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Review Article

Pharmacotherapy-Induced Hepatitis B Reactivation Among Patients With Prior Functional Cure: A Systematic Review

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Abstract

Objective: To describe and quantify the incidence and morbidity of hepatitis B reactivation (HBVr) secondary to pharmaceutical agents (eg, rituximab, tumor necrosis factor inhibitors, direct-acting antivirals [DAAs] for hepatitis C) among patients with previously resolved hepatitis B infection. **Data Sources:** The MEDLINE database was searched from inception through July 2018 using the terms *hepatitis B* + (*reactivation* OR [drug or drug class linked to HBVr]). **Study Selection and Data Extraction:** Relevant English-language cohort studies or randomized trials quantifying the incidence of HBVr secondary to pharmacotherapy among patients negative for hepatitis B surface antigen and DNA and positive for hepatitis B core antibody were included. **Data Synthesis:** Among 2045 articles, 102 met inclusion criteria. Receipt of rituximab was associated with the highest risk of HBVr (for oncological indication: 6.2% rate [225/3601 patients]) and subsequent hepatitis (up to 52.4% of all HBVr cases). Biologic agents for autoimmune disease were uncommonly associated with HBVr (2.4%, 56/2338), with only 4 cases of hepatitis, all attributable to rituximab. Reactivation caused by DAAs was rare (0.3%, 28/8398), with no cases of hepatitis. **Relevance to Patient Care/Clinical Practice:** This review compares and contrasts the incidence and clinical relevance of HBVr for various pharmacotherapies among patients with functionally cured hepatitis B, with discussion of appropriate risk mitigation strategies. **Conclusions:** Among patients with prior functional cure of hepatitis B, prophylactic antiviral therapy is recommended with rituximab administration irrespective of indication because of a high risk for HBVr-associated morbidity. Enhanced monitoring alone is reasonable for patients receiving nonrituximab biologics or DAAs.

Keywords

hepatitis B, reactivation, drug safety, rituximab, direct-acting antiviral, immunosuppressant

Introduction

Hepatitis B virus (HBV) is recognized as a global health concern, with an estimated 257 million people currently living with hepatitis B.[1] Failure to resolve the infection (persistence of hepatitis B surface antigen [HBsAg]) may result in severe liver disease, including progression to cirrhosis and the development of hepatocellular carcinoma, with an estimated 887 000 global deaths in 2015 caused by complications of chronic hepatitis B.[1] Within the United States, HBV is less prevalent than in other global regions; however, up to 2.2 million people are chronically infected.[2] Additionally, incident infection rates have increased since 2014, which has been linked to escalating rates of injection drug use.[3]

Chronic hepatitis B is defined by the failure to clear HBsAg, with at least 2 positive tests spaced at least 6 months apart.[4] Sustained loss of HBsAg in conjunction with undetectable HBV DNA within the serum is considered the hallmark of recovery from HBV infection, described as "resolved" infection or "functional cure." Almost all these patients will have detectable antibodies against hepatitis B core antigen (anti-HBc), and 80% will also develop antibodies against HBsAg (anti-HBs), which has been associated with enhanced viral suppression and improved prognosis.[5] Although patients with resolved HBV infection were once thought to have lifelong

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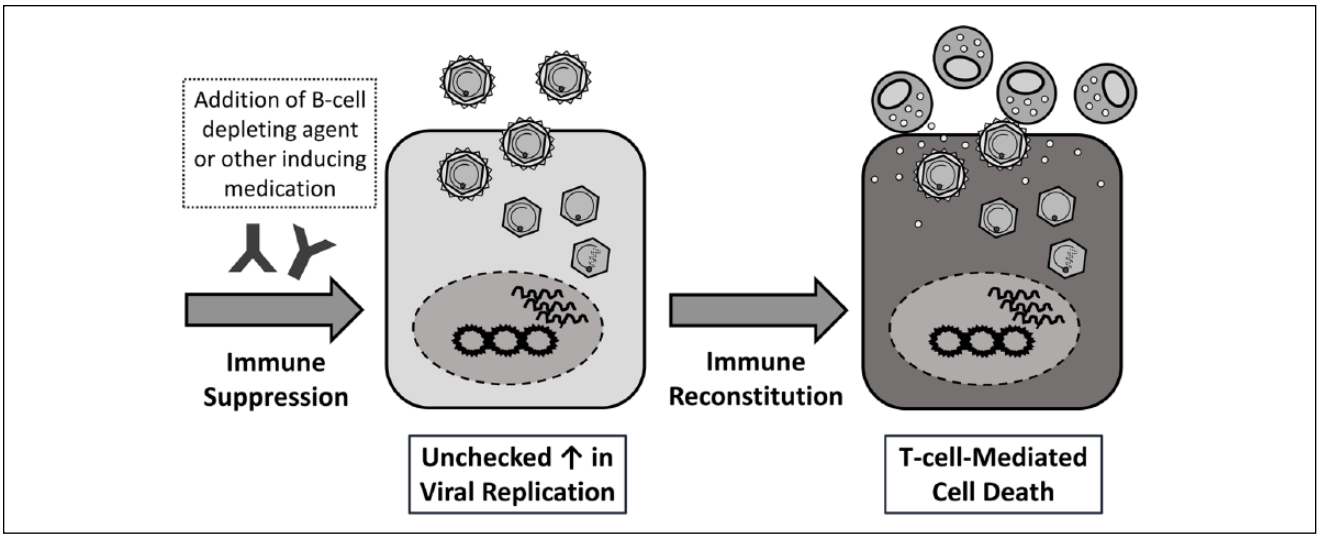

Figure 1. Hepatitis B reactivation. Patients with functional cure are at risk for reactivation because within the hepatitis B virus (HBV) life cycle, viral DNA is converted to covalently closed circular DNA (cccDNA), a stable template for viral transcription and replication within the hepatocyte nucleus. This cccDNA is not eradicated by the host immune system or antiviral therapy and serves as a lifelong reservoir of HBV. The addition of immunomodulating agents can result in a loss of immune control of HBV and resumed viral replication within the hepatocyte. Following reconstitution of the immune system, these cells may be targeted by cytotoxic T cells, resulting in clinical hepatitis.

immunity, within the past decade it has been recognized that even among patients with anti-HBs, individuals with preexisting HBV infection may be at risk for reactivation of hepatitis B following the receipt of immunosuppressing pharmacotherapies (Figure 1).

