Reactivation of hepatitis B virus infection in rheumatic diseases: risk and management considerations

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Abstract: In patients with rheumatic diseases undergoing immunosuppressive treatment, hepatitis B virus reactivation (HBVr) has been long recognized as a major treatment-related adverse event with substantial morbidity and mortality. Because HBVr is easily preventable with appropriate screening and monitoring strategies, and, when indicated, prophylactic antiviral treatment, awareness of this complication is of the utmost importance, especially in the era of biologic treatments. As a condition, it continues to be topical, in view of the emergence of novel classes of immunosuppressive drugs (i.e. Janus kinase inhibitors) acquiring licenses for a variety of rheumatic diseases. The class-specific risk of these agents for HBVr has not yet been determined. Moreover, ambiguity still exists for the management of patients planned to be treated with traditional agents, such as cyclophosphamide and glucocorticoids, particularly in the setting of resolved HBV infection. Clinicians in the field of rheumatic diseases should be tailoring their practice according to the host's profile and treatment-specific risk for HBVr. In this review, the authors attempt to critically review the existing literature and provide practical advice on these issues.

Keywords: hepatitis B virus, reactivation, rheumatic disease, screening, biologics, DMARD, immunosuppression

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Introduction

Hepatitis B virus (HBV) infection still poses a significant worldwide morbidity and mortality burden, despite the availability of an efficacious vaccine and antiviral treatment. The global prevalence of chronic HBV infection has been recently estimated at 3.61%,[1] and, although it seems to be in decline, approximately 887,000 deaths were attributed to HBV complications in 2015.[2] There is substantial geographical variance in the rates of chronic HBV infection, which is highly endemic in the Western Pacific (6.2%) and African (6.1%) areas, but less common in Europe (1.6%) and America (0.7%).[2] However, the streams of immigration and influx of refugees to Western Europe and North America is likely to be changing the prevalence and endemicity in these latter regions, which underlines the need for physicians to be familiar with the disease.

Most relevant studies suggest that the prevalence of HBV in patients with rheumatic disease follows the pattern of the general population. Chronic HBV infection rates in rheumatoid arthritis (RA) and ankylosing spondylitis (AS) have been estimated at 3.0% and 3.5%, respectively, whereas resolved HBV infection rate ranges between 13% and 50%.[3–5]

HBV is a partially double-stranded DNA virus that is transmitted *via* the parenteral route, and can cause acute or chronic infection. The risk of chronicity is dependent mainly on the age of the host at the time of infection, as the vast majority of infants (>90%) and only <5% of adults develop chronic HBV infection after exposure. Distinguishing between acute, chronic, past (resolved), and occult infection lies in HBV serological markers and measurement of serum HBV-DNA (Table 1 and Figure 1).[6,7]

HBV is unique in its ability to integrate its viral genome in its host's DNA by forming covalently

Table 1. HBV serology (adapted from Koutsianas and colleagues[5]).

Nomenclature for HBV infection based on biochemistry, serology and viral load						
	Acute HBV infection	**Chronic HBV infection**		**Inactive carrier**	**Past infection**	
		Chronic hepatitis			**Resolved infection**	**Occult infection**
		HBeAg (+)	**HBeAg (−)**			
HBsAg	+	+	+	+	-	−
Anti-HBc (total)	+/−	+	+	+	+	Usually +/−
Anti-HBc IgM	+	−	−	−	−	−
Anti-HBs	−	−	−	−	+/−	+/−
HBeAg	+	+	−	−	−	-
Anti-HBe	−	−	+	+/−	+	+/−
Serum HBV-DNA	Variable[a]	Usually >20,000 IU/mL[b]	Usually >2000 IU/mL[b]	Undetectable	Undetectable	Detectable (low levels)
ALT	Markedly elevated	Elevated	Elevated	Normal	Normal	Normal

[a]HBV-DNA levels are usually elevated, but may vary depending on the host's immune response and the exact timing of the test performed.
[b]The 2,000 and 20,000 IU/mL cut-offs are arbitrary values deriving from the detection limits of historical non-PCR methods of measurement. As HBV-related complications have been identified in patients with lower HBV-DNA levels, it is important to interpret HBV-DNA taking into consideration other factors (age, duration, ALT, disease stage).
ALT, alanine aminotransferase; anti-HBc, antibody against hepatitis B core antigen; anti-HBe, antibody against HBeAg; anti-HBs, antibody against HBsAg; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HBV-DNA, HBV-deoxyribonucleic acid; PCR, polymerase chain reaction.

closed circular DNA (cccDNA), which is responsible for its persistent presence in hepatocyte nuclei.[8] The virus itself does not have a direct cytopathic effect. On the contrary, hepatocellular injury is mediated by innate and adaptive immunity. A strong immune response is associated with viral clearance in acute HBV infection, but is also responsible for hepatocyte damage and fibrosis in the immune active phases of chronic HBV infection.

Hepatitis B virus reactivation
HBV reactivation (HBVr) is a well-recognized complication of immunosuppressive treatment in cancer, rheumatic diseases, and organ transplantation.[9] It typically occurs in patients with chronic HBV infection [Hepatitis B surface Antigen (HBsAg) positive], but, less commonly, it can complicate immunosuppressive treatment in patients with resolved HBV infection [HBsAg negative/antibody against Hepatitis B core antigen (anti-HBc) positive]. HBVr is usually defined as: a rise in serum HBV-DNA compared with baseline levels or detection of HBV DNA if undetectable at baseline, or reverse seroconversion (re-emergence) of HBsAg from negative to positive (see Table 2 for full definitions).[10,11] Factors that influence the risk of HBVr are related to the patient, the virus, and the type and duration of immunosuppression used (Table 3).[12]

