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Preventing Hepatitis B reactivation in immunosuppressed patients: is it time to revisit the guidelines?

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Hepatitis B virus (HBV) infection remains a serious global health concern. Approximately one third of the world's population has evidence of previous HBV infection, and 350 million people are chronic HBV carriers.[1] In the United States, the rate of new HBV infections has declined by approximately 82% since 1991, when a national strategy to eliminate HBV infection was implemented.[2] The greatest decline has been among those born since 1991, when universal vaccination of children was first recommended.[2] Despite these improvements, HBV remains prevalent in the United States; 800,000 to 1.4 million individuals are estimated to be chronic carriers.[2] Although intravenous drug users and homosexual men are at high risk for chronic HBV, most cases in the United States are in those emigrating from high prevalence areas (e.g. Asia or Africa), where early life horizontal and vertical transmission is common.[3]

Reactivation of HBV in immunosuppressed individuals has been well-documented in the literature for several decades. Reactivation can occur either at the cessation of therapy when immune reconstitution occurs, or with prolonged immunosuppression that can result in an accelerated course of HBV infection.[4-6] Most cases occur in individuals with cancer undergoing chemotherapy, where reactivation among HBV positive patients is common (e.g. >50% in some lymphoma series) and sometimes fatal.[7-18] In rheumatology, HBV reactivation has been reported with a number of disease modifying anti-rheumatic drugs (DMARDs), although the lack of large studies makes it hard to ascertain the exact risk for most drugs. However, it is increasingly apparent that newer biologic therapies, such as TNF-α inhibitors and rituximab, may pose a significant risk of HBV reactivation. Therefore, it is especially timely to take stock of how rheumatologists approach HBV in clinical practice.

In this issue of *Arthritis Care & Research*, Stine et al. report the results of a national survey of rheumatologists regarding screening for and management of HBV infection in patients initiating immunosuppressive therapies. Although only 15% of the over 1000 rheumatologists approached completed the survey, the authors' findings are nonetheless interesting and provide a useful starting place for evaluating rheumatologists' awareness of HBV and their practice patterns regarding screening and management. The study highlights areas of significant practice variation among rheumatologists, especially pertaining to screening (e.g. who is screened and which laboratory tests are used for screening), prophylaxis against reactivation, and monitoring intervals for HBV laboratories in chronic carriers receiving immunosuppressive therapies. This observed variation in physician practice patterns likely reflects a number of factors, including the lack of a strong evidence-base in some of these areas, heterogeneity among patient populations, and the absence of clear and specific guidelines regarding HBV screening and management in patients with rheumatic disease. The study also highlights several areas where quality improvement efforts should be targeted.

Screening

With regard to screening, 42% of respondents routinely screen for HBV before beginning non-biologic DMARDs and 69% before beginning biologic DMARDs. The former number is somewhat difficult to interpret as specific DMARDs were not defined, and therefore medications that carry little or no risk of causing HBV reactivation, such as hydroxychloroquine, may have figured into physicians' responses. Nevertheless, given the known risk of reactivation with most non-biologic DMARDs, these results may be a cause for concern. Almost all physicians reported screening in the presence of certain HBV risk factors (e.g. HIV, intravenous drug use, men who have sex with men). However, respondents were less likely to universally screen other well-established high-risk populations, such as individuals deriving from endemic regions or health care workers. These variations in screening highlight a limitation of identifying individuals with HBV by assessing risk factors in clinical practice: screening for risk factors may not be performed or may be incomplete. Another important limitation is that screening strategies to identify individuals at high risk may have poor predictive value, since a large percentage of infected individuals may not have easily identifiable risk factors.[19, 20] Taking these realities into consideration, we agree with the recent Centers for Disease Control and Prevention (CDC) guidelines that recommend universal screening among persons with rheumatologic disorders receiving immunosuppressive therapies.[3]

Risk awareness

The authors' findings regarding rheumatologists' awareness of drug package inserts are notable given the high percentage of respondents who were unaware or unsure of HBV screening recommendations, from a low of 19% for anakinra, to a high of 53% for rituximab. If we assume that awareness of drug package inserts is a reasonable proxy for awareness of risk, then these findings may also be a cause for concern. Evidence is very clear that rituximab can induce HBV reactivation, even in patients with remote HBV infection (HBsAg negative but anti-HBs positive),[8-10, 14, 16, 17, 21] and there have been several deaths reported from fulminant liver failure in these patients. These reports are extremely compelling, and strongly suggest that all patients initiating therapy with rituximab should be screened, regardless of the absence of risk factors. Experience with TNF-α inhibitors in patients with chronic HBV infections remains limited, but a growing number of case reports suggest that reactivation is a concern (Table). Corroborating the reports in the literature, Stine et al. found that 7.4% of the rheumatologists surveyed had also witnessed HBV reactivation with biologic DMARDs (4 cases with infliximab and 1 case with etanercept were reported). Reflecting the growing concern about HBV reactivation with these agents, in 2006, Health Canada issued a class warning regarding HBV reactivation with TNF-α inhibitors. The Food and Drug Administration (FDA) followed suit soon thereafter, and package inserts for TNF-α inhibitors now carry similar warnings.

