$). Of the 152 (22%) subjects receiving TCZ who met our definition for inappropriate HBV testing, 59 had complete appropriate HBV screening, while 91 had undergone partial appropriate HBV screening, and 2 had no appropriate HBV screening (Figure 1).

Of the 391 subjects initiating TOF, 94 (24%) underwent complete appropriate HBV screening, 195 (50%) experienced partial appropriate HBV screening, and 102 (26%) had no appropriate HBV screening (Figure 1). Only 16 subjects received TOF without prior csDMARD or bDMARD therapy. Of the 89 (23%) subjects with inappropriate HBV testing, 25 had undergone complete appropriate HBV screening, while 60 had undergone partial appropriate HBV screening, and 4 had no appropriate HBV screening (Figure 1).

In a multivariable analysis, we used GEEs to account for provider- and hospital-level clustering while adjusting for sex, race/ethnicity, drug (TCZ or TOF), and use of prior csDMARDs or bDMARD (Table 2). White subjects were less likely to undergo complete HBV screening (OR 0.74, 95% CI 0.57–0.95) compared to non-White subjects. Neither TCZ nor TOF was more associated with complete appropriate

Table 1. Baseline characteristics of subjects initiating TCZ or TOF at MGB prior to December 31, 2018.

	TCZ, n = 678	TOF, n = 391
Age, yrs, mean (SD)	61 (16)	60 (13)
Female	529 (78)	343 (88)
Race/ethnicity		
White, non-Hispanic	568 (84)	328 (84)
Black, non-Hispanic	32 (5)	17 (4)
Hispanic	25 (4)	19 (5)
Asian	21 (3)	9 (2)
Other	17 (3)	7 (2)
Not reported	15 (2)	11 (3)
Diagnosis		
Rheumatoid arthritis	362 (53)	301 (77)
Vasculitis	151 (22)	2 (1)
Other inflammatory arthritis	119 (18)	44 (11)
Psoriatic arthritis	9 (1)	24 (6)
Other diagnosis	37 (5)	20 (5)
Previous medications		
csDMARD only	88 (13)	44 (11)
bDMARD only	53 (8)	51 (13)
csDMARD and bDMARD	385 (57)	280 (72)
No prior csDMARD or bDMARD	152 (22)	16 (4)

Values are expressed as n (%) unless otherwise indicated. bDMARD: biologic disease-modifying antirheumatic drug; csDMARD: conventional synthetic disease-modifying antirheumatic drug; MGB: Mass General Brigham; TCZ: tocilizumab; TOF: tofacitinib.

Table 2. Factors associated with complete appropriate HBV screening prior to receipt of TCZ or TOF in multivariable logistic regression using generalized estimating equations[a].

	Adjusted OR (95% CI)
Drug therapy	
TOF	Ref
TCZ	1.08 (0.87–1.34)
Sex	
Female	Ref
Male	0.93 (0.70–1.24)
Race/ethnicity	
Non-White	Ref
White	0.74 (0.57–0.95)*
Immunosuppression history	
No prior csDMARD or bDMARD	Ref
Prior csDMARD only	1.05 (0.72–1.55)
Prior bDMARD[b]	0.73 (0.48–1.12)

[a] Complete appropriate screening includes all 3: HBV surface antigen, HBV surface antibody, and total anti-HBV core antibody. [b] With or without prior csDMARD. * $P < 0.05$. bDMARD: biologic disease-modifying antirheumatic drug; csDMARD: conventional synthetic disease-modifying antirheumatic drug; HBV: hepatitis B virus; TCZ: tocilizumab; TOF: tofacitinib.

HBV screening (TCZ vs TOF: OR 1.08, 95% CI 0.87–1.34). Subjects with prior use of immunosuppression were not more likely to have complete appropriate HBV screening (csDMARD only: OR 1.05, 95% CI 0.72–1.55; bDMARD with or without prior csDMARD: OR 0.73, 95% CI 0.48–1.12).

DISCUSSION

HBV reactivation is a preventable complication of immunosuppressive drug therapy, yet fewer than one-third of rheumatology patients initiating TCZ or TOF at a large health system completed appropriate HBV screening. We focused on these 2 agents as they are being used with increasing frequency as first-line agents for an expanding number of rheumatic indications. The majority of patients had previously received other csDMARD or bDMARD therapy, but they were no more likely to have complete appropriate HBV screening than those without prior use of immunosuppression.