With the expected further increase in the use of biologics and new oral targeted synthetic agents [i.e. Janus kinase (JAK) inhibitors] in treating rheumatic diseases, rheumatologists should be aware of the potential risk, the screening recommendations, and management options for prophylaxis and monitoring for HBVr.[15] The majority of the literature data around HBVr derives from the fields of hematology and oncology, where combinations of biologic and cytotoxic agents with higher immunosuppressive potential are routinely used, usually for a short period of time (months). These data need to be interpreted with caution when applied to rheumatic diseases, where the potency of immunosuppression is lower and the duration of therapy longer (years).
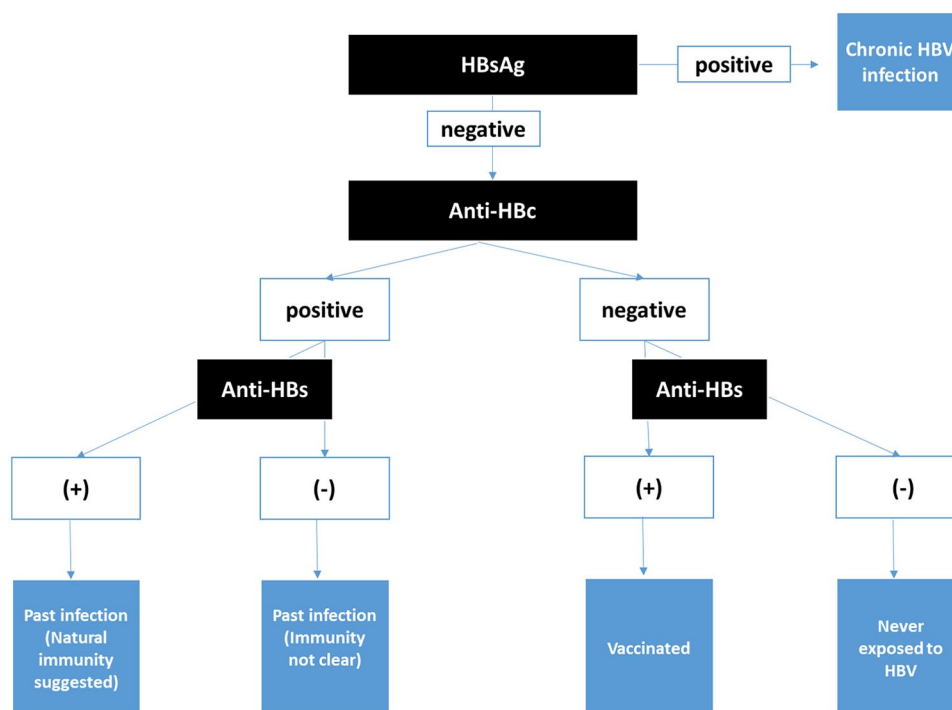
Figure 1. Serologic screening for HBV and interpretation of results.
anti-HBc, antibody against hepatitis B core antigen; anti-HBs, antibody against hepatitis B surface antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

Table 2. HBV reactivation definitions (literature data).[6,10]

Definition	Population	Baseline serum HBV DNA	Change in virological, serological or biochemical markers during therapy
Virological	HBsAg (+) Anti-HBc (+)	(+)	↑ of HBV DNA by ≥2 logs$_{10}$ (100-fold)
		(−)	HBV-DNA: ≥1000 IU/mL (3 logs)
		Unknown	HBV-DNA: ≥10,000 IU/mL (4 logs)
	HBsAg (−) Anti-HBc (+)	(−)	Detectable HBV DNA (+)
Serological 'reverse seroconversion'	HBsAg (−) Anti-HBc (+)		HBsAg (+)
Biochemical 'hepatitis flare'	All		↑ of ALT by ≥3× from baseline levels + ALT ≥ 100 IU/mL + No other explanation possible

ALT, alanine aminotransferase; anti-HBc, antibody against hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

In a recent meta-analysis for the prevalence of HBVr in rheumatic diseases being treated with conventional or biologic agents, the pooled HBVr estimate was 1.4%, thus much lower than the relevant estimation in hematology/oncology.[16]

In recent years, there has been an effort to stratify HBVr risk according to the patient's serological status and the type and duration of the immunosuppressive treatment used. The American Gastroenterological Association (AGA) classified

Table 3. Risk factors for HBV reactivation (literature data).[12–14]

Host factors	Male sex Older age Cirrhosis Type of disease needing immunosuppression (lymphoma) Co-infection status (e.g. HCV, HIV, HDV)
Virological factors	High baseline HBV-DNA Chronic HBV infection HBeAg positivity Non-A HBV genotype
Immunosuppression	Type Duration (see main text for details)

ALT, alanine aminotransferase; anti-HBc, antibody against hepatitis B core antigen; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HBV-DNA, HBV-deoxyribonucleic acid; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus.

HBVr risk as low (<1%), moderate (1–10%), and high (>10%) based on the above factors.[17] However, the emergence of new agents and the long duration of biologic treatments, especially in rheumatic diseases where there usually are no set stopping rules for treatment, pose further controversy on HBVr management and monitoring guidance.

In the current paper, we will critically review the existing literature on HBVr risk in patients with rheumatic diseases treated with different biologic and nonbiologic agents, and provide practical advice for its prevention and management.

Type of immunosuppression and HBVr risk and management

Glucocorticoids

Glucocorticoid (GC) use in patients with HBV infection was known to relate to HBVr as early as the 1970s,[18] although its reported incidence varies significantly in the published literature (4–50%). The proposed pathophysiological mechanism seems to be twofold: GCs suppress T-cell cytotoxic function, thus diminishing the host's immune check on the virus, but also directly stimulate HBV-DNA replication by activating a GC-responsive transcriptional regulatory element in the HBV genome.[17,19]

There is robust literature evidence that even short courses of more than moderate-dose GC treatment in chronic HBV infection can lead to HBVr.[17,20–22] Chemotherapy for chronically HBV-infected patients with lymphoma was less likely to cause HBVr in 9 months if it did not contain GCs (38% *versus* 73% if containing prednisolone).[23] An HBVr incidence rate of 6.1% has been reported in chronic HBV patients with asthma or chronic obstructive pulmonary disease (COPD) receiving GCs. The risk was higher among patients receiving systemic GCs, especially when they were used continuously (for at least 3 months) and in medium to high (>20 mg/day) doses.[24] Patients with chronic HBV infection and rheumatic diseases are also at risk for HBVr and hepatic flare when treated with GCs. For patients not receiving antiviral prophylaxis, and especially when GCs are used in combination with conventional and biologic agents, the hazard ratio (HR) has been reported at 5.1.[25] Peak doses of >40 mg prednisolone equivalents were associated with an adjusted HR for HBVr of 1.64.[26] HBVr risk is higher depending on the patient's HBV status (i.e. chronic hepatitis *versus* inactive carrier state), on the continuous oral GC use *versus* intravenous (IV) pulses[27,28] and on the GC dose used.[29,30]