Hepatitis B reactivation (HBVr) among patients with previously resolved HBV infection is defined by the American Association for the Study of Liver Diseases (AASLD) as the presence of detectable HBV DNA or reappearance of HBsAg.[4] Pharmacotherapies associated with HBVr include B-cell depleting agents (eg, rituximab) utilized in oncology and transplant centers, other immunosuppressants (eg, tumor necrosis factor [TNFα] inhibitors for autoimmune disease), and most recently in 2016, the direct-acting antivirals (DAAs) for treatment of hepatitis C infection.[6,7] Strategies to mitigate HBVr risk, from most to least aggressive, include the administration of prophylactic antiviral therapy (eg, lamivudine, entecavir), increased monitoring for HBVr (eg, regular testing for HBV DNA reappearance), or monitoring for clinical disease only (eg, testing for alanine aminotransferase [ALT] elevation).[4]

However, few studies have attempted to compare the incidence of HBVr across the different pharmacological classes to aid providers in assessing the true HBVr risk for their particular patient's planned drug regimen, which is necessary to devise the most appropriate risk management strategy. To further cloud the clinical picture for providers, reported rates of HBVr among patients with prior functional cure vary widely in the published literature, even for the same drug, from <1% to 30% or higher.[8,9]

Additionally, although classically HBVr occurs in 3 phases—increased viral replication caused by immunosuppression, clinical disease (eg, hepatitis flare) upon immune system reconstitution with hepatocyte necrosis, and recovery[10]—some patients with evidence of increased viral replication never develop clinical disease, and although most reactivation cases resolve spontaneously, mortality resulting from acute hepatic failure is possible. Thus, systemic evaluation of HBVr severity by drug class is warranted in order for providers to perform an accurate risk assessment; however, this is also lacking in the literature. Although several clinical practice guidelines are available that address HBVr risk mitigation in functionally cured patients (Table 1),[4,11-16] these recommendations are often discordant. For example, the AASLD considers HBVr monitoring alone adequate with initiation of TNFα therapy[4]; conversely, the American Gastroenterological Association advocates for prophylaxis with biologic therapy.[16]

Given these clinical uncertainties, the objective of the article is to systematically review HBVr secondary to pharmacotherapy among individuals with resolved HBV infection (HBsAg-negative, HBV DNA-negative, and anti-HBc-positive with or without anti-HBs), evaluate reactivation incidence and severity across the implicated pharmacologic classes, and differentiate management strategies among the patient populations at risk for this complication.

Table 1. Selected Guideline Documents Addressing Risk Mitigation of Hepatitis B Reactivation Among Patients With Resolved Hepatitis B.

Organization	Year	HBV Serology	Drug(s)	Strategy	Recommendations
General guidelines					
American Association for the Study of Liver Diseases[4]	2018	HBsAg (−); anti-HBc (+)	HCV DAA therapy	Preemptive	• Monitor ALT at baseline, end of DAA therapy, and during follow-up • Test for HBsAg and HBV DNA only if ALT increases or fails to normalize with resolution of HCV infection • Initiate antiviral therapy (ETV, TDF, TAF) if evidence of HBVr
			Biologics for rheumatologic conditions, inflammatory bowel disease, or psoriasis	Preemptive	• Monitor ALT, HBV DNA, and HBsAg status every 1-3 months • Initiate antiviral therapy (ETV, TDF, TAF) if evidence of HBVr
			Rituximab and other anti-CD20 therapies	Prophylaxis	• Give prophylaxis (ETV, TDF, TAF) prior to cytotoxic therapy and for 12 months after drug discontinuation
			Immunosuppression for nonliver SOT	Prophylaxis or preemptive	• May consider prophylaxis (ETV, TDF, TAF) for 6-12 months post-SOT and during periods of intensified immunosuppression • Monitor ALT every 3 months off prophylaxis • Test for HBV DNA if ALT rises
Centers for Disease Control and Prevention[11]	2008	HBsAg (−); anti-HBc (+)	Immunosuppressive therapy	N/A	• Monitor for signs of liver disease
Oncology guidelines					
American Society of Clinical Oncology[12]	2015	HBsAg (−); anti-HBc (+)	Rituximab and other anti-CD20 therapies	Prophylaxis or preemptive	• Give prophylaxis (ETV, TDF, TAF) prior to cytotoxic therapy and for 12 months after drug discontinuation or • Monitor ALT and HBV DNA every 3 months during therapy • Initiate antiviral therapy (ETV, TDF, TAF) if evidence of HBVr
			Other immunosuppressive cancer therapy	Preemptive	• Monitor ALT and HBV DNA every 3 months during therapy • Initiate antiviral therapy (ETV, TDF, TAF) if evidence of HBVr
National Comprehensive Cancer Network[13]	2018	HBsAg (−); Anti-HBc (+)	Rituximab and other anti-CD20 therapies	Prophylaxis	• Give prophylaxis (ETV) prior to cytotoxic therapy and for 12 months after drug discontinuation • Monitor HBV DNA monthly during treatment and every 3 months after

(continued)

Table 1. (continued)

Organization	Year	HBV Serology	Drug(s)	Strategy	Recommendations
		HBsAg (−); Anti-HBc (+); Anti-HBs (+) ["high" level]	Rituximab and other anti-CD20 therapies	Prophylaxis or preemptive	• As above or • Serial HBV DNA monitoring alone • Initiate antiviral therapy (ETV) if evidence of HBVr
Transplant guidelines					
Kidney Disease: Improving Global Outcomes[14]	2009	HBsAg (−); anti-HBc (+)	"Intensified" immunosuppression post–kidney transplant	Prophylaxis	• Give prophylaxis (3TC) • HBV vaccination for all patients with anti-HBs titer $<$100 mIU/mL
Autoimmune disease guidelines					
American College of Rheumatology[15]	2015	HBsAg (−); anti-HBc (+); anti-HBs (+)	Immunosuppression for rheumatoid arthritis	Preemptive	• Monitor HBV DNA every 6-12 months
American Gastroenterological Association[16]	2015	HBsAg (−); anti-HBc (+)	$\geqslant$10 mg prednisone daily or equivalent for $\geqslant$4 weeks	Prophylaxis	• Give prophylaxis (ETV, TDF, TAF) prior to therapy and for 6 months after drug discontinuation • Withholding prophylaxis is a reasonable alternative
			Biologic agent	Prophylaxis	• Give prophylaxis (ETV, TDF, TAF) prior to therapy and for 6 months after drug discontinuation • Withholding prophylaxis is a reasonable alternative
			Anthracycline derivatives (eg, doxorubicin)	Prophylaxis	• Give prophylaxis (ETV, TDF, TAF) prior to therapy and for 6 months after drug discontinuation • Withholding prophylaxis is a reasonable alternative
			Traditional DMARD or low-dose prednisone	N/A	• Prophylaxis not recommended • No recommendation for preemptive therapy

