Editorial

Hepatitis B Screening Before Biologic or Targeted Synthetic Disease-modifying Antirheumatic Drug Therapy: Many Roads to Improvement

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Biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) have long been recognized to cause hepatitis B virus (HBV) reactivation in individuals chronically infected with or previously exposed to HBV.¹ Despite this knowledge, many patients treated with b/tsDMARDs experience HBV reactivation each year because of inconsistent screening.² Because of its largely asymptomatic clinical expression and low testing rates, the HBV burden in patients with rheumatic diseases is difficult to determine. However, HBV is likely more common than we may suspect, based on studies conducted in the general population. In the US, an estimated 875,000 persons are living with chronic HBV (HBsAg-positive), although prior or resolved HBV (HBcAb-positive, HBsAg-negative, with or without HBsAb) is much more common, affecting up to 11 million persons.^{3,4} Most of these individuals are either undiagnosed or unaware of their HBV status, as is the case with up to 75% of persons with chronic HBV.⁵ Because HBV infection is common and underdiagnosed, and immunosuppression with b/tsDMARDs can lead to HBV reactivation with deleterious consequences ranging from HBV DNA elevations to fatal liver failure,¹ HBV screening prior to b/tsDMARD initiation is a relatively simple, low-cost step critical to delivering high-quality rheumatologic care.

The article by Mohareb et al in this issue of *The Journal of Rheumatology* is a timely addition to research on drug safety of newer b/tsDMARDs in patients with rheumatic diseases,

exploring deficiencies in HBV screening practices in individuals initiating tocilizumab (TCZ) or tofacitinib (TOF) in an integrated health network.⁶ Both agents are increasingly recognized to carry a risk of HBV reactivation^{7,8} and despite their growing use in rheumatology, little is known about practices to ensure their safe administration. This study found that HBV screening in new users of TCZ or TOF was remarkably low, with fewer than one-third having been tested with the full complement of HBsAg, total HBcAb, and HBsAb tests.⁶ Surprisingly, the investigators also found that some HBV testing was incorrect or inappropriate. For example, more than one-fifth of subjects without evidence of active infection had HBeAg, HBcAb IgM, or HBV DNA testing, a finding that highlights the need to target interventions around HBV testing, as well as reduce unnecessary healthcare spending.

In this study, individuals of non-White race were tested more frequently than White users of TCZ or TOF, possibly reflecting clinicians' awareness of the epidemiology of HBV infection.⁶ However, the prevalence of HBV exposure in the general population is high enough to warrant universal screening before immunosuppression. In the US, an estimated 0.34% and 4.3% of the population have chronic and prior or resolved HBV, respectively. This can vary dramatically depending on the patient population: for instance, the prevalence of chronic and prior or resolved HBV is 2.7% and 21.5% in Asians, and 0.6% and 8.9% in non-Hispanic Blacks, respectively.⁵ Given that many rheumatic diseases disproportionately affect non-White populations, it is critical to develop standardized protocols to screen all patients initiating immunosuppression.

The results of Mohareb et al⁶ are notable in the context of published guidelines on HBV screening prior to immunosuppression and the literature on HBV reactivation, but they are not altogether surprising. There is ample evidence of widespread deficiencies in HBV screening prior to immunosuppression, and in the national Rheumatology Informatics System for

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Effectiveness (RISE) registry of practices in the US, less than one-third of patients had complete HBV testing (defined in this paper as HBsAg and HBcAb).⁹ The study by Mohareb et al provides a powerful motivation to enhance procedures to reduce patient safety risks associated with b/tsDMARDs.⁶

Universal screening with appropriate HBV testing

The study by Mohareb et al adds to the growing literature supporting universal HBV screening for all new users of b/tsDMARDs.⁶ In the absence of clear guidelines or safety checks for hepatitis testing, there is evidence that clinicians are making individual, patient-specific decisions about who should be tested for HBV. These assessments depend on a range of factors, including established and perceived risk factors for HBV. However, clinicians consistently overlook or underplay the most important risk factor for acquiring HBV and developing chronic infection: birth in a high-prevalence region.¹⁰ Many studies have revealed suboptimal knowledge of HBV risk factors in a variety of medical professionals, as well as a tendency to place more importance on certain patient characteristics when assessing HBV risk, such as injection drug use.^{11,12,13}