With regards to IV GC pulse therapy in HBsAg positive patients, data are limited and confounded by the concomitant use of other immunosuppressives and the continued use of oral GCs after the IV pulses. A small retrospective study showed no increased HBVr risk for low dose GC pulses (12.5–100 mg/day) given for up to 1 week,[27] whereas, on the contrary, a retrospective Taiwanese study revealed a HBVr rate of 15% (11/72) in patients treated with IV GC pulses (625–750 mg/day) for 3 days.[28] These data should be interpreted with caution, since most of these patients

continued therapy with oral GCs (mean daily dose = 23 mg) and other immunosuppressives (biologics or non-biologics).[28] Recent AGA guidelines do not offer any specific recommendations regarding patients treated with IV GC pulses due to the absence of data, but note that any GC dose given for <1 week is considered low risk (<1%), and, thus, no antiviral prophylaxis is recommended.[17]

There is a relevant paucity of data looking into the effect of GC in HBVr risk specifically for patients with resolved HBV infection, but certainly this risk seems to be lower than in chronic HBV infection. In a retrospective Chinese study of a large HBsAg negative/anti-HBc positive population treated with at least one dose of systemic GCs for all indications, the incidence rate of HBsAg seroreversion was 1.8% at 1 year and 5.5% at 10 years. GC peak daily dose >20 mg prednisolone equivalents and treatment duration for >4 weeks were independent risk factors for a hepatitis flare but not for HBsAg seroreversion.[31] The authors could not identify studies from geographical areas with less prevalent HBV infection to confirm this relatively high HBVr rate.

GC use at the doses needed for adrenal insufficiency has been reported to be safe, and does not increase the risk for HBVr.[32]

Based on the aforementioned data, guidance from AGA and expert advice suggests that daily doses of GCs >20 mg prednisolone equivalents for treatment durations >4 weeks should be considered as having at least moderate risk for HBVr and warrant antiviral prophylaxis in HBsAg positive patients.[17,33] On the contrary, the risk is low in HBsAg negative/anti-HBc positive patients and monitoring, rather than prophylaxis treatment, is advised.

Non-biologic agents
Methotrexate and other conventional synthetic disease-modifying antirheumatic drugs. Methotrexate (MTX) is an inhibitor of folate metabolism, and has served as the anchor drug for RA for several decades, while it is also frequently used in the management of other rheumatic diseases [spondyloarthropathies, systemic lupus erythematosus (SLE), vasculitis, myositis, scleroderma, etc.]. MTX is associated with direct acute (hepatitis) and more rarely with chronic (fibrosis) hepatotoxicity. With appropriate pre-treatment screening and regular monitoring, these events are rarely seen today.

In a retrospective analysis of a Thai population with rheumatic diseases being treated with MTX for an average of 9.9 years, no cases of HBVr or hepatitis flares were identified,[34] whereas in a similar data analysis from a national Taiwanese health database, no increased risk of liver cirrhosis was seen (compared with non-users of MTX).[35]

With regards to other non-biologic agents such as leflunomide (LEF), sulfasalazine (SSZ), hydroxychloroquine (HCQ), and azathioprine (AZA), cases of HBVr are extremely rare, and these drugs should be generally considered safe.[17] In a recent prospective study of chronically HBV-infected RA patients treated with MTX, LEF, SSZ, or HCQ without antiviral prophylaxis, only 4/211 (1.8%) developed HBVr; all 4 patients were also receiving GCs, and, thus, the exact contribution of these agents to HBVr is unclear.[36] Similarly, among patients with rheumatic disease and resolved HBV infection taking part in a large prospective multicenter study, use of MTX was not associated with increased risk for HBVr (RR = 0.4).[37]

Overall, MTX and the other non-biologic agents should be considered as low risk treatment for HBVr in patients with both chronic and resolved HBV infection. Nevertheless, for those agents with potential direct hepatotoxic effect (MTX, LEF), appropriate monitoring precautions should always be in place.

Mycophenolate mofetil. Mycophenolate mofetil (MMF) is an oral inhibitor of *de novo* purine synthesis in lymphocytes, and is prescribed for a variety of approved and off-label indications in rheumatology, such as SLE, ANCA-associated vasculitides (AAV), scleroderma, etc. No clear association between MMF administration and HBVr has been identified so far. Interestingly, earlier *in vitro* data supported an inhibitive effect of MMF on replication of several viruses, HBV included,[38,39] whereas other clinical studies in solid organ transplant recipients exhibited neutral impact of MMF on HBV replication.[40,41]

While data from the rheumatology field are limited, Li and colleagues compared a standard prednisone regimen (1 mg/kg daily) *versus* MMF (500–1000 mg twice daily) and lower prednisone dose (0.5 mg/kg daily) in HBsAg-positive patients with idiopathic nephrotic syndrome and 'undetectable' HBV-DNA (<1.000 copies/mL).[42] HBVr

(defined as HBV-DNA >1.000 copies/mL) during follow up was recorded in 64% (14/22) and 37% (7/19) of patients on standard prednisone monotherapy and MMF/lower prednisone combination, respectively ($p = 0.047$), highlighting the role of high GC doses in the replicative potential of HBV. In a retrospective study of SLE patients with chronic or resolved HBV infection from Taiwan, MMF was not found to be among risk factors for HBVr.[43]

Taking into account the available data, one can conclude that MMF carries a low risk for HBVr, similar to that of other conventional synthetic disease modifying antirheumatic drugs (csDMARDs).