Abbreviations: 3TC, lamivudine; ALT, alanine aminotransferase; Anti-HBc, hepatitis B core antibody; Anti-HBs, hepatitis B surface antibody; DAA, direct-acting antiviral; DMARD, disease-modifying anti-rheumatic drug; ETV, entecavir; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HBVr, hepatitis B reactivation; HCV, hepatitis C virus; N/A, not applicable; SOT, solid organ transplant; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Methods

Potential studies for inclusion were identified using the PubMed/MEDLINE database from inception through July 2018, incorporating the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[17] The terms used to search MEDLINE included *hepatitis B + reactivation* as well as MeSH terms *hepatitis B +* (drug or drug class of interest based on prior reports of HBVr risk, eg [*rituximab* or *ofatumumab* or *veltuzumab* or *etanercept* or *infliximab* or *adalimumab* or *certolizumab* or *golimumab* or *tocilizumab* or *abatacept* or *sofosbuvir* or *ledipasvir, sofosbuvir drug combination* or *sofosbuvir-velpatasvir drug combination* or *daclatasvir* or *ombitasvir* or *velpatasvir* or *elbasvir* or *pibrentasvir* or *simeprevir* or *paritaprevir* or *grazoprevir* or *glecaprevir* or *voxilaprevir* or *dasabuvir* or *immunosuppressive agents*]). Articles were limited to original research studies published in the English language of a cohort or randomized controlled trial (RCT) design. Included studies quantified the incidence of HBVr among functionally cured patients with HBV infection as a result of pharmacotherapy. Studies describing mixed populations (eg, also included patients with active HBV infection) were included only if the relevant population could be separated numerically from the overall cohort. Exclusions included pediatric-only studies or HBVr attributed to hematopoietic stem cell transplant (HSCT), liver transplantation (because reappearance of HBV DNA or HBsAg in this circumstance is reflective of reinfection of the transplanted liver rather than HBVr[10]), or chemotherapy administered via transcatheter arterial chemoembolization.

Identification of potential studies was performed by 2 independent reviewers using the outlined search strategy, and any study that met inclusion criteria was retrieved in full. Relevant information was extracted manually using a data collection form. Any discrepancies were resolved by a third, independent reviewer. No quantitative assessment of bias was performed for the individual studies; however, potential sources of bias affecting the cumulative evidence are discussed in the limitations section of the article. Because of variability in patient population, inciting drug regimen, implemented intervention, and reporting of outcome measures, results are summarized descriptively with the exception of select dichotomous variables analyzed via the χ^2 or Fisher exact test.

HBVr, hepatitis flare, and liver failure were defined per AASLD definitions[4]; thus, the reported rates may differ in some instances from those reported by the article's authors (eg, if the authors set a minimum HBV DNA threshold for HBVr). For studies where some, but not all, patients received rituximab for an oncological indication (and the rituximab subcohort could not be numerically separated), a 10% threshold was established for grouping the study with rituximab versus nonrituximab therapy, given its high known propensity to cause HBVr. Similarly, for studies where some, but not all, patients received biologic therapies for autoimmune diseases, a 20% threshold (higher because of the lower anticipated HBVr risk of biologics such as the TNFα inhibitors vs rituximab) was used for study classification purposes.

Results

A total of 2045 studies were screened, excluding duplicates. After applying inclusion and exclusion criteria, 102 studies were included in the systematic review. The most common reasons for exclusion were noncohort/RCT study (42.7%), no quantification of HBVr incidence (22.9%), and missing or alternate HBV serology (14.7%). Of the included studies, the most common study design was a retrospective cohort (65.7%), followed by prospective cohort (31.4%), with 2 RCTs and 1 study with both prospective and retrospective cohort arms. Details of the included studies are summarized in Tables 2 to 4. Studies examining multiple pharmacotherapies may be represented in more than 1 table.

A total of 37 studies including 3601 patients with resolved HBV infection evaluated the use of rituximab for hematological malignancies or solid tumors, generally in addition to other cytotoxic chemotherapeutic agents (Table 2).[8,9,18-52] In most of the studies, patients did not receive prophylaxis. The incidence of HBVr ranged from 0% to 30.2%, with an overall rate of 6.2% (225/3601). The majority (52.4%, 118/225) of HBVr patients experienced hepatitis flare, and 13.8% (31/225) had reported liver failure. Of note, no studies highlighting the effects of other anti-CD20 agents (eg, ofatumumab, veltuzumab) were identified. Fewer studies (16) evaluated HBVr secondary to chemotherapeutic agents without rituximab for hematological malignancy or solid tumor (Table 3).[48,49,53-66] Only 2 studies reported the receipt of prophylaxis. Among the 2041 patients evaluated, 54 (2.6%) experienced HBVr. Hepatitis flare was reported among 20.4% (11/54) of the HBVr cases, with a 3.7% rate of liver failure (2/54). Among all patients with oncological disorders, HBVr was more common among patients who received rituximab-containing regimens (6.2% vs 2.6%, $P < 0.001$). Comparing the HBVr cases, rituximab therapy was additionally associated with an increased likelihood of both hepatitis flare and liver failure ($P < 0.001$ and $P = 0.04$, respectively, versus non–rituximab-containing chemotherapy).

A total of 32 studies were identified evaluating immunosuppressing biologics and other disease-modifying antirheumatic drugs (DMARDs) for autoimmune diseases, which included rheumatoid arthritis, psoriasis, systemic lupus erythematosus, and aplastic anemia (Table 4).[67-98] TNFα inhibitors were the most common agents evaluated, and 6 studies included rituximab. Use of prophylaxis was rare. For the studies where ⩾20% of the cohort received

Table 2. Rituximab (>10% Cohort) for Hematological Malignancy or Solid Tumor.