Laboratory Testing

The authors queried rheumatologists regarding the laboratory tests routinely used to assess HBV. They did not assess which combination of tests rheumatologists use; instead they report the percentage of rheumatologists that use each of six assays (liver function tests, HBsAg, anti-HBs, anti-HBc, HBV DNA, and hepatitis panel). A vast majority of rheumatologists use HBsAg (92%), the classic assay to determine HBV infection. Somewhat surprising is the lower percentage of respondents who routinely assess anti-HBc. In recent years, the importance of this test in defining a carrier state in some individuals has become clear, with worrisome reports, such as those cited above, of individuals who were HBsAg negative reactivating their disease. Based on this literature, many experts, as well as the

recent CDC recommendations,[3] suggest that screening for HBV in patients initiating immunosuppressive therapy should routinely include HBsAg, anti-HBs, and anti-HBc. Assessment of anti-HBs is important to determine the need for vaccination in patients initiating immunosuppressive therapy. In addition, although HBV DNA was reported by 7% of respondents, this assay is not appropriate for screening. Instead, HBV DNA should be used to evaluate viral replication or response to antiviral therapy in patients with established chronic HBV infections.

Prophylaxis and Monitoring

Lastly, the survey questioned rheumatologists about prophylaxis and monitoring of individuals with HBV infection. Although avoiding immunosuppression in the setting of HBV may be preferable, poorly controlled rheumatic disease that results in reduced function, decreased quality of life, or significant morbidity and mortality, may lead physicians and patients to consider therapy. Unfortunately, experience in the form of randomized controlled trials in this area is not available. However, there is growing evidence in the literature that anti-viral prophylaxis, along with careful monitoring for HBV reactivation, may be a reasonable strategy if the patient understands the risks of this approach.[22-24] Still, the fact that most rheumatologists feel uncomfortable in this scenario is evidenced by the finding that most respondents (81%) would prefer to defer to a gastroenterologist or hepatologist to determine prophylactic therapy. Most respondents report that patients were given lamivudine, a medication that is associated with a high degree of viral resistance; many experts now recommend use of newer anti-viral agents such as adefovir or entecavir, especially if the anticipated duration of treatment is long (>12 months).[25, 26]

Revisiting the ACR Guidelines

Although assessing the effectiveness of dissemination strategies for ACR guidelines was not an explicit goal of the study by Stine et al., their findings on this topic are interesting nonetheless. The authors report that many rheumatologists in their sample were unaware of any ACR guidelines regarding screening for HBV prior to starting biologic therapy (30%) or non-biologic DMARD therapy (47%). These results are interesting given that the study was conducted several months after the publication and widespread dissemination of the ACR 2008 recommendations for the use of nonbiologic and biologic DMARDs in rheumatoid arthritis.[27] Contained in the guideline, which was developed using a validated method for combining scientific evidence and expert consensus, are several recommendations regarding HBV screening and management.

Given the lack of robust scientific evidence regarding hepatitis B screening strategies in RA patients, the recent ACR recommendations are based largely on expert consensus. For screening, the recommendations state that high-risk patients (e.g. individuals using intravenous drugs, those with multiple sex partners in the previous 6 months, health care personnel) receiving leflunomide or methotrexate should be screened for HBV. They go on to say that an appropriate evaluation *might* include tests for HBsAg, anti-HBsAg, and anti-HBc. Noticeably absent is a recommendation for HBV screening prior to starting biologic DMARD therapy. Rather than representing an omission, it is likely that the process used to establish the recommendations yielded neither enough scientific evidence nor a high enough degree of expert consensus to result in advocating specific screening practices. However, the fact that the authors grappled with the issue is apparent in another section of the guideline that lists contraindications for starting or resuming immunosuppressive therapy in RA. In that section, the authors state that *acute* infection with HBV is a contraindication to starting all DMARDS except hydroxychloroquine. For *chronic* HBV infection, the recommendations

are somewhat more complicated and based on the patients' Child-Pugh class. In patients treated with anti-viral therapy for HBV, leflunomide and methotrexate were contraindicated for all Child-Pugh classifications, and minocycline and sulfasalazine were contraindicated for Child-Pugh class C only. For untreated chronic HBV, leflunomide, methotrexate, minocycline and sulfasalazine were contraindicated for all Child-Pugh classifications, and hydroxychloroquine for Child-Pugh Class C. Biologic agents were contraindicated in all HBV patients with Child Pugh classes B or C.