Cyclophosphamide. Cyclophosphamide (CYC)-containing regimens have been recognized among those carrying the highest risk for HBVr in patients with hematological malignancies. In this particular context, however, CYC is administered in combination with other cytotoxic drugs implicated in HBVr (i.e. doxorubicin), and the resulting state of immunosuppression cannot be compared with that of rheumatic patients treated with CYC. For the majority of circumstances in rheumatology, CYC is prescribed alongside GCs for induction of remission in patients with severe manifestations of SLE and systemic vasculitides, such as AAV, polyarteritis nodosa (PAN), and CNS vasculitis. Whereas things are more-or-less clear-cut with patients with chronic HBV infection being candidates for prophylactic antiviral treatment, data on the management of rheumatic patients with resolved HBV infection planned to be treated with CYC-containing regimens remain scarce. In a large cohort of 2054 rheumatic patients,[44] (anti-HBc positive: 5%, $n = 183$ with vasculitis), eight cases of HBVr were recorded, but only one occurred in a patient with granulomatosis with polyangiitis (GPA) treated with CYC.

The kinetics and outcomes of HBVr in various immune-mediated inflammatory diseases from a wide spectrum of medical specialties were described in a French study combining physician-collected and published patients.[45] The authors included a total of 138 HBV-infected patients, most with chronic HBV infection ($n = 99$, 72%); among them, 11 (8%) had been treated with CYC and experienced HBVr. CYC-induced HBVr occurred earlier than that associated with rituximab (RTX) or tumor necrosis factor inhibitors (TNFi) (8 *versus* 13 *versus* 26 weeks, respectively, $p = 0.009$).

Lin *and* colleagues reported HBVr rates in a cohort of 195 SLE patients who were treated with GCs and various immunosuppressives (including CYC) with chronic ($n = 38$) or resolved ($n = 157$) HBV infection.[43] Among 34 patients with chronic HBV infection not on antiviral prophylaxis, HBVr occurred in 15 (44%), whereas in contrast, only 3 (1.9%) patients with resolved infection experienced HBsAg seroreversion. However, in multivariate analysis, CYC was not associated with increased HBVr risk, and the main driver of HBVr in this cohort was an average prednisolone daily dose of >5 mg.

From these limited data, it appears that the risk for HBVr in CYC-containing schemes is high, and occurs relatively early in HBsAg positive patients, while the respective risk in patients with resolved HBV infection is rather low. Prophylactic antiviral prophylaxis should be used for the former group. We believe that current evidence does not support universal antiviral protection for patients with resolved HBV infection prior to induction of remission with CYC-containing regimens.

Biologic disease-modifying antirheumatic drugs
TNFi. TNF inhibition has revolutionized the treatment of several rheumatic diseases since the late 1990s. When it comes to HBV infection, however, TNFα is an important cytokine to assist in the eradication of the virus from the liver. Low levels of TNFα have been associated with reduced cytotoxic CD8+ responses against HBV and TNFα neutralization may favor HBVr.[46]

The risk of HBVr in chronic HBV infection patients receiving TNFi has been identified and is well described in several publications. Incidence rates of HBVr in chronically HBV infected patients who did not receive antiviral prophylaxis range between 7.1% and 75% in the setting of rheumatic diseases.[25,47–54] Most HBVr cases were associated with a hepatitis flare and in their majority they appeared within the first year of TNFi treatment. Nucleos(t)ide analogue treatment at the time of HBVr usually results in prompt control of the HBV replication and improvement of the hepatic function, although there have been cases of severe liver injury and hepatic failure despite antiviral treatment at the time of HBVr. It has been also shown that antiviral treatment is efficacious in preventing HBVr as supported by the negligible rates of HBVr in this setting.[5]

On the contrary, it seems that the HBVr risk in resolved HBV infection patients treated with TNF inhibitors is significantly lower.[47–49,52,55,56] In a recent meta-analysis of 468 published HBsAg negative/anti-HBc positive rheumatic patients treated with TNFi, Lee and colleagues reported an HBVr incidence rate of 1.7%.[57] Similarly, in a prospective multicenter Italian study,[58] no cases of HBVr were found among 146 resolved HBV infection patients treated with TNFi for a mean period of 56 months, whereas in a prospective Japanese study, the respective rate of HBVr was 4% (8/199).[37] It is unclear why these differences in HBVr between European and Asian studies exist, but it could be due to different states of the underlying HBV infection (occult *versus* resolved) or due to different HBV strains.

On the basis of these data, TNF inhibition in patients with chronic HBV infection (HBsAg+) carries a significant HBVr risk and it is recommended that all patients receive appropriate oral antiviral prophylaxis with the newer antiviral agents (entecavir, tenofovir). However, in patients with resolved HBV infection, the HBVr risk is rather low, and careful monitoring of aminotransferases (AST, ALT) with prompt HBV-DNA measurement in the case of their elevation should be sufficient in managing these patients.

RTX and other B-cell depleting therapies. Anti-CD20 agents (rituximab, ofatumumab, ocrelizumab) are monoclonal antibodies targeting CD20, a surface cell antigen of B lymphocytes. The immune complexes formed after their binding are recognized and destroyed by phagocytes, thus leading to B-cell depletion. RTX has been used for various rheumatic diseases including RA, AAV, cryoglobulinemic vasculitis, and off-label for several connective tissue diseases including SLE, scleroderma, myositis, and Sjögren's syndrome.

The observation that anti-CD20 monoclonal antibodies can cause HBVr dates back to more than 20 years ago. So far, 183 RTX-associated HBVr cases were identified in a medical literature search between 1997 and 2009.[59] This eventually led to the addition of a black box warning for HBVr risk to the RTX product label.[60] Once again, the majority of studies of HBVr in HBsAg-positive patients derive from the hematology and oncology literature.[61,62] In studies looking into the benefit of using antiviral prophylaxis in chronic HBV infection patients receiving RTX-containing regimens, the HBVr rate was as high as 53%, but was essentially nullified by the use of lamivudine or entecavir. [63–65]

In the setting of rheumatic diseases, the available HBVr data for HBsAg-positive patients receiving immunosuppression without antiviral prophylaxis is scarce, but the HBVr risk should be considered as high. Overall, it should be considered that there is robust data to support that RTX use in chronic HBV infection is associated with very high HBVr rates (30–60%)[17,33] and antiviral prophylaxis is warranted. There is also evidence that, in the setting of rheumatic disease, the duration of immunosuppression should be taken into account when choosing the agent for antiviral prophylaxis, as there are case reports of virological escape with the use of drugs with low genetic barrier (e.g. lamivudine).[66] Third-generation antiviral agents with high genetic barrier (entecavir, tenofovir) should be used.