Citation	n	Anti-HBs (+)	Primary Drug(s)	Mean/Median Follow-up	PPX	HBVr	Median time to HBVr	Hepatitis Flare[a]	Liver Failure[a]
Al-Mansour et al (2018)[18]	41	NR	RTX-chemotherapy	NR	28 (68.3%), 17 ETV, 11 3TC	0	N/A	0	0
Buti et al (2017)[19]	61	39 (63.9%)	RTX +/− chemotherapy	18 Months	33 (54.1%), TDF	3 (4.9%); No PPX	4 Months	1 (33.3%)	0
Castelli et al (2016)[20]	82	78% cohort	RTX-chemotherapy	NR	82 (100%), 3TC	9 (11.0%)	Range 2-6 cycles	9 (100%)	3 (33.3%)
Chen et al (2013)[21]	25	NR	Chemotherapy +/− RTX (~24%)	3 Years	25 (100%), 22 ETV, 3 3TC	1 (4%)	2 Years	0	0
Chen et al (2015)[22]	55	52 (94.5%)	RTX-chemotherapy	NR	No	6 (10.9%)	Range 2-7 cycles	6 (100%)	3 (50%)
Cho et al (2016)[23]	108	51 (47.2%)	RTX-chemotherapy	33.5 Months (range 4.2-130.5)	39 (36.1%), Telbivudine 56.4%	8 (7.4%)	7.1 Months (range 4.2-44.9)	6 (75.0%)	1 (12.5%)
Francisci et al (2010)[24]	56	43 (76.8%)	Chemotherapy +/− RTX	⩾6 Months	No	3 (5.4%)	2-4 Cycles	0	0
Francisci et al (2012)[25]	75	58 (77.3%)	RTX-chemotherapy (71%)	NR	No	5 (6.7%)	NR	0	0
Guarino et al (2017)[26]	47	13 (27.7%)	Chemotherapy +/− RTX (14.9%)	NR	6 (12.8%)	2 (4.3%) [28.8% RTX]	1.5 Months	2 (100%)	0
Hsiao et al (2015)[27]	424	297/381 (78%)	RTX +/− chemotherapy	NR	No	23 (5.4%)	39.9 Weeks (range 15-168)	19 (82.6%)	4 (17.4%)
Hsu et al (2014)[28]	150	116 (77.3%)	R-CHOP	27.4 Months (range 1.1-45.7)	No	17 (11.3%)	21 Weeks (range 3-57)	10 (58.8%)	0
Huang et al (2013)[29]	50	58/80 (72.5%)	R-CHOP	18.5 Months	41/80 (51.3%), ETV	6 (12.0%)	NR	1 (16.7%)	0
Ji et al (2010)[30]	88	65 (73.9%)	R-CHOP (48.9%)/CHOP	NR	No	1 (1.1%) [2.3% R-CHOP]	2 Cycles	1 (100%)	0
Junus et al (2017)[31]	32	NR	RTX +/− chemotherapy	NR	7 (21.9%)	2 (6.3%)	6, 8 Cycles	2 (100%)	0
Kim et al (2014)[32]	675	537 (80.1%)	Chemotherapy +/− RTX	14.7 Months (range 0.5-43)	No	13 (1.9%)	NR	10 (76.9%)	2 (15.4%)
Kim et al (2013)[33]	178	130 (73.0%)	RTX-chemotherapy	NR	NR	17 (9.6%)	8.9 Months (range 0.9-29.5)	14 (82.4%)	3 (17.6%)
	83	58 (70.0%)	RTX-chemotherapy	NR	NR	2 (2.4%)	NR	2 (100%)	1 (50%)
Koo et al (2010)[34]	48	68% cohort	Chemotherapy +/− RTX (68.7%)	NR	10.4% Cohort	1 (2.1%)	2 Months	1 (100%)	1 (100%)
Koo et al (2011)[35]	62	33 (71.7%)	RTX-chemotherapy (77.4% R-CHOP)	32 Months (range 4.7-47.2)	No	2 (3.2%)	NR	2 (100%)	2 (100%)
Kusumoto et al (2015)[36]	243	194 (79.8%)	RTX-chemotherapy (87.8% R-CHOP)	562 Days	No	21/243 (8.6%)	112.5 Days (range 32-754)	0	0
Liu et al (2013)[37]	17	NR	RTX +/− chemotherapy (94.1%)	NR	No	0	N/A	N/A	N/A
Liu et al (2016)[8]	59	NR	Chemotherapy +/− RTX (90.2%)	24.8 Months (range 2.6-62.8)	No	0	N/A	N/A	N/A

(continued)

Table 2. (continued)

Citation	n	Anti-HBs (+)	Primary Drug(s)	Mean/Median Follow-up	PPX	HBVr	Median time to HBVr	Hepatitis Flare[a]	Liver Failure[a]
Lu et al (2015)[38]	150	104 (69.3%)	RTX-chemotherapy	28 Months (range 2-100)	4 (2.7%)	4 (2.7%) [8.7% sAb (-)]	5.5 Cycles	3 (75.0%)	3 (75.0%)
Marrone et al (2018)[39]	68	44 (64.7%)	RTX-chemotherapy (67.4%)	63 Months (range 10-102)	68 (100%), 3TC	3/47 (6.4%)	28 Months (range 3-37)	2 (66.7%)	0
Masarone et al (2014)[40]	96	NR	Chemotherapy +/− RTX (~50%)	NR	No	10 (10.4%)	24 Weeks (range 12-44)	9 (90%)	0
Matsubara et al (2017)[41]	71	52 (73.2%)	RTX-chemotherapy (88.3%)	987 Days (range 7-2759)	No	10 (14.1%)	158 Days (range 9-673)	2 (20%)	0
Matsue et al (2010)[42]	56	37 (66.1%)	RTX-chemotherapy	24 Months	No	5 (8.9%)	NR	4 (80%)	0
Matsui et al (2013)[43]	59	39 (66.1%)	Chemotherapy +/− RTX (75%)	20.5 Months (range 1.0-58.6)	No	4 (6.8%)	Range 42-398 days	0	0
Méndez-Navarro et al (2011)[44]	25	0	RTX-chemotherapy	6 Months postchemotherapy	No	0	N/A	N/A	N/A
Oh and Lee et al (2013)[45]	66	NR	RTX +/− chemotherapy	NR	No	2 (3.0%)	47 Weeks +/− 19.3	2 (100%)	2 (100%)
Papadopoulos et al (2017)[46]	55	29 (52.7%)	RTX-chemotherapy (70.9%)	8 Months (1-36)	31 (56.4%)	9/39 (23.1%)	6.5 Months (range 3-24 Months)	NR	2 (5.1%)
Pompili et al (2015)[47]	11	10 (90.9%)	RTX-chemotherapy (81.8%)	35 Months (range 18-45)	No	0	N/A	N/A	N/A
Seto et al (2014)[9]	63	49 (77.8%)	RTX +/− chemotherapy	70 Weeks (range 6-104)	No	19 (30.2%)	23 Weeks (range 4-100)	0	0
Su et al (2018)[48]	78	77% Cohort	RTX-chemotherapy	14.8 Months (IQR 6.9-25.5)	2.6% Cohort	4 (5.1%)	6.6 Months (range 3.57-7.3)	4 (100%)	2 (50.0%)
Watanabe et al (2011)[49]	20	11 (55.0%)	RTX-chemotherapy	13 Months (range 6-31)	NR	5 (25.0%)	5 Months (range 4-13)	0	0
Yang et al (2014)[50]	28	NR	Chemotherapy +/− RTX (~32.1%)	⩾1 Year	No	0	N/A	N/A	N/A
Yeo et al (2018)[51]	75	54/65 (83.1%)	RTX-chemotherapy	2 Years	38 (50.7%)	3 (4.0%)	NR	1 (33.3%)	1 (33.3%)
Yeo et al (2009)[52]	21	30/46 (65.2%)	R-CHOP	6 Months postchemotherapy	No	5 (23.8%)	Range 5-8 cycles	5 (100%)	1 (20%)

Abbreviations: 3TC, lamivudine; Anti-HBs, hepatitis B surface antibody; ETV, entecavir; HBVr, hepatitis B virus reactivation; IQR, interquartile range; N/A, not applicable; NR, not reported; PPX, prophylaxis; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; RTX, rituximab; TDF, tenofovir disoproxil fumarate.
[a]For these percentages, denominator equals the total number of HBVr cases.