Existing American College of Rheumatology (ACR) guidelines are likely contributing to the uneven standard of care and need updating. The 2021 ACR rheumatoid arthritis (RA) guidelines acknowledge patients with HBV as a special patient population of interest and specify recommendations for viral load monitoring and antiviral treatment in those with chronic and prior or resolved HBV.¹⁴ These recommendations imply systematic HBV screening by clinicians, although this is not stated explicitly, and prior RA guidelines have instead advised a risk-based strategy of HBV testing.¹⁵ This is in contrast with other national guidelines, such as those issued by the Centers for Disease Control and Prevention and the American Association for the Study of Liver Diseases, which advocate universal HBV screening prior to any immunosuppressive agent.^{16,17}

Updated recommendations on universal screening will need to be explicit about when to screen for HBV. In the study by Mohareb et al,⁶ a surprising finding was that complete HBV screening was not associated with prior conventional synthetic DMARD or bDMARD use, suggesting that HBV screening is suboptimal across multiple classes of immunosuppression. Since there is clear evidence of HBV reactivation with almost every form of immunosuppression, including moderate-to-high doses of steroids and b/tsDMARDs, universal screening would likely be more practical and less confusing if the scope of the recommendation included all immunosuppressive medications, including b/tsDMARDs, despite small-to-modest differences in HBV risk from agent to agent. Current ACR guidelines tend to be disease-specific, but disseminating drug safety recommendations across rheumatic diseases may be beneficial, as in a recent DMARD safety guideline for patients with inflammatory arthritis in the UK.¹⁸ An added benefit of universal screening is the promotion of drug safety with newly approved b/tsDMARDs, many of which were investigated in trials that excluded patients with HBV infection. This can safeguard our

patients while observational data is collected on HBV reactivation risks associated with newly approved medications.

Clear guidelines on universal screening will be most successful if they are also specific about what tests to order. The ACR RA guidelines fail to specify this information, and there is ample evidence in the literature that nonhepatology and noninfectious disease clinicians frequently order HBV tests that are incomplete or simply incorrect, or misinterpret the results of those tests.¹⁹ A novel contribution of the study by Mohareb et al is the surprising finding that inappropriate HBV testing was quite common in the health system examined.⁶ This incomplete and inappropriate HBV testing likely reflects the complexity of HBV infection, which has different stages in individuals and over time. As shown in Table 1, rheumatologists require 3 tests (HBsAg, total HBcAb, and HBsAb) for a comprehensive assessment of a patient's HBV status and reactivation risk; this should be emphasized in guidelines as well as medical educational efforts.^{1,20} Importantly, these 3 tests can identify prior or resolved HBV, which assumes clinical relevance in the setting of immunosuppression, and can identify patients in need of HBV vaccination. The inappropriate tests in Table 1 have minimal utility outside of the contexts of acute or chronic HBV, and thus should be discouraged in HBV screening efforts.

An important step in the implementation of these practice standards will be to demonstrate the cost-effectiveness of universal screening, which should be confirmed in future studies. Standard screening practices for HBV infection could avert costs associated with inappropriate HBV laboratory orders and the sequelae of HBV reactivation, including hepatitis or immunosuppression interruptions/switches.

Improving health systems

HBV screening is most likely to be effective when integrated in local health systems. There are several evidence-based strategies for doing so that could be adopted in diverse settings. One of the most powerful in the literature is the use of clinical decision support systems (CDSSs), which are defined as manual or electronic systems that "provide clinicians with patient-specific assessments or recommendations to aid clinical decision making."²¹ CDSSs are usually implemented in the form of alerts, reminders, or order sets in the electronic health record (EHR) and are particularly suited to issues of drug safety. CDSSs have improved HBV screening rates prior to b/tsDMARD administration in multiple studies by acting as safety checklists and helping clinicians with the ordering and interpretation of laboratory tests.^{22,23} Bullard et al reported on a multisite implementation of a CDSS in the US Veterans Health Administration system, in which new prescriptions for anti-CD20 monoclonal antibodies were linked with a helpful EHR alert that displayed a patient's prior laboratory results, highlighted deficiencies in HBV testing, and even integrated lab orders and subspecialty referrals.²³ CDSSs can facilitate standardization of preimmunosuppression testing, reduce site- and provider-level heterogeneity, minimize inappropriate HBV testing, and facilitate treatment of patients newly diagnosed with HBV.^{22,23}

Physician-focused strategies are additional tools that have

Table 1. Indicated and nonindicated tests for HBV screening prior to starting immunosuppression in individuals with rheumatic diseases.