In comparison with other biologic agents, RTX has been associated with high HBVr rates also in patients with resolved HBV infection.[63,67–71] In their technical review, which supported the AGA guidelines, Perrillo and colleagues calculated a pooled baseline risk estimate of HBVr at 16.9% in this group of patients, which was based on hematology/oncology studies.[17] However, in prospective or retrospective studies with patients suffering with rheumatic diseases, the rate of HBVr under RTX therapy was much lower (6/266 patients or 2%).[58,72–76] Interestingly, the majority of reported patients with HBVr (4/6) came from a high-incidence HBV country (Taiwan).[76]

Although it remains an area of controversy, the authors believe that in patients with resolved HBV infection and undetectable baseline serum HBV-DNA, serial monitoring of aminotransferases, HBsAg, or serum HBV-DNA is a preferable alternative to long-term commitment to antiviral prophylaxis.

Abatacept. Abatacept (ABA) is a fusion protein composed of the Fc portion of the immunoglobulin IgG1 fused to the extracellular domain of CTLA-4; ABA acts by binding to the CD80/CD86 molecule, thus inhibiting the activation of T-cells by an antigen-presenting cell. The agent has been approved for RA and psoriatic arthritis, and there are ongoing trials for other rheumatic diseases (giant cell arteritis, polymyalgia rheumatica, myositis).

The HBVr risk for chronically infected HBV patients on ABA treatment has been explored only in small retrospective studies. In a study by Kim and colleagues,[77] four of eight HBsAg positive patients who did not received prophylaxis developed HBVr after a mean period of 10.5 months. An Italian retrospective multicenter study collected data on 72 RA patients treated with ABA who had either chronic or resolved HBV infection.[78] All of the chronically infected patients received antiviral prophylaxis. No HBVr cases were identified in either group.

In the setting of resolved HBV infection, a few case reports of HBVr cases have been published.[79,80] Three cases of HBVr in a recently studied Japanese cohort were reported on resolved HBV infection patients treated with ABA (total $n = 29$, 10.3%).[81] In another study, among 24 patients with resolved HBV infection on ABA treatment, three cases of HBVr were reported (12.5%),[37] but these were mild elevations of HBV-DNA without overt hepatitis and without the need to use antivirals. Reassuringly, no HBVr cases were observed among the nine resolved HBV infection patients treated with ABA in the prospective trial by Barone and colleagues.[58] Considering the high number of patients who have been treated with ABA since its approval, cases of HBVr in resolved HBV infection appear to be rare, especially in geographical areas with lower prevalence, such as Europe and the United States.

Taken together, these data would suggest that, in ABA-treated HBV patients with rheumatic disease, there is a need for antiviral prophylaxis in chronic HBV infection, but close monitoring in resolved HBV infection seems to be a safe alternative.

Interleukin-6 inhibitors. Inhibition of interleukin (IL)-6 provides a new mechanism of action for the treatment of rheumatic disease, and two agents have been approved for use in RA and systemic Juvenile Idiopathic Arthritis (sJIA) (tocilizumab-TCZ, sarilumab) and giant cell arteritis (GCA; tocilizumab) with several others being investigated. Most of the available HBVr relevant data is limited,[82] and focus on the use of TCZ, which is a humanized IgG1k monoclonal antibody against the soluble and membrane forms of the IL-6 receptor that inhibits the characteristic signalling pathway of IL-6, a pleiotropic cytokine.

There are only few case reports and small studies showing that HBVr can occur with TCZ therapy in patients with chronic HBV infection without antiviral prophylaxis.[25,83–86] In all published data, the use of antivirals prevented HBVr in this setting. In rheumatic patients with resolved infection, HBVr is rare,[58,87] and has been reported only in the form of transient HBV viremia.[37,88]

Similarly to ABA and TNFi, antiviral prophylaxis is warranted for HBsAg-positive patients, whereas aminotransferase monitoring (with HBV-DNA measurement in the case of AST or ALT elevation) is sufficient for HBsAg negative/anti-HBc positive patients.

Interleukin-17 inhibitors. IL-17 inhibitors have recently been approved for the treatment of psoriasis, psoriatic arthritis, and axial spondyloarthropathy. As patients with HBV infection were excluded from the initial controlled clinical trials for these novel agents, data regarding their potential for HBVr are scarce.

There are few case reports and case series showing no safety signals for HBVr with secukinumab (a human IgG1k anti-IL17A monoclonal antibody)[89–92] or ixekizumab (a humanized monoclonal anti-IL17A antibody).[93,94] The risk for HBVr with secukinumab was studied in a multicenter prospective cohort study of 49 Taiwanese patients with either chronic or resolved HBV infection. Among those with chronic HBV infection who did not receive antiviral prophylaxis, 27% (6/22) developed virological HBVr without a hepatitis flare, while the respective rate of virological HBVr in those with resolved HBV infection was 4% (1/24).[95]

In the absence of solid data showing that IL-17A inhibition is associated with a substantial increase in HBVr risk, an approach similar to that used with other biologic agents is suggested.

Interleukin-12/23 inhibitors. Ustekinumab is a fully human IgG1 monoclonal antibody that inhibits the p40 subunit of both IL-12 and IL-23, rendering them unable to bind to their receptors. It has been approved for psoriasis, psoriatic arthritis, and inflammatory bowel disease (Crohn's disease, ulcerative colitis).

Several case reports and two retrospective studies have looked into HBVr risk in patients treated

with ustekinumab. In a single-center Taiwanese retrospective cohort,[96] 11 chronic HBV and 3 resolved HBV infection patients with psoriasis received ustekinumab. HBVr was observed in two of the seven chronic HBV infection patients who did not receive antiviral prophylaxis; in both cases the HBVr was mild and only virological, without biochemical hepatitis. In a similar Asian study by Ting and colleagues of 54 psoriasis patients treated with ustekinumab,[97] the rate of HBVr was 17% for chronically infected patients and 1.5% for those with resolved infection.

Based on these data, it appears that the risk for HBVr with ustekinumab is similar to that of TNF inhibitors and the advice on prophylaxis and monitoring is the same.