Table 3. Non–Rituximab-Containing Chemotherapy for Hematologic Malignancy or Solid Tumor.

Citation	n	Anti-HBs (+)	Primary Drug(s)	Mean/Median Follow-up	PPX	HBVr	Median time to HBVr	Hepatitis Flare[a]	Liver Failure[a]
Elkady et al (2013)[53]	17	NR	Steroid-based chemotherapy	NR	No	4 (23.5%)	4.5 Months (range 4-6)	1 (25.0%)	0
Federico et al (2017)[54]	32	NR	Miscellaneous chemotherapy	24 Months (range 2-36)	No	0	N/A	N/A	N/A
Gill et al (2018)[55]	15	11 (73.3%)	Ruxolitinib (Janus kinase inhibitor)	19.2 Months (range 2.2-24)	No	4 (26.7%)	10.5 Months (range 6.9-12.8)	1 (25.0%)	0
Hagiwara et al (2012)[56]	27	23 (85.2%)	Cisplatin (73.9%)	12 Months	No	2 (7.4%)	30 Days	0	0
Laurenti et al (2015)[57]	19	71% Cohort	Miscellaneous chemotherapy	NR	9 (47.4%)	2 (10.5%)	4-8 Weeks	0	0
Lok et al (1991)[58]	45	27 (60.0%)	Miscellaneous chemotherapy	4 Years	No	2 (4.4%)	NR	2 (100%)	0
Markovic et al (1999)[59]	30	NR	Miscellaneous chemotherapy +/− CS	NR	No	1 (3.0%)	NR	NR	NR
Matsuzaki et al (2015)[60]	197	NR	Miscellaneous chemotherapy or other IS	2 Years	NR	4 (2.0%)	Range 2-12 months	1 (25.0%)	0
Picardi et al (2003)[61]	8	6 (75.0%)	Fludarabine-based chemotherapy	NR	No	1 (16.7%)	15 Weeks	1 (100%)	0
Sorà et al (2017)[62]	10	9 (90.0%)	TKIs	45.8 Months	No	0	N/A	N/A	N/A
Stebbing et al (2004)[63]	30	NR	Miscellaneous chemotherapy	NR	No	5 (16.7%)	NR	NR	0
Su et al (2018)[48]	938	77% Cohort	Miscellaneous chemotherapy	14.8 Months (IQR 6.9-25.5)	2.6% Cohort	3 (0.3%)	12.7 Months (range 2.4-15.5)	2 (66.7%)	1 (33.3%)
Totani et al (2015)[64]	24	21 (87.5%)	Miscellaneous chemotherapy	238 Days (range 57-1420)	No	3 (12.4%)	Range 71-541 days	0	0
Tsukune et al (2017)[65]	580	76% Cohort	Miscellaneous chemotherapy (>80% bortezomib)	101 Weeks (range 1-541)	No	20 (3.4%)	NR	17.2% Cohort	1.7% Cohort
Watanabe et al (2011)[49]	18	15 (83.3%)	Miscellaneous chemotherapy, ~60% + CS	13 Months (range 6-31)	NR	0	N/A	N/A	N/A
Yilmaz et al (2016)[66]	51	51 (100%)	Miscellaneous chemotherapy	295 Days (range 38-1715)	NR	3 (5.9%)	NR	NR	1 (33.0%)

Abbreviations: Anti-HBs, hepatitis B surface antibody; CS, corticosteroids; HBVr, hepatitis B virus reactivation; IQR, interquartile range; IS, immune suppressant; N/A, not applicable; NR, not reported; PPX, prophylaxis; TKI, tyrosine kinase inhibitor.

[a]For these percentages, denominator equals the total number of HBVr cases.

Table 4. Other Pharmacotherapies for Autoimmune Disease, Transplant, and Hepatitis C.

Citation	n	Anti-HBs (+)	Primary Drug(s)	Mean/Median Follow-up	PPX	HBVr	Median time to HBVr	Hepatitis Flare[a]	Liver Failure[a]
Biologics (>20% cohort) for autoimmune disease									
Ahn et al (2018)[67]	15	12 (80.0%)	Tocilizumab (anti-IL-6)	NR	No	0	N/A	N/A	N/A
Barone et al (2015)[68]	179	145 (81.0%)	Miscellaneous biologics, 81.6% anti-TNFα, 7.8% RTX	45.5 Months (IQR 20-72)	No	0	N/A	N/A	N/A
Biondo et al (2014)[69]	20	14 (70.0%)	Anti-TNFα	45 Months +/− 22	No	0	N/A	N/A	N/A
Caporali et al (2010)[70]	67	28 (41.8%)	Anti-TNFα	42.5 +/− 21.3	No	0	N/A	N/A	N/A
Cassano et al (2011)[71]	62	50 (80.6%)	Anti-TNFα	55 Months	No	1 (1.6%)	10 Months	0	0
Charpin et al (2009)[72]	21	21 (100%)	Anti-TNFα	27.2 Months (range 7-56)	No	0	N/A	N/A	N/A
Fukuda et al (2017)[73]	915	725 (79.2%)	Miscellaneous biologics (26.3%)	2 years	No	32 (4.4%)	66 Months (range 3-182)	0	0
Giardina et al (2013)[74]	7	4 (57.1%)	Anti-TNFα	2 years	No	0	N/A	N/A	N/A
Lan et al (2011)[75]	66	58 (87.8%)	Anti-TNFα	NR	No	0	N/A	N/A	N/A
Mitroulis et al (2013)[76]	12	9 (75.0%)	RTX-DMARDs	18.9 Months +/− 13.5	No	0	N/A	N/A	N/A
Mori (2011)[77]	60	NR	Anti-TNFα (51.7%)	NR	No	2 (3.3%)	NR	0	0
Morisco et al (2014)[78]	59	36 (61.0%)	Miscellaneous biologics (67.8%)	54 Months	No	0	N/A	N/A	N/A
Nakamura et al (2016)[79]	49	38 (77.6%)	Miscellaneous biologics, ⩾80% anti-TNFα	18 Months (range 2-27)	No	3 (6.1%)	NR	0	0
Navarro et al (2014)[80]	13	8 (61.5%)	Anti-TNFα	NR	No	0	N/A	N/A	N/A
Padovan et al (2016)[81]	21	NR	Abatacept (CTLA-4 Ig), 85.7%	24 Months	4 (19.0%), 3TC	0	N/A	N/A	N/A
Papalopoulos et al (2018)[82]	71	52 (73.2%)	RTX, abatacept, and/or tocilizumab	NR	7 (9.9%)	2 (2.8%)	10, 32 Months	1 (50%)	1 (50%)
	85	61 (71.8%)	Anti-TNFα	NR	1 (1.2%)	0	N/A	N/A	N/A
Pauly et al (2018)[83]	178	109 (61.2%)	Anti-TNFα (28.7% ⩾2)	NR	No	0	N/A	N/A	N/A
Sanz-Bueno et al (2015)[84]	20	13 (65.0%)	Miscellaneous biologics	40 Months (range 9-84)	No	0	N/A	N/A	N/A
Snast et al (2017)[85]	25	17 (68.0%)	Miscellaneous biologics (60.0% ⩾2)	4.45 Years (range 1-10.3)	2 (8.0%)	0	N/A	N/A	N/A
Spinicci et al (2018)[86]	20	19 (95.0%)	RTX	19 Months (range 2-36)	No	1 (5.0%)	8 Months (2 cycles)	0	0
Tamori et al (2011)[87]	45	36 (80.0%)	Miscellaneous biologics (93.3%)	23 Months (range 12-32)	No	1 (2.2%); MTX only	10 Months	0	0
Tien et al (2017)[88]	44	NR	RTX	25.4 Months +/− 4.6	NR	4 (9.1%)	Range 24-32 Months	3 (75%)	1 (25%)
Ting et al (2018)[89]	44	38 (86.4%)	Ustekinumab	24 Months +/− 12	No	1 (2.3%)	12 Months	0	0
Urata et al (2011)[90]	123	85 (69.1%)	Miscellaneous biologics (38.5%)	12 Months	No	7 (5.7%)	NR	0	0
Varisco et al (2016)[91]	33	28 (84.8%)	RTX-DMARDs	18 Months post-RTX (range 0-70)	No	1 (3.0%)	6 Months (1 cycle)	0	0
Vassilopoulos et al (2010)[92]	19	10 (52.6%)	Anti-TNFα	2 years	No	0	N/A	N/A	N/A
Zhao et al (2017)[93]	65	NR	Antithymocyte or antilymphocyte globulin (~24%)	47.5 Months (range 1-94)	No	1 (1.5%)	11 Months	0	0
Nonbiologic DMARDs for autoimmune disease									
Fang et al (2017)[94]	745	544 (73.0%)	Miscellaneous IS (91.4% CS)	NR	No	27 (5.0%)	24 Months (range 14-34)	NR	1 (3.7%)
Kato et al (2011)[95]	35	NR	Miscellaneous IS (CS, cyclophosphamide (37.1%))	24 Weeks (range 8-124)	No	6 (17.1%)	Range 4-8 weeks	1 (16.7%)	0
Laohapand et al (2015)[96]	64	38.7% overall cohort	MTX	>52 Weeks	No	0	N/A	N/A	N/A
Ming-Xu et al (2015)[97]	36	NR	Leflunomide	35 Months (range 1-86)	No	0	N/A	N/A	N/A
Tan et al (2012)[98]	184	NR	Miscellaneous IS (35.3% CS)	4.5 Years (range 1-10.3)	2 (8.0%)	0	N/A	N/A	N/A

(continued)

Table 4. (continued)

Citation	n	Anti-HBs (+)	Primary Drug(s)	Mean/Median Follow-up	PPX	HBVr	Median time to HBVr	Hepatitis Flare[a]	Liver Failure[a]
Immune suppression for kidney transplant									
Kanaan et al (2012)[99]	93	74 (79.6%)	TAC/CsA + MMF/AZA + CS	73 Months (range 44-114)	No	6 (6.5%)	39 Months (range 24-49)[b]	1 (16.7%)	0
Lee et al (2016)[100]	38	NR	RTX + BAX + TAC + MMF + CS	1 Year	No	3 (7.9%)	NR	NR	1 (33.3%)
Lee et al (2017)[101]	49	43 (87.8%)	RTX desensitization, BAX + TAC + CS +/− MMF	58 Months (range 4-95)	No	5 (10.2%)	11 Months (range 5-22)	4 (80.0%)	2 (40.0%)
	123	104 (84.6%)	BAX (92.7%), TAC + CS +/− MMF	58 Months (range 4-95)	No	2 (1.6%)	24, 48 Months[b]	1 (50.0%)	0
Maekawa et al (2016)[102]	7	5 (71.4%)	BAX + TAC + MMF + CS +/− RTX (42.9%)	1038 Days (range 393-1997)	2 (28.8%)	0	N/A	N/A	N/A
Masutani et al (2018)[103]	48	45 (97.8%)	RTX + BAX + TAC/CsA + MMF + CS	NR	2 (4.2%)	1 (2.2%)	6 Weeks[b]	0	0
	28	23 (82.1%)	BAX + TAC/CsA + MMF + CS	NR	No	1 (3.6%)	5.5 Years[b]	0	0
Meng et al (2018)[104]	95	86 (90.5%)	TAC/CsA + MMF/AZA + CS; 31.6% BAX, 17.9% ATG[c]	93 Months (IQR 58-146)	No	2 (2.1%)	5, 8 Years[b]	2 (100%)	1 (50.0%)
Direct-acting antivirals for hepatitis C									
Belperio et al (2017)[105]	7276	0 (Exclusion)	Miscellaneous DAAs	7 Days post-DAA	299/7295 (4.1%), Most TDF	3 (0.04%)	NR	0	0
Calvaruso et al (2018)[106]	37	12 (32.4%)	Miscellaneous DAAs, 68.3% sofosbuvir based	24 Weeks (12 post-DAA)	No	3 (8.1%)	Range 4-24 weeks	0	0
Doi et al (2017)[107]	155	75 (48.4%)	Ledipasvir-sofosbuvir or sofosbuvir-ribavirin	24 Weeks (12 post-DAA)	No	3 (1.9%)	Range 4-12 weeks	0	0
Kawagishi et al (2017)[108]	82	47 (57.3%)	Miscellaneous DAAs	24 Weeks (12 post-DAA)	No	5 (6.1%)	Range 8-12 weeks	0	0
Lee et al (2018)[109]	53	NR	Miscellaneous DAAs	24 Weeks (12 post-DAA)	No	0	N/A	N/A	N/A
Liu et al (2017)[110]	81	35 (43.2%)	Miscellaneous DAAs, 86.4% sofosbuvir based	24 Weeks (12 post-DAA)	No	0	N/A	N/A	N/A
Loggi et al (2017)[111]	40	23 (54.8%)	Miscellaneous DAAs (75.0% sofosbuvir based)	36 Weeks (24 post-DAA)	No	1 (2.5%)	NR	0	0
Londoño et al (2017)[112]	64	NR	Miscellaneous DAAs, 50% ProD	24 Weeks (12 post-DAA)	No	1 (1.6%)	12 Weeks	0	0
Mücke et al (2017)[113]	260	NR	Miscellaneous DAAs, 40% ledipasvir-sofosbuvir	24 Weeks (12 post-DAA)	No	8 (3.1%)	NR	0	0
Ogawa et al (2018)[114]	63	33 (52.4%)	Sofosbuvir-based DAAs	36 Weeks (24 post-DAA)	No	4 (6.3%)	Range 4-12 weeks	0	0
Sulkowski et al (2016)[115]	103	NR	Ledipasvir-sofosbuvir	24 Weeks (12 post-DAA)	No	0	N/A	N/A	N/A
Yanny et al (2018)[116]	127	NR	Ledipasvir-sofosbuvir	24 Weeks (12 post-DAA)	NR	0	N/A	N/A	N/A
Yeh et al (2017)[117]	57	NR	Miscellaneous DAAs (63.2% sofosbuvir based)	24 Weeks (12 post-DAA)	No	0	N/A	N/A	N/A

Abbreviations: 3TC, lamivudine; Anti-HBs, hepatitis B surface antibody; ATG, anti-thymocyte globulin; AZA, azathioprine; BAX, basiliximab; CS, corticosteroids; CsA, cyclosporine; CTLA4, cytotoxic T-lymphocyte-associated protein 4; DAA, direct-acting antiviral; DMARD, disease-modifying anti-rheumatic drug; HBVr, hepatitis B virus reactivation; Ig, immunoglobulin; IL, interleukin; IQR, interquartile range; IS, immune suppressant; MMF, mofetil mycophenolate; MTX, methotrexate; N/A, not applicable; NR, not reported; PPX, prophylaxis; ProD, paritaprevir/ritonavir, ombitasvir, dasabuvir; RTX, rituximab; TAC, tacrolimus; TDF, tenofovir; TNFα, tumor necrosis factor α.

[a]For these percentages, denominator equals the total number of HBVr cases.

[b]Time from transplant.

[c]As induction therapy or as part of acute rejection treatment.

one or more biologic agents, 56 of 2338 patients (2.4%) experienced HBVr; however, only 4 cases of hepatitis or liver failure were reported. All 4 of these patients had received rituximab. Among the 5 studies evaluating nonbiologic DMARDs, 33/1064 patients (3.1%) experienced HBVr, with 2 patients experiencing hepatitis flare and/or liver failure.

Six studies evaluated HBVr risk post–kidney transplant (Table 4).[99-104] A total of 4/481 patients (<1%) received prophylaxis. The rate of HBVr among patients receiving rituximab desensitization ranged from 0% to 10.2%, with an overall percentage of 6.5% (9/138). Hepatitis flare was reported with 4 of the 9 HBVr cases (44.4%) and liver failure for 3 of the 9 cases (33.3%). Among those patients who received immunosuppressive regimens without rituximab, the HBVr rate ranged from 0% to 6.5% (overall rate 3.2%, 11/343), with 4 reported cases of hepatitis flare among the 11 HBVr cases (36.4%) and 1 of liver failure (9.1%). A higher percentage of patients receiving rituximab experienced HBVr versus those with no rituximab therapy (6.5% vs 3.2%), though this difference was not statistically significant. Similarly, a nonsignificant trend was again observed associating rituximab with more HBVr cases resulting in hepatitis or liver failure (44.4% vs 36.4%).

Finally, 13 articles evaluating HBVr resulting from DAA therapy for the treatment of hepatitis C were identified (Table 4).[105-117] Among 8398 patients, 28 cases of HBVr were described (0.3% incidence), all of which were the result of detectable HBV DNA only, often below the level of quantification, with no reported cases of hepatitis or liver failure.

Relevance to Patient Care and Clinical Practice

HBV infection history has been increasingly recognized as an important consideration in the management of patients with comorbidities requiring the receipt of immunosuppressive pharmacotherapies. Although at lower risk for HBVr than patients with active chronic infection (presence of HBsAg),[4] patients with functionally cured hepatitis B are still vulnerable to reactivation and associated hepatic complications. Thus, multiple guidelines advocate for enhanced pharmacovigilance when agents known to increase the risk for HBVr are administered, with recommendations ranging from heightened monitoring for signs of HBVr (eg, detectable HBV DNA) to the administration of a prophylactic antiviral agent during the period of greatest immunosuppression and extending through immune reconstitution (Table 1).[4,11-16] However, this study emphasizes that not all drugs associated with HBVr confer an equal risk for reactivation, nor do they lead to equivalent clinical outcomes. Therefore, the optimal strategy for managing HBVr should be tailored based on patient characteristics and the specific drug of concern.

In 2013, the Food and Drug Administration (FDA) revised the product labels of rituximab and ofatumumab (anti-CD20 antibodies) to include HBVr-induced "fulminant hepatitis, hepatic failure and death" in the boxed warning.[6] Of the 109 cases cited by the FDA, 32 cases met the criteria for HBVr based on the availability of sufficient and validated serological and clinical information, and notably, 19 (56.4%) represented patients with previously resolved infection. Consistent with the FDA's findings, we found rituximab to be associated with the highest HBVr rates. Among patients with oncological disorders, HBVr was more than twice as common among patients who received rituximab-containing regimens in this study (6.2% vs 2.6%) and, notably, tended to be more severe, with >10% of all reactivation cases resulting in hepatic failure. It should be acknowledged that these numbers may be influenced by the fact that a greater proportion of lymphoma patients are represented among the rituximab group, with lymphoma associated with a significantly increased risk for HBVr versus solid tumor independent of rituximab.[32] However, multiple studies identified rituximab as an independent risk factor for HBVr,[26,48,52] with the risk increasing with multiple (>6) cycles.[27] Given the high risk for HBVr and associated morbidity observed with rituximab-based chemotherapy regimens, we support universal prophylaxis for these patients, which is consistent with AASLD, American Society of Clinical Oncology, and National Comprehensive Cancer Network (NCCN) guidelines.[4,12,13]