The first important finding of this study is the low frequency of pretreatment HBV screening. While we focused on TCZ or TOF, we noted that most subjects had previously received other csDMARD or bDMARD agents that have been definitively associated with HBV reactivation.[14] These findings suggest that HBV screening is too infrequent among patients with rheumatic diseases on immunosuppressive therapy regardless of the immunosuppressive medications. An analysis of a national registry of patients with rheumatic conditions similarly found that only 28.8% of patients had completed HBsAg and total anti-HBcAb testing prior to immunosuppression with any DMARD.[5] Perhaps not unexpectedly, these screening patterns conform more with recommendations from the ACR, which do not explicitly stipulate universal HBV screening, compared with guidelines from CDC or AASLD that recommend universal HBV screening for patients initiating immunosuppressive drug therapy, or from the CRA that recommend screening prior to certain medications. Further, the US Food and Drug Administration package inserts of TCZ and TOF do not include specific recommendations for HBV screening, even though HBV reactivation has been observed in postmarketing studies of both IL-6 receptor antagonists and oral JAK inhibitors.[13,16] Consistent and explicit recommendations for HBV screening across societal recommendations could improve HBV screening frequency.

A second important finding is that 22% of the subjects underwent inappropriate HBV testing, frequently in the absence of completing appropriate HBV screening. An analysis of HBV laboratory tests conducted among all patients in a health system in Canada found that > 70% of patients who underwent testing with HBeAg, HBV e-antibody, or HBV DNA did not have evidence of past or present infection.[17] Those investigators estimated that 30% of HBV testing costs could be saved in their health system if clinicians pursued HBeAg, HBV e-antibody, and HBV DNA testing based only on positive results of HBsAg or total anti-HBcAb. Relative to the lifetime costs of DMARD therapy, the costs of 1-time HBV tests are negligible. However, we found that inappropriate HBV testing was often conducted in lieu of, rather than in addition to, HBsAg or total anti-HBcAb testing. We worry that clinicians may be erroneously reassured by negative HBeAg, HBcAb IgM, or HBV DNA results without accurately confirming the absence of latent infection in their patients. Clinical decision support systems may help to reduce inappropriate laboratory testing.[18]

Our findings should be interpreted within the limitations of the study design. The data in this study were retrospectively

collected. Some subjects may have had HBV screening in laboratories outside of the MGB health system or prior to 1995 (i.e., the earliest date of testing data captured in our study), or > 30 days after initiating TCZ or TOF. Some subjects may have initiated TCZ or TOF by clinicians outside the MGB system; however, this rarely occurred in a manual chart review of 5% of the subjects. We were unable to characterize the dose or duration of corticosteroid use in this dataset, and were therefore unable to include that important factor as a covariate. Our findings may not be generalizable to nonrheumatic settings or other immunomodulators, although studies in other patient populations (e.g., solid organ cancer, inflammatory bowel disease) have identified similarly low HBV screening frequencies.[1,19,20]

We propose at least 3 reasons why universal HBV screening should be reconsidered in clinical society recommendations. First, HBV risk factors are frequently unreported by patients and unrecognized by physicians. In a previous study, fewer than 3% of patients from HBV-endemic regions were correctly identified by their rheumatologists as being at increased risk for HBV.[21] Second, HBV prevalence may be rising due to the opioid epidemic, despite recommendations for universal childhood vaccination.[22] Reported outbreaks of acute HBV, particularly in young, nonurban populations affected by the opioid epidemic, may only be the tip of the iceberg for national trends of rising HBV transmission; if so, there may soon be a growing population of patients with prior HBV infection who would be at risk of reactivation if exposed to immunosuppressive drug therapy.[22] Third, the true incidence of HBV reactivation related to immunosuppressive drug therapy may be underreported in observational cohorts because of ascertainment bias due to the low prevalence of HBV testing, even among those at high risk of HBV infection.

Fewer than one-third of people completed appropriate HBV screening prior to initiating TCZ or TOF for rheumatic diseases, and many underwent inappropriate HBV testing in lieu of HBsAg or total anti-HBcAb testing. Consistency in HBV screening recommendations across society recommendations may improve HBV detection prior to initiation of TCZ and TOF and decrease untoward outcomes related to HBV reactivation.

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