Interleukin-23 inhibitors. Novel anti-IL23 agents, such as guselkumab, risankizumab, and tildrakizumab have been approved for the treatment of psoriasis and are currently under investigation for psoriatic arthritis. No literature data on their use in the setting of HBV infection are available and, thus, no relevant recommendations exist.

csDMARD and biologic disease-modifying antirheumatic drug combinations. The question of whether csDMARD and biologic disease-modifying antirheumatic drug (bDMARD) combination treatment in rheumatic patients carries higher risk for HBVr compared with bDMARD monotherapy has not been specifically addressed in the published literature. In a retrospective study by Chen and colleagues looking into HBsAg positive patients treated without antiviral prophylaxis, there was no significant difference in HBVr risk when comparing csDMARD monotherapy to csDMARD and bDMARD combination treatment.[25] The majority of bDMARD agents used were TNF inhibitors (26/36, 72%).

Oral targeted therapies
JAK inhibitors. JAK inhibitors belong to a novel class of targeted synthetic agents that were recently introduced into daily clinical practice for treatment of RA, psoriatic arthritis, and ulcerative colitis. JAK inhibitors have a unique mode of action, inhibiting production of various pro-inflammatory cytokines from T-lymphocytes and dendritic cells.[98] To date, three agents of this family have been approved for use in RA (tofacitinib, baricitinib, and upadacitinib), with another currently under investigation (filgotinib). As for psoriatic arthritis, tofacitinib is the only JAK inhibitor currently approved for use after methotrexate or other csDMARD failure. Data for their HBVr potential are rare, given that these agents' pivotal clinical trials excluded patients with evidence of chronic or resolved HBV infection.

Two recent studies attempted to investigate the risk for HBVr with JAK inhibitor use. In a retrospective cohort of 116 tofacitinib-treated RA patients from Taiwan, 6 (5%) had chronic and 75 (65%) resolved HBV infection.[99] Two of the HBsAg positive patients were prophylactically treated with antivirals upon tofacitinib initiation and did not experience HBVr. Amongst the four HBsAg-positive patients not treated with antivirals, two had HBVr after 6 and 12 months of tofacitinib therapy, with one having only virological and the other virological and biochemical reactivation. Both were being cotreated with low-dose corticosteroids (5 and 10 mg of prednisolone daily, respectively). Patients who were HBsAg negative/anti-HBc positive did not experience HBVr.

Harigai and colleagues studied the effect of baricitinib in RA patients with past HBV infection in a *post hoc* analysis of baricitinib clinical trials.[100] They included 269 patients, 255 of whom were anti-HBc positive/antibody against hepatitis B surface antigen (anti-HBs) positive and 14 anti-HBc positive/anti-HBs negative. Among the former group, seven (3%) patients had detectable baseline HBV DNA (median viral load 256 IU/mL), while among the latter group, one (7%) had marginally detectable HBV viral load (36 IU/mL). From the total of eight patients with detectable baseline HBV DNA, half discontinued baricitinib, and three out of four were treated with antivirals. The remaining four patients continued baricitinib without antivirals. None of those patients experienced clinical or biochemical hepatitis.

From these preliminary data, a profile of JAK inhibitors similar to that of anti-TNFs is emerging with regards to HBVr. Thus, the aforementioned strategy should also be used in this patient population.

Role of anti-HBs titers in HBVr rates. In a significant proportion (73–84%) of patients with resolved HBV infection (HBsAg negative/anti-HBc positive), circulating anti-HBs antibodies can be detected in the serum.[101,102] A number of

retrospective studies in hematology and oncology patients have shown that the presence of anti-HBs antibodies reduces the risk for HBVr during chemotherapy (including RTX-containing regimens).[68,103,104] The results of these studies were corroborated by a relevant meta-analysis of 20 studies looking into the role of anti-HBs levels in HBVr risk of patients with hematological malignancy, which found that the presence of detectable anti-HBs reduced HBVr [pooled odds ratio (OR) = 0.21], even in patients with lymphoma receiving RTX chemotherapy.[105]

Similar data have been reported in rheumatic patients with resolved HBV infection treated with different immunosuppressives and prospective studies support the predictive value of anti-HBs. Over a period of 4 years, 380 rheumatic patients on biologic therapy from a single Chinese center were identified as having resolved HBV infection, and were classified according to anti-HBs levels to 'negative' (<10 IU/mL), 'low' (10–100 IU/mL), and 'high' (>100 IU/mL) groups. There were no HBVr cases in the 'high' group, whereas cases of transient HBV viremia were seen in the both the 'low' (2.5/100 person-years) and 'negative' group (4.7/100 person-years).[106] Among 1042 Japanese patients with rheumatic diseases and resolved HBV infection who received both conventional and biological treatments, HBVr incidence was overall low (1.93/100 person-years), but increased to 4.32/100 person-years in anti-HBc positive/anti-HBs negative patients. The risk ratios for HBVr were 2.8 and 3.1 for anti-HBs titres below the median (71.4 IU/mL) and the cut-off for detection (<10 IU/mL), respectively.[37]

Finally, a meta-analysis of HBVr in studies of patients with resolved HBV infection from all medical fields showed that the total pooled rate of HBV reactivation was lower in patients with positive anti-HBs (5.2% *versus* 17.0%; RR: 0.29).[107]

Overall, these (mainly retrospective) data suggest that the presence of anti-HBs antibodies in patients with resolved HBV infection, especially when present in high titers (>100 IU/mL), significantly decreases the risk for HBVr after immunosuppressive therapies. Physicians should be vigilant in the care of patients with isolated HBc positivity when high risk treatments are used. Nevertheless, in the absence of prospective data from randomized trials showing that patients with high anti-HBs titers do not need appropriate monitoring, or, in certain cases, antiviral prophylaxis for HBVr, we cannot currently recommend serial anti-HBs measurements replacing monitoring with serum HBV DNA.