In the next iteration of the ACR guideline, recommendations regarding HBV should be strengthened and simplified. We believe a major impediment to a widely understood and accepted screening strategy is the use of wording requiring an assessment of personal risk before testing. Such language (incorporated in both ACR guidelines and most package inserts) suggests that HBV risk assessment is reliable and routinely obtained. While we agree that all patients at high risk for HBV infection should be screened, it would serve the rheumatology community far better to state that all patients initiating high-risk drugs (i.e. those contraindicated in acute and chronic forms of HBV infection) should be screened with an appropriate panel regardless of predetermined risk. Screening for HBV should include HBsAg to establish the presence of chronic infection, anti-HBs to establish the need for vaccination, and anti-HBc to determine whether the patient may be an occult carrier. Consultation with a gastroenterologist or hepatologist to specify a monitoring regimen and prophylactic therapy for those with chronic HBV prior to initiating immunosuppressive therapy is also prudent.

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Table

Case reports of HBV reactivation among rheumatic patients treated with TNF-α inhibitors or rituximab

Drug	Indication	Age	Sex	Pre-treatment serology	Duration	Other Drugs	Anti-viral prophylaxis	Outcome
Infliximab[28]	RA	49	M	HBSAg+, anti-HBe+, anti-HBc+	18 months	MTX 10 mg/wk, prednisone 8 mg	No	Hepatitis (AST 336 and ALT 573, HBV DNA 1492 pg/ml). Treated with lamivudine.
Etanercept[29]	RA	62	F	HBSAg+, anti-HBe+, anti-HBc+	2 years	MP 8 mg, MTX 10-15 mg/wk, HCQ 200 mg	No	Hepatitis (AST 112 and ALT 234, HBV DNA 1590 copies/mL). Etanercept later restarted with lamivudine prophylaxis.
Etanercept[30]	RA	48	F	HBsAg+, HBV DNA-	13 months	MTX, SSZ, HCQ	No	Slight increase in transaminases; HBV DNA 514 copies/ml.
Infliximab[31]	AS	43	M	HBsAg+, HBeAg-, anti-HBe+, anti-HBc+	14 weeks (5 mg/kg)	None	No	ALT increased to 49. HBV DNA became positive. Lamivudine started and infliximab successfully continued.
Etanercept[32]	AS	73	M	HBsAg-, anti-HBs+, anti-HBc+, anti-HBe+	14 months	Prednisone 5 mg	No	AST rose to 141, ALT to 65. HBV DNA 1507 IU/ml. Treated with lamivudine. Etanercept later restarted successfully with concomitant lamivudine.
Infliximab[33]	AS	35	F	HBsAg+, HBe-, anti-HBe+, HBV DNA-	3 infusions	MTX 15 mg/week	No	Hepatitis (ALT 10 times normal; HBV DNA positive). Treated with lamivudine and infliximab successfully continued.
Infliximab[34]	AS	31	M	HBsAg+, HBe-, anti-HBe+, HBV DNA -	3 infusions (5 mg/kg)	--	No	Hepatitis (AST 457, ALT 1054, HBV DNA 3,130,000 IU/ml). Resolved with entecavir. This patient was the only patient to reactivate out of 8 HBV carriers in a population of 103 patients treated with anti-TNFα therapy.
Rituximab[21]	RA	56	F	HBsAg+, HBe-, anti-HBe+, HBV DNA 9.6×10^2 IU/ml	2 infusions (1000 mg)	--	Yes	Hepatitis (AST 110, ALT 150, HBV DNA$>1.1 \times 10^8$ IU/ml). Tenofivir added to lamivudine; transaminases normalized.
Rituximab[35]	ANCA-vasculitis	73	M	HBsAg-, Anti-HBc+	4 infusions (375 mg/m^2)	Prednisolone 40 mg	No	HBsAg+, HBV DNA$>110 \times 10^6$ IU/ml 11 months later. Patient died of renal failure; unclear if HBV reactivation contributed to decline.

RA=rheumatoid arthritis, AS=Ankylosing spondylitis, ANCA=anti-neutrophil cytoplasmic antibodies, MTX=methotrexate, MP= methylprednisolone, HCQ=hydroxychloroquine, SSZ=sulfasalazine, TNF=tumor necrosis factor.

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