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Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports

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Background: Rituximab has been associated with hepatitis B virus reactivation (HBV-R). However, the characteristics and scope of this association remain largely undefined.
Methods: We completed a comprehensive literature search of all published rituximab-associated HBV-R cases and from the Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) MedWatch database. Literature and FDA cases were compared for completeness, and a meta-analysis was completed.
Results: One hundred and eighty-three unique cases of rituximab-associated HBV-R were identified from the literature ($n = 27$ case reports, $n = 156$ case series). The time from last rituximab to reactivation was 3 months (range 0–12), although 29% occurred >6 months after last rituximab. Within FDA data ($n = 118$ cases), there was a strong signal for rituximab-associated HBV-R [proportional reporting ratio = 28.5, 95% confidence interval (CI) 23.9–34.1; Empiric Bayes Geometric Mean = 26.4, 95% CI 21.4–31.1]. However, the completeness of data in FDA reports was significantly inferior compared with literature cases ($P < 0.0001$). Among HBV core antibody (HBcAb(+)) series, the pooled effect of rituximab-based therapy showed a significantly increased risk of HBV-R compared with nonrituximab-treated patients (odds ratio 5.73, 95% CI 2.01–16.33; $Z = 3.33$, $P = 0.0009$) without heterogeneity ($\chi^2 = 2.12$, $P = 0.5473$).
Conclusions: The FDA AERS provided strong HBV-R safety signals; however, literature-based cases provided a significantly more complete description. Furthermore, meta-analysis of HBcAb(+) series identified a more than fivefold increased rate of rituximab-associated HBV-R.
Key words: FDA, HBV reactivation, hepatitis B virus, non-Hodgkin's lymphoma, rituximab

introduction

Although effective vaccines for prevention of hepatitis B virus (HBV) infection have been available for >25 years, nearly 400 million persons are infected worldwide [1, 2]. Many individuals infected with active HBV maintain a persistent carrier state, defined as serologic presence of HBV surface antigen (HBsAg+). Immunosuppressive therapy with glucocorticosteroids and immunosuppressant drugs or with anticancer chemotherapy has been shown to cause a flare or 'reactivation' of HBV that may lead to liver failure and death.

Without prophylaxis, hepatitis B virus reactivation (HBV-R) occurs in up to 85% of HBsAg(+) non-Hodgkin's lymphoma (NHL) patients who receive steroid-containing chemotherapy with associated HBV-related death rates of 30%–50% [3–8]. With appropriate antiviral prophylaxis, chemotherapy-related HBV-R is significantly decreased [9–11], although the risk of reactivation and liver failure/death remains [12, 13]. Many patients with prior HBV infection have cleared the virus serologically; these patients typically have core HBV antibody-positive (HBcAb+) and HBsAg(−) disease. When treated with chemotherapy and/or steroids, these patients have a low risk of HBV-R (<1% to 2%) [6, 14]. The risk of rituximab-associated HBV-R in HBcAb+ patients has not been adequately analyzed or quantified.

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The anti-CD20 monoclonal antibody, rituximab, has revolutionalized the treatment of NHL. Rituximab is an overall well-tolerated drug with minimal late toxicity. However, recent data have suggested an increased risk of infectious complications, in particular viral mediated [15]. In July 2004, based on three case reports [16–18], the Food and Drug Administration (FDA) and manufacturers of rituximab issued a 'Dear Health Care Professional' letter regarding rituximab-associated HBV-R and encouraged health care professionals to submit any related reports to the FDA Adverse Event Reporting System (AERS) MedWatch system [19]. Since that time, multiple case reports and several retrospective series of rituximab-induced HBV-R have been reported in the literature and submitted to the FDA. In addition, several recent reports have documented fatal 'late' HBV-R occurring >6 months after completion of rituximab [20–24], which is an unusual occurrence with chemotherapy-associated HBV-R (i.e. without rituximab) [14]. Despite these reports, the characteristics and scope of rituximab-induced HBV-R remain poorly characterized. Moreover, the absolute risk that rituximab contributes to HBV-R in HBcAb(+) or HBsAg(+) patient populations is not known.