Recommendations for HBVr screening and management

Screening
The valued benefit of screening for HBV infection prior commencing immunosuppressive treatment has been established in several medical society guidelines. Increasing physician awareness for the risk of HBVr has improved clinical outcomes in the past,[108] whereas, with appropriate screening, up to 80% of HBVr could be preventable.[45]

The cost-effectiveness of HBV screening has been studied in several studies from the hematology-oncology field, where a universal screening strategy was found to be cost-effective in studies with patients having solid tumors and hematologic malignancies before chemotherapy.[109,110] A tool for HBV risk calculation was used in a US cohort with hematologic or solid malignancies,[111] and it seemed to improve cost-effectiveness by screening high-risk patients only. We were unable to identify similar studies assessing HBV screening cost-effectiveness in rheumatic patients prior to immunosuppression.

Given the increased risk of HBVr associated with the immunosuppressive potency of the treatment used, we recommend universal screening in patients scheduled to start biologic and targeted synthetic DMARD therapy, as well as moderate to high doses of glucocorticoids for prolonged periods (>4 weeks duration). For conventional DMARDs, the risk of drug-related hepatotoxicity should be also of concern (especially for methotrexate and leflunomide) and, thus, screening should be performed in all patients.[5] A suggested algorithm for screening and interpretation of results is presented in Figure 1.

The authors support the inclusion of anti-HBs in the serological screening markers (HBsAg, anti-HBc) as suggested by recent American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) guidelines,[10,11] in order to identify cases that may benefit from initial or booster vaccination, but also cases of occult HBV infection in

anti-HBs positive patients that have not been vaccinated in the past and have lost their anti-HBc.

Vaccination

Vaccination still remains the most effective intervention for prevention of acute and chronic HBV infection. The available vaccine containing recombinant HBsAg shows excellent efficacy in younger individuals (90% in those <40 years old); however, these responses could be attenuated in older persons.[112,113]

A screening algorithm that includes HBsAg, anti-HBc, and anti-HBs (Figure 1) is capable of identifying rheumatic patients not exposed to HBV [HBsAg/anti-HBc/anti-HBs(–)], and a complete series of vaccination should be offered to those at risk of HBV exposure according to their occupation, medical status, or sexual behavior. The complete vaccination schedule with the recombinant HBsAg vaccine consists of three doses (20 μg per dose) administered at 0, 1, and 6 months. Patients on dialysis should be vaccinated with high-dose (40 μg) vaccines with the same time intervals.[114]

A new two-dose HBV vaccine was recently approved by the United States Food and Drug Administration (FDA) and is already recommended by Advisory Committee on Immunization Practices (ACIP) for individuals >18 years. This vaccine includes a novel oligonucleotide adjuvant that activates the toll-like receptor 9 (TLR-9) pathway and has been shown to have higher vaccine efficacy compared with recombinant vaccine, even in difficult populations, such as patients with diabetes.[115,116] To date, data on the efficacy and safety of this novel vaccine in rheumatic patients are lacking.

Management

The management of HBVr (Figure 2) should be based on individual HBVr risk according to the patient's HBV status (chronic or resolved infection), but also on the HBVr potential of the immunosuppressive treatment used (Table 4).

Patients who are at moderate or high risk of HBVr should be considered candidates for prophylactic antiviral treatment. Unlike in the oncology field, in the setting of rheumatic disease, immunosuppressive treatment is usually used for prolonged periods of time, even lifelong. Thus, there is need for enduring and potent control of viral replication with negligible drug resistance. Given lamivudine's low genetic barrier and potential development of drug resistance (ranging from 24% in the first year up to 70% at 5 years),[11] currently the newer nucleos(t)ide analogues (NAs) with high barrier to genetic resistance, such as entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) are the antiviral agents of choice (Figure 2).[10,11]

The ideal timing for commencing antiviral prophylaxis, especially in the setting of high baseline viral loads, is 1–2 weeks before starting immunosuppressive treatment.[15] If delaying the start of immunosuppression is not feasible, antivirals should be started as soon as possible. From the available literature data on the timing for cessation of prophylaxis, the suggestion is to continue with prophylactic treatment for at least 6 months after the end of antirheumatic treatment (12 months if that treatment is RTX). Reaching the therapeutic endpoint as per hepatology guidelines should guide the decision for stopping NAs when they are used for treating chronic hepatitis B rather than for prophylaxis of reactivation.[10,11]

For patients that are identified as never been exposed to HBV (HBsAg/Anti-HBc/Anti-HBs–), HBV vaccination should be considered and offered to the patient. This has greater value in patients in high risk groups, including patients with high-risk sexual activity, sexual partners and household contacts of HBV-infected individuals, injectable drug users, hemodialysis patients, health care workers, and patients from endemic areas. The vaccination should ideally take place before commencing immunosuppression, especially if this is B-cell depleting treatment.[113]

Patients with chronic HBV infection (HBsAg+) form the group with the highest HBVr risk. Decisions about managing these patients should be always taken after consulting a specialist with experience in treating HBV infection (gastroenterologist, hepatologist, infectious disease specialist, etc.).

In chronic active hepatitis B (elevated ALT and HBV DNA levels, or at least moderate liver necroinflammation) or cirrhosis, patients should be treated with antiviral therapy according to the most recent liver societies' guidelines,[10,11] regardless of their administered immunosuppressive therapy.
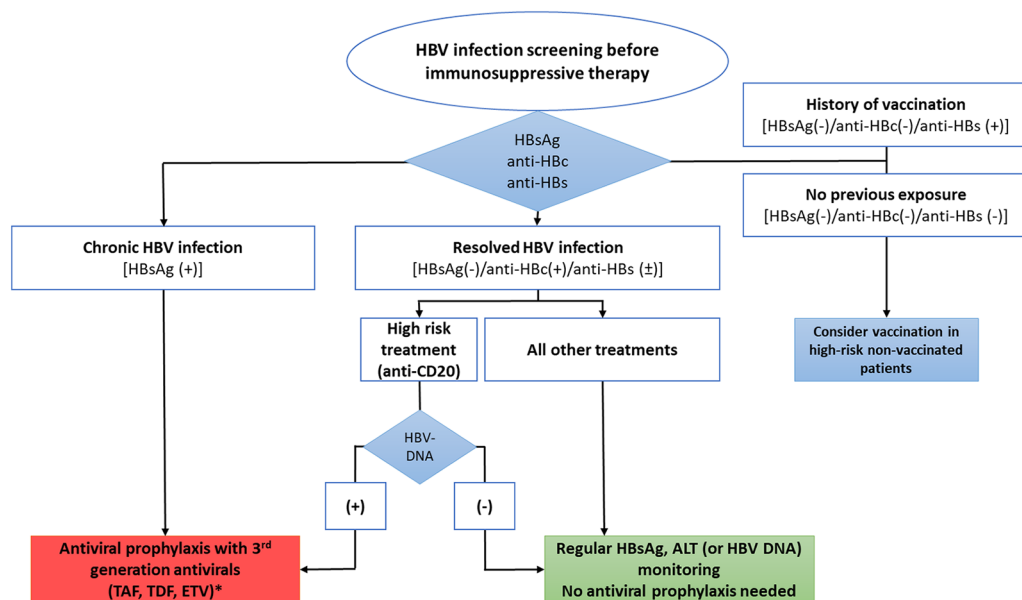
Figure 2. Suggested algorithm for the management of HBVr in rheumatic diseases.
*In certain cases, close monitoring without antiviral therapy may be chosen after appropriate consultation. See text for details.
ALT, alanine aminotransferase; anti-HBc, antibody against Hepatitis B core antigen; anti-HBs, antibody against HBsAg; ETV, entecavir; HBsAg, hepatitis B surface antigen; HBV-DNA, HBV-deoxyribonucleic acid; HBVr, hepatitis B virus reactivation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Table 4. Risk of HBVr stratified per HBV status and agent used.