Indicated HBV Tests		Nonindicated HBV Tests	
Test	Description	Test	Description
HBsAg	<ul style="list-style-type: none"> • Detects component of the HBV lipoprotein envelope • A hallmark of acute or chronic HBV, of which the latter is characterized by the persistence of HBsAg > 6 months 	HBV DNA	<ul style="list-style-type: none"> • Detects HBV DNA in blood and is thus a marker of active viral replication • Should not be tested in contexts other than acute HBV or confirmed chronic HBV • A negative HBV DNA result does not rule out chronic HBV
HBcAb (total)	<ul style="list-style-type: none"> • Detects IgG and IgM antibodies to an intracellular viral antigen • Antibody response develops after natural infection, and thus can identify patients with prior or resolved HBV • Also positive in chronic HBV but will be negative in vaccinated individuals 	HBcAb IgM	<ul style="list-style-type: none"> • Detects early IgM antibody response to HBcAg, which is most useful in the setting of acute HBV during the window period of infection (period of time between disappearance of HBsAg and appearance of HBsAb) • Should not be tested in contexts other than acute HBV
HBsAb	<ul style="list-style-type: none"> • Detects antibodies to HBsAg that develop after either natural infection or inoculation • In most immunocompetent individuals, confers lifelong immunity • Can be positive or negative in those with prior or resolved HBV • In immunocompromised individuals with prior or resolved HBV, the presence of HBsAb does not preclude HBV reactivation 	HBeAg	<ul style="list-style-type: none"> • Detects viral secretory protein that is associated with HBV replication and infectivity in chronic HBV • Should not be tested in contexts other than confirmed chronic HBV
		HBeAb	<ul style="list-style-type: none"> • Detects antibodies to HBeAg, which are associated with improvements in HBV DNA and liver disease in chronic HBV • Should not be tested in contexts other than confirmed chronic HBV

HBV: hepatitis B virus; HBsAg: HBV surface antigen; HBcAb: HBV core antibody; HBsAb: HBV surface antibody; HBeAg: HBV e antigen; HBeAb: HBV e antibody.

been successfully implemented in projects to improve HBV screening rates. Prior research has suggested that the level of physician knowledge or familiarity with HBV is correlated with appropriate screening.¹¹ In the study by Bullard et al, HBV screening improved from a rate of 60–70% to > 90%, in part due to a coordinated physician education campaign that included seminars and online learning modules.²³ These interventions were complemented by a feedback mechanism that provided clinics with their performance on HBV testing; this is an example of audit and feedback, another evidence-based strategy that allows clinicians to compare their performance to their peers or to professional standards.²⁴ The Centers for Medicare & Medicaid Services recently announced a new quality measure for US practices enrolled in the RISE registry that links appropriate HBV screening prior to b/tsDMARD initiation with financial incentives, which could further motivate clinicians and practices to adhere to quality benchmarks.

Successful quality improvement (QI) integrates diverse disciplines and roles in the healthcare system. For instance, in the studies above that improved HBV testing prior to immunosuppressive therapy, appropriate hepatitis screening was adopted by pharmacists as a criterion for administration of anti-CD20 monoclonal antibodies; the projects also collaborated with hepatologists to facilitate timely consultation and triage of patients in need of antiviral therapy.^{22,23} The spectrum of HBV

care potentially spans additional disciplines and roles in the healthcare system, including other subspecialties prescribing high-risk medications and infusion centers.

Successful QI efforts to improve drug safety, including HBV screening, have often combined several of the above strategies to optimize success. One novel approach to QI that could be applied to drug safety is the learning collaborative, in which shared quality improvement problems are tackled simultaneously by separate health systems under the guidance of content experts.²⁵ Such learning collaboratives have led to demonstrable improvements in the care of juvenile idiopathic arthritis and RA,²⁵ and could very well be critical to enhancing screening and drug safety across multiple healthcare systems.

Conclusion

In summary, the study by Mohareb et al reveals important gaps in the care of patients with rheumatic diseases initiating TCZ and TOF, with less than a third undergoing appropriate HBV testing, and a substantial number of patients tested with noninformative and nonindicated HBV tests.⁶ The study underscores the urgency of improving HBV testing in patients initiating immunosuppression; this can be achieved through various approaches to simplify and standardize screening practices. Rheumatologists should implement universal and appropriate HBV testing in patients starting immunosuppressive drugs. In addition, local

health systems must monitor their preimmunosuppression care quality, and can use any combination of evidence-based approaches to improve substandard HBV screening.

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