Through a systematic literature review, we examined the characteristics, incidence, and clinical outcomes of patients with lymphoproliferative diseases, who developed HBV-R after exposure to rituximab-based therapy. Further, we analyzed the quality and completeness of case reports available in the medical literature compared with those reported to the FDA. We also completed a meta-analysis in order to estimate the risk that rituximab adds to HBV-R.

methods

data sources

The literature search covered the period from November 1997, the date rituximab received its initial FDA approval, through 30 September 2009 (Medline and EMBASE MeSH search terms: hepatitis, HBV, rituximab, monoclonal antibody, lymphoma, and lymphoproliferative diseases, including chronic lymphocytic leukemia (CLL). Data sources included two surveillance cases at Northwestern Memorial Hospital, two cases at Chang Gung Memorial Hospital in Taiwan, and 183 unique reports from the medical literature. The FDA AERS data was from the same time period (November 1997 through September 2009), using all Medical Dictionary for Drug Regulatory Affairs preferred terms that contained 'HBV' and was limited to patients whose documented indication for rituximab included lymphoproliferative diagnoses. We identified 118 unique cases in the FDA MedWatch database (104 of which submitted as 'expedited' reports).

study selection

Three independent reviewers extracted data from all case reports, case series, and cohort series that reported an association of rituximab with HBV-R. Inclusion criteria for rituximab-associated HBV-R included receipt of at least one dose of rituximab (alone or combined with other therapy) for the treatment of a lymphoproliferative disease before HBV-R and no history of prior solid organ transplant or hematopoietic stem cell transplantation. Duplicate reports were identified based on demographic and clinical criteria, including age, sex, concomitantly administered drugs, and underlying illnesses. Two literature reports of rituximab-associated HBV-R not associated with NHL were excluded (vasculitis [25] and gloumerulonephritis [26]).

For literature reports, HBV-R was defined as a >10-fold rise in serum HBV DNA levels with an accompanying increase in serum ALT compared with baseline. HBV-related hepatitis was defined as an increase in serum ALT more than two times greater than baseline and a 10-fold increase in serum HBV DNA levels, while HBV-related liver failure was defined as elevated serum ALT level together with prolonged prothrombin time or other evidence of coagulopathy. HBV-related death was defined as death of a patient, who had documented HBV-R, evidence of fulminant liver failure, and no other apparent cause of death.

data analysis

The statistical signal strength of the association between rituximab exposure in lymphoproliferative patients and HBV-R was calculated using the proportional reporting ratio (PRR) and the Empirical Bayesian Geometric Mean (EBGM) [27–29]. The PRR and EBGM were calculated by identifying all patients in the FDA AERS from rituximab's initial FDA approval, who were treated for a lymphoproliferative disease. These signal detection calculations provide assessments of the disproportionality of the frequency of a specific reaction for a given drug in comparison to what would be predicted for that drug based on reports of that adverse effect associated with all other drugs in the dataset. A completeness analysis was carried out comparing completeness of cases submitted to the FDA AERS database compared with cases abstracted from the medical literature or from our active surveillance efforts; we prespecified the covariates to be collected prior to data abstraction. To compare frequencies, we used Fisher's exact test. The Wilcoxon rank sum test was utilized to analyze differences in patient ages and time to HBV-R. We used Thomas Lumley's Bioconductor package 'rmeta', version 2.16: to carry the calculations for the meta-analysis of the incidence of rituximab-associated HBV-R, to conduct the Mantel–Haenszel analysis [and confidence intervals (CIs)], to carry the Woolf test for heterogeneity, and to create the forest plots. In order to obtain forest plots for studies that contained a zero count, we added a single count to all cells in the corresponding 2×2 table.

results

patients' characteristics

From 1997 through 2009, 183 rituximab-associated HBV-R unique cases were reported in the medical literature: 27 published as case reports and 156 through case series. The vast majority (99%) of these cases were reported after 2004 with 85% reported in the last 2 years. The 2 Northwestern cases, 2 Taiwan surveillance cases and 27 literature case reports were grouped together for purposes of analysis. In this group of 31 patients, 16 had HBcAb(+) (HBsAg−) rituximab-associated HBV- R, while 15 had HBsAg(+) (Tables 1 and 2). The median age at HBV-R was 55 years, range 21–79 (19 males/12 females); median age for HBcAb(+) patients was 60.5 years, and 42 years for the HBsAg(+) group ($P = 0.05$). Lymphoproliferative histologies were diffuse large B-cell lymphoma ($n = 19$), indolent NHL ($n = 8$), CLL ($n = 2$), and mantle-cell lymphoma ($n = 2$). Of note, 25 of these 31 patients had received concurrent immunosuppressive therapy (chemotherapy ± glucocorticosteroids $n = 23$, glucocorticosteroids alone $n = 2$), while only 6 cases involved single-agent rituximab treatment. Each of these six latter patients had received additional immunosuppressive therapy prior to rituximab treatment (at 2, 3, 4, 12, 24, and 34 months).