Medication	Chronic HBV infection [HBsAg (+)]	Resolved HBV infection [HBsAg (−) / anti-HBc (+)]
GCs		
GC >20 mg/day and >4 weeks	Moderate	Low
Nonbiologics		
MTX, AZA, MMF, LEF, HCQ	Low	Low
CYC	Moderate	Low
Biologics		
TNFi	Moderate	Low
RTX	Very high	Moderate
ABA	Moderate	Low
IL-6 inhibitors	Moderate	Low
IL-17 inhibitors	Moderate	Low
IL-12/23 inhibitors	Moderate	Low
Oral targeted therapies		
JAK inhibitors	Moderate	Low

ABA, Abatacept ; anti-HBc, antibody against Hepatitis B core antigen; AZA, azathioprine; CYC, Cyclophosphamide; GC, glucocorticoids; HBsAg, Hepatitis B surface antigen; HCQ, hydroxychloroquine; IL, interleukin; JAK, Janus kinase; LEF, leflunomide; MMF, mycophenolate mofetil; MTX, methotrexate; RTX, Rituximab ; TNFi, tumor necrosis factor inhibitors.

For inactive HBV carriers (normal ALT, low or undetectable HBV DNA, minimal liver necroinflammation, and no fibrosis), the exact risk with the different immunosuppressive regimens has been difficult to discern due to the lack of prospectively collected, high-quality data. AASLD and EASL recommend antiviral therapy for all patients with at least detectable HBV DNA levels.[10,11]

Taking into account the chronic nature of immunosuppression in most rheumatic patients, the unknown real risk conferred with these agents and the need for repeated laboratory monitoring (including HBV DNA measurement) in these patients, we believe that all such patients should receive long-term prophylactic antiviral therapy with the newer antivirals (as for patients with chronic hepatitis B). In individual patients (i.e. those scheduled for short term GCs: <1 month or treated with low risk nonbiologics such as AZA, SSZ, HCQ), close monitoring with frequent monitoring of ALT and HBV DNA levels may by chosen, after appropriate consultation with an HBV specialist.

The issue of antiviral prophylaxis in rheumatic patients with resolved HBV infection (HBsAg+, Anti-HBc–) treated with immunosuppressives remains currently the most controversial. The discrepancies in the literature relate to the underlying disease indication (hemato-oncology *versus* rheumatic) and to the geographical area studied (Asia *versus* Europe). For example, a recent meta-analysis of HBVr in resolved HBV infection patients found that the pooled HBVr rates were much lower in non-hematological (3.6%) *versus* hematological (10.9%) diseases.[107] In the studies described above, one can easily detect differences in reported HBVr incidence between the Western Asia/Pacific and European regions, with the former showing significantly higher rates. This could be explained by several factors, including divergence in HBV prevalence, variance in host immune responses, different viral genotypes and inconsistent monitoring intervals.

There is general agreement that rheumatic patients treated with non-biologics, as well as biologics other than B-cell-depleting agents (like RTX), do not require prophylactic antiviral therapy.[10,11] These patients should be monitored with ALT, HBsAg or HBV DNA, and treated with antivirals when HBsAg or HBV DNA are detected (Table 2, Figure 2).[10,11] There is also

consensus that, for patients with hematologic or oncologic diseases treated with B-cell-depleting agents like RTX, prophylactic antiviral therapy is also necessary.[10,11]

For rheumatic patients treated with RTX, such prophylactic antiviral therapy is either not recommended or not specifically mentioned.[10,11] Based on the literature data presented in this review and the worldwide accumulated experience with the use of RTX in large populations of rheumatic patients with resolved infection (ranging from 5% to 50% in the general population), we believe that the risk of RTX-induced HBVr is low and prophylactic antiviral therapy is not required.[6] Nevertheless, baseline screening with HBV DNA and close monitoring with ALT, HBsAg, or HBV DNA (every 3–6 months) is advised for all patients treated with RTX (Figure 2). Patients with detectable HBV DNA at baseline, or during monitoring, as well as those with seroreversion (HBsAg+) during monitoring, should be treated with oral antivirals as described above.

Summary
In patients with rheumatic disease under immunosuppressive treatment and HBV infection, HBVr is a potentially severe and life-threatening complication that rheumatologists need to be aware of. HBVr rates depend on baseline HBV status of the patient and on the therapeutic agent used, with the highest prevalence connected to biologic and targeted synthetic drugs, especially those causing B-cell depletion. Screening for HBV prior to commencing treatment, and subsequent risk stratification, is of the utmost importance, as HBVr is a largely preventable complication *via* either the use of antiviral prophylaxis or careful and regular monitoring. Questions remaining unanswered in this field include the need for prophylaxis in certain risk groups, the optimal frequency of liver function and viral load monitoring and the potential use of alternative biomarkers for the management of HBVr.

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The authors declare that there is no conflict of interest.

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