Although the use of prophylactic antiviral therapy is most emphasized with the use of rituximab in conjunction with cytotoxic chemotherapy, where the data are most robust, we believe that our findings also support enhanced consideration of antiviral prophylaxis even when rituximab is given for nononcological indications. Rituximab has increasingly been utilized in the management of several immune-mediated diseases, including rheumatoid arthritis. A typical cycle consists of 1000 mg for 2 doses spaced 2 weeks apart, with cycles able to be repeated after 6 months. Although only 6 studies using rituximab for immune disease were identified,[68,76,82,86,88,91] the approximate 6% HBVr rate for rituximab was more than twice that of the 2.4% rate observed for other biologic agents, and reactivation was observed even after just 1 cycle.[91] Additionally, among the patients receiving biologic agents for autoimmune disease, all 4 noted cases of hepatitis flare were observed with rituximab, whereas no cases were observed among patients receiving other biologic agents. Of note, methylprednisolone 100 mg intravenous is administered concurrently with each cycle of rituximab, which may augment the resulting immunosuppression. Rituximab is also used off-label for desensitization in ABO-incompatible transplant recipients or with the presence of preformed donor-specific antibodies. Of concern, despite the lower rituximab doses used for this indication (375 mg/m^2 or 200 mg in 1 or 2 divided doses within 8 days prior to transplant) among kidney

transplant patients, rituximab was again associated with increased HBVr rates when compared with those with no rituximab therapy (6.5% vs 3.2%), with a high associated incidence of hepatitis or liver failure. Therefore, we would recommend prophylaxis over preemptive therapy for any patient receiving rituximab, particularly when given in addition to other immunosuppressing pharmacotherapies and continuing prophylaxis for at least 6 months following rituximab discontinuation.

In contrast, despite the recent FDA black box warning for HBVr on all DAAs,[7] among the 8398 patients with resolved HBV infection included in this study, HBVr was rare (0.3% incidence), transient, or quickly resolved following administration of antiviral therapy and clinically insignificant, with no reported cases of hepatitis. Although it should be noted that a case of fulminant HBVr has been reported in the literature,[118] these results suggest that patients with resolved HBV infection are at low risk of HBVr with DAA therapy, and withholding universal prophylaxis in favor of clinical monitoring for liver dysfunction (ie, ALT elevation) alone appears appropriate. Similarly, HBVr following the receipt of non–rituximab-based DMARD therapy was uncommon despite prolonged therapeutic courses and rarely resulted in hepatitis, supporting successful management without prophylactic therapy.

Although anti-HBs serology is rarely addressed by guidelines in the assessment of the need for prophylactic antiviral therapy (Table 1), lack of anti-HBs was noted to be a profound predictor of HBVr in numerous studies across varying patient populations (oncologic, autoimmune, and transplant).* In one study,[95] it was noted that anti-HBs titers were significantly lower in patients with HBVr (median 2.83 vs 99.94 mIU/mL; $P = 0.036$), and similarly in another study of rituximab-containing chemotherapy with an overall 7.4% HBVr rate, it was noted that no patient with an anti-HBs titer of $\geqslant$100 mIU/mL experienced reactivation.[23] Of note, the NCCN considers serial HBV DNA monitoring and preemptive therapy to be a reasonable alternative to prophylaxis for patients receiving rituximab-based chemotherapy with high anti-HBs titers.[13] We believe that evaluation of whether select anti-HBs positive patients with resolved HBV infection may be able to forgo prophylactic therapy in lieu of enhanced monitoring should be a subject of future research, though it should be cautioned that anti-HBs titers may decrease with the introduction of immunosuppressive therapies† and even become negative.[21,91,104,114] Thus, periodic monitoring of anti-HBs is likely needed, particularly for patients with borderline ($>$10-100 mIU/mL) levels, if prophylaxis is decided against on the basis of high anti-HBs titers. Alternatively, the KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guidelines advocate for vaccination of patients with resolved HBV infection to achieve anti-HBs titers $>$100 mIU/mL[14]; this also deserves consideration as a possible strategy to reduce HBVr risk. Given the evidence for a protective role of anti-HBs among patients with resolved HBV infection, we advocate for the routine monitoring and reporting of anti-HBs serology in future studies.

Limitations of the current study should be recognized. First, the majority of the included studies were conducted in HBV-endemic areas (eg, Asian populations), where acquisition of HBV occurs most commonly during the perinatal period or childhood and is more likely to lead to immune tolerance and chronic HBV infection than HBV acquisition in adulthood. Whether or not this may affect the likelihood of HBVr is not currently known. Second, we did not exclude studies where HBVr prophylaxis was utilized in order to capture more studies and to reflect "real world" practice; however, it should be acknowledged that this may result in a falsely low impression of an agent's baseline risk when evaluating HBVr rates. Third, to address the issue of studies where $<$100% of the cohort received a drug of interest, a study was included with the rituximab for chemotherapy group if at least 10% of the cohort received rituximab and a study was included with the biologics for autoimmune disease group if at least 20% of the cohort received a biologic. Therefore, potential "dilution" of the specific drug's true HBVr risk is possible, without affecting our ultimate recommendations for management. Conversely, the potential for publication bias resulting in an inflated impression of HBVr risk must be acknowledged, though we were still able to identify several published studies reporting no HBVr. Finally, the potential for drug-induced hepatotoxicity independent of HBVr risk should also be recognized. The majority of liver function test (LFT) elevations among HBV infected patients is not a result of HBVr,[58,119] and HBV infected individuals may be at increased risk for hepatotoxicity than uninfected individuals.[22] Therefore, more frequent LFT monitoring may be indicated for patients with resolved HBV infection receiving hepatotoxic immunosuppressants even if the associated risk for HBVr is low.

Conclusion

Among patients with resolved HBV infection, rituximab was associated with an elevated risk of clinically significant HBVr and hepatitis, and thus, the use of prophylactic therapy is justified, even for nononcological indications. Conversely, HBVr was rare among patients receiving biologic/DMARD therapy or DAA treatment of hepatitis C and was associated with a low risk of hepatic complications. HBV DNA or LFT monitoring, but not universal prophylaxis, is a reasonable management strategy. Screening for anti-HBs is advised to better assess HBVr risk.

*References 9, 23, 28, 32, 33, 36, 38, 41, 42, 48, 52, 73, 94, 99, 101
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