The median number of rituximab doses received before HBV-R was 6 (range 3–10). The median time from last rituximab dose to HBV-R was 3 months (range 0–12), while

Table 1. HBV core antibody-positive (surface antigen negative) rituximab-associated HBV reactivation: case reports

Author	NHL type	Age/ gender	Co-morbidity	Prior immunosuppressive therapy	Concurrent immune suppressants	Time to reactivate from first rituximab	Doses of rituximab	Time to reactivate from last rituximab	Liver outcome	Treatment of reactivation	Death
Dervite et al. [18]	FL	69/M	None	7 cycles CHEP and IFN, then 6 cycles HDAC (1 year prior)	Steroids for 6 months immediately prior	7 months	4	6 months	Hepatitis	NR	No
Westhoff et al. [16]	DLBCL	73/M	None	CHOP 3 months prior	None	3 months	NR	1 month	Liver failure	Lamivudine	Yes
Niscola et al. [30]	CLL	51/M	None	Fludarabine 34 months prior	None	26 months	10	1 month	Liver failure	Lamivudine	Yes
Sarrecchia et al.[31]	CLL	53/M	HTN	Fludarabine 2 years prior	None	4 months	3	1 month	Liver failure	Lamivudine	Yes
Law et al [32]	DLBCL	67/M	None	None	CHOP	5 months	8	1 month	Liver failure	Lamivudine	Yes
Sera et al. [33]	Indolent NHL	59/M	None	CHOP 3 years prior, Dex and VCR 1 year prior	Etoposide, prednisone	2 months	3	0 month	Liver failure	Lamivudine	Yes
Ozgonenel et al. [34]	DLBCL	21/M	Evans syndrome	None in 6 years prior	CHOP	2 months	3	0 month	Liver failure	Lamivudine	Yes
Yamagata et al. [35]	DLBCL	55/M	None	None	CHOP	6 months	7	1 month	Liver failure	Lamivudine	Yes
Colson et al. [36]	DLBCL	48/M	None	None	CHOP	4 months	4	1 month	Hepatitis	Entecavir	No
Garcia-Rodriguez et al. [21]	FL	53/F	None	Yes (not stated-third-line therapy)	CHOP	11 months	3	9 months	Hepatitis	Lamivudine	No
Garcia-Rodriguez et al. [21]	DLBCL	68/F	None	None	CHOP	17 months	6	12 months	Liver failure	Lamivudine	Yes
Miyagawa et al. [37]	DLBCL	75/M	None	None	CHOP	10 months	6	6 months	Hepatitis	Lamivudine	No
Koo et al. [38]	MCL	71/M	None	None	CHOP	15 months	9	0	Liver failure	NR	NR
Northwestern active surveillance, 2007	DLBCL	61/M	Prior GIST	None	CHOP and radiation	5 months	6	1 month	Liver failure (warranting liver transplant)	Adefovir	No
Northwestern active surveillance, 2009	DLCBL	47/F	None	None	CHOP	10 months	6	0 months	Hepatitis	Tenofovir	No
Taiwan active surveillance, 2009	DLBCL	79/F	None	None	CHOP	6 months	6	2 months	Hepatitis	Telbivudine	No

NHL, non-Hodgkin's lymphoma; FL, follicular lymphoma; CLL, chronic lymphocytic leukemia; FSGN, focal segmental glomerulonephritis; M, male; F, female; pts, patients; HBV, hepatitis B virus; DLBCL, diffuse large B-cell lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CHEP, cyclophosphamide doxorubicin, etoposide, prednisone; CP, cyclophosphamide, prednisone; AZA, azathioprine; IFN, interferon; HDAC, high-dose cytarabine; GIST, gastrointestinal stromal tumor; SLL, small lymphocytic lymphoma; NR, not reported; VCR, vincristine; Dex, dexamethasone.

Table 2. HBV surface antigen positive rituximab-associated HBV reactivation: case reports

Author	NHL type	Age/gender	Comorbidity	Received prophylaxis (lamivudine)	Prior immunosuppressive therapy	Concurrent immune suppressants	Time to reactivate from first rituximab	Doses of rituximab	Time to reactivate from last rituximab	Liver outcome	Treatment of reactivation (drug)	Death
Tsutsumi et al. [39]	DLBCL	68/F	None	No	None	CHOP	4 months	3	3 months	Liver failure	Yes (lamivudine)	Yes
Dai et al. [20]	DLBCL	21/M, 33/M, 41/F, 42/M	None	Yes (through 4 weeks after R-CHOP)	None	CHOP (all pts)	8–12 months	6 (all pts)	4, 6, 6, and 8 months	Hepatitis	Yes (lamivudine—all)	None
Law et al. [40]	FL	57/M	None	Yes	None	CHOP	9 months	6	5 months	Liver failure	Yes (tenofovir; lamivudine resistant)	Yes
Perceau et al. [23]	Cutan NHL	78/F	None	No	CVP 6 years prior, CEP 2 year prior	None	13 months	4	12 months	Liver failure	Yes (lamivudine)	Yes
Kaled et al. [41]	WM	32/F	None	No	None	Fludarabine	9 months	7	5 months	Hepatitis	Yes (lamivudine and adefovir)	No
Yang et al. [24]	FL	41/F	None	No	Leukeran 1 year prior	None	13 months	4	12 months	Hepatitis	Yes (lamivudine)	No
Marino et al. [42]	DLBCL	59/M	None	No	None	CHOP	9 months	8	3 months	Liver failure	Yes (lamivudine resistant)	Yes
Wasmuth et al. [43]	Indolent NHL	55/M	None	No	None	Fludarabine based	6 months	6	2 months	Liver failure	Yes (lamivudine)	Yes
He et al. [22]	DLBCL	29/F	None	Yes	None	Chemotherapy	12 months	NR	7 months	Hepatitis	Yes (lamivudine)	No
Dillon et al. [44]	DLBCL	21/F	None	No	None	CHOP	3 months	4	0 months	Liver failure	Yes (lamivudine)	Yes
Aomatsu et al. [45]	DLBCL	57/F	None	No	No	CHOP	10 months	6	5 months	Liver failure	Yes (lamivudine and plasma exchange)	Yes
Taiwan active surveillance, 2009	SLL	56/M	None	Yes (lamivudine)	R-CVP × 8 (1 year prior) and rituximab maintenance	No	14 months	10	1 month	Hepatitis	Yes (adefovir and entecavir; lamivudine resistant)	No

NHL, non-Hodgkin's lymphoma; FL, follicular lymphoma; WM, Waldenstroms macroglobulinemia; SLL, small lymphocytic lymphoma; M, male; F, female; Cutan, cutaneous; pts, patients; HBV Hepatitis B virus; DLBCL, diffuse large B-cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP, rituximab, cyclophosphamide vincristine, prednisone; CEP, cyclophosphamide, etoposide, prednisone; NR, not reported.

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HBV-R occurred at a median of 1 month (range 0–12) after the last dose of rituximab for HBcAb(+) patients compared with 5 months (range 0–12) for HBsAg(+) cases ($P = 0.021$). Of note, 29% of all HBV-Rs occurred ≥6 months after the last dose of rituximab [12.5% of HBcAb(+) versus 40% of HBsAg(+) cases]. Of the HBsAg(+) HBV-R group, 7 of 15 patients received prophylactic antiviral therapy (most commonly lamivudine); 5 of 7 HBV-Rs occurred after discontinuation of antiviral therapy. In terms of outcome, 55% of patients experienced fulminant liver failure (17 of 31), while the remaining had HBV-related hepatitis. Furthermore, 48% (15 of 31) of patients with rituximab-associated HBV-R died.

FDA MedWatch data

Over the same 12-year period, 118 cases of rituximab-associated HBV-R were submitted to the FDA AERS database that met our search criteria. The statistical signal in the AERS database was very strong for an association of HBV-R in lymphoproliferative patients treated with rituximab (PRR = 28.5, 95% CI 23.9–34.1, EBGM = 26.4, 95% CI 21.4–31.1). Sixty-eight percent of all cases were reported after 2004 with 31% being reported in the last 2 years. Further, 54% (64 of 118) of FDA HBV-R cases were reported from the United States, while the remaining cases were reported from outside the US. This compares to medical literature HBV-R cases, where only 9% (17 of 183) were from the United States ($P < 0.002$). Median age of FDA cases was 57.5 years (range 21–83) with a male-to-female ratio of 1.73. The case fatality rate among FDA AERS reports was 58.4%. Twenty-seven random FDA AERS cases, matched to year reported, were extracted and compared with literature case reports for data completeness. Comparison of completeness of source data of the literature case reports versus the FDA AERS reports is contained in Table 3. The literature cases were more complete with an overall completeness ratio for literature reports versus the FDA cases of 2.37 ($P < 0.0001$).

case series: meta-analysis of HBV reactivation

Of rituximab-associated HBV-R cases reported through case series ($n = 156$), 80 were HBcAb(+)/HBsAg(−) and 76 HBsAg(+) (Tables 4 and 5). Of all case series, five included a control group (i.e. treated with nonrituximab therapy) [46,48,49,51,53]; the series by Wang et al. [54] was not included as HBV-R was not adequately defined. The cumulative incidence of rituximab-associated HBV-R among these five series was significantly higher at 8.2% (20 of 244) compared with 0.6% (3 of 453) for the chemotherapy-alone group ($P < 0.0001$). The pooled effect of rituximab-based therapy on HBV-R remained significantly increased under a fixed effects model [odds ratio (OR) 5.64, 95% CI 2.18–14.54, $P = 0.0003$] with no evidence of heterogeneity between studies (Figure 1).

Since only one of the five series in the meta-analysis contained a HBsAg(+)-related series [53], it is difficult to draw definitive conclusions among this patient group regarding the added risk that rituximab contributes to reactivation. If only the four HBcAb(+) case series are included in the meta-analysis [46,48, 49,51], the OR remained highly significant at 5.73 (95% CI 2.01–16.33; $Z = 3.33$, $P = 0.0009$) without heterogeneity ($\chi^2 = 2.12$, $P = 0.5473$). It should also be noted, that the incidence and mortality rates of rituximab-associated HBV-R varied considerably across all case series. Among all HBcAb(+) case series, the incidence of HBV-R ranged from 2.7% to 45%, while the associated mortality rates varied from 0% to 50% (Table 4). For HBsAg(+) cases, the rate of HBV-R ranged from 16% to 80% (Table 5).

antiviral prophylaxis data

Among HBsAg(+) case series, data regarding the effectiveness of prophylactic antiviral medications in rituximab-treated patients was mixed. Tsutsumi et al. [53] showed that 0 of 10 rituximab-treated patients who received antiviral prophylaxis had HBV-R, while 4 of 15 (27%) without lamivudine prophylaxis experienced

Table 3. Completeness/quality of case reports: literature versus FDA MedWatch database

Type of information	Literature case reports ($n = 27$) % reporting	FDA AERS cases ($n = 27$) % reporting	Completeness ratio	P^a
HBV status[b]	100	15	6.67	<0.0001
NHL subtype	93	78	1.19	0.145
Age and gender	93	81	1.15	0.226
Prior/current immunosuppressive therapy	100	63	1.59	0.001
Number of doses of rituximab received	93	59	1.58	0.011
Time from last dose of rituximab	100	74	1.35	0.008
Liver outcome	96	52	1.85	0.001
Treatment of reactivation	89	19	4.68	0.000
Survival	96	89	1.08	0.312
Overall completeness	96 (232/242)	59 (143/242)	1.63	<0.0001

[a]Two-sided Fisher P value.

[b]HBcAb(+) or HBsAg(+).

HBV, hepatitis B virus; NHL, non-Hodgkin's lymphoma; FDA, Food and Drug Administration; AERS, Adverse Event Reporting System.

Table 4. HBV core antibody positive (surface antigen negative) rituximab-associated HBV reactivation: case series

Author	NHL type	Concurrent immune suppression	Incidence of rituximab-associated HBV reactivation (versus nonrituximab reactivation, if available)	Time from last rituximab and/or chemotherapy	Mortality rate (rituximab groups)[a]
Hui et al. [46]	Mixed NHL and HL ($n = 233$)	Rituximab/chemotherapy ($n = 88$); chemotherapy alone ($n = 145$)	8.0% (7/88) with rituximab/chemotherapy (versus 0.1% (1/145) chemotherapy, $P < 0.001$)[b]	8–28 weeks conversion to HBsAg(+), but 8–212 weeks HBV DNA (after last therapy)[c]	43%
Li et al. [47]	DLBCL ($n = 11$)	CHOP	45% (5/11) with HBV reactivation	NR	40%
Targhetta et al. [48]	Mixed ($n = 319$)	Rituximab/chemotherapy ($n = 74$) and chemotherapy alone ($n = 245$)	2.7% (2/74) with rituximab/chemotherapy (versus 0.8% (2/245) with chemotherapy, $P < 0.05$)	NR	0
Yeo et al. [49]	DLBCL ($n = 46$)	Rituximab/CHOP ($n = 21$); CHOP ($n = 25$)	24% (5/21) with R-CHOP (versus 0/25 with CHOP, $P < 0.0148$)	1–5 months	20%
Hanbali et al. [50]	Mixed ($n = 26$)	Mixed ($n = 26$)	27% (7/26) acute liver events[d] with rituximab-based therapy; 5/7 with liver failure	Median onset acute liver events[d] 6.2 months after rituximab (2 pts developed acute liver events at 21 and 36 months)	NR
Fukushima et al. [51]	Mixed ($n = 48$)	Mixed ($n = 48$)	6% (2/32) who received rituximab with HBV reactivation (versus 0/16 without rituximab)	8 months from last rituximab dose	0
Kusumoto et al. [52]	Mixed ($n = 50$)	None/rituximab alone ($n = 2$), R-CHOP ($n = 40$), R-chemotherapy without steroids ($n = 4$), ASCT ($n = 3$)	NR; 50 total pts with reactivation; 40% of pts with fulminant liver failure	NR	50%

[a]Among pts with HBV reactivation.

[b]Six of 49 pts receiving rituximab plus steroid-containing regimen versus 2/195 pts without rituximab plus steroid-containing regimen developed HBV-related hepatitis (12.2% versus 1.0%, respectively, $P < 0.001$); on multivariate analysis, rituximab plus steroid-containing regimen was the only independent factor associated with HBV-related hepatitis after chemotherapy (RR, 13.8; 95% CI 2.8–68.3; $P < 0.001$).

[c]HBV DNA level preceded de novo HBV-related hepatitis by median 18.5 weeks.

[d]Acute liver events were defined by acute elevation of liver enzymes, abnormal liver biopsy diagnostic of hepatitis or liver necrosis, hepatic encephalopathy, or demonstration of active viral DNA replication by PCR.

NHL, non-Hodgkin's lymphoma; HL, Hodgkin lymphoma; wks, weeks; pts, patients; HBV Hepatitis B virus; DLBCL, diffuse large B-cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; ASCT, autologous stem cell transplantation; NR, not reported; RR, relative risk.

HBV-R. However, we recently reported that use of prophylactic lamivudine did not decrease the risk of HBV-R with a rate of reactivation of 80% among rituximab-based treated patients regardless of use of antiviral prophylaxis (Table 5) [55]. In our case series, we noted two episodes of breakthrough HBV-related hepatitis associated with lamivudine-resistant tyrosine–methionine–aspartate–aspartate HBV mutants.

discussion

Through a comprehensive literature review and meta-analysis, we attempted to characterize the scope of rituximab-associated HBV-R. The vast majority of rituximab-related clinical trials have excluded patients with history of HBV exposure; thus, the extent of rituximab-associated HBV-R data is primarily from the medical literature and through reports to the FDA

Table 5. HBV surface antigen-positive rituximab-associated HBV reactivation: case series

Author	NHL type	Received prophylaxis (lamivudine)	Concurrent immune suppressants	Incidence of rituximab-associated HBV reactivation (versus nonrituximab reactivation, if available)	Mortality
Tsutsumi et al. [53]	Mixed	10/25 rituximab-based with prophylaxis[a]	Rituximab alone, rituximab/chemotherapy, chemotherapy alone ($n = 47$)	20% (1/5) rituximab alone and 16% (3/20) rituximab/chemotherapy (versus 0/22 chemotherapy, $P = 0.07$)	NR
Wang et al. [54]	DLBCL	None	CHOP ($n = 13$)	33% (13/40) rituximab/chemotherapy with hepatic dysfunction (versus 34% (14/41) chemotherapy)	NR
Hanbali et al. [50]	Mixed	None	Mixed ($n = 6$)	65% (4/6) with acute liver events[b] and 30% (2/6) with liver failure	NR
Pei et al. [55]	Mixed	5/15 received lamivudine	Mixed ($n = 15$)	80% (12/15) with reactivation[d]	17%[c]
Kusumoto et al. [52]	Mixed	NR	None/rituximab alone ($n = 7$), R-CHOP ($n = 24$), R-chemotherapy without steroids ($n = 15$)	NR (47 total pts with reactivation); 21% of pts with fulminant liver failure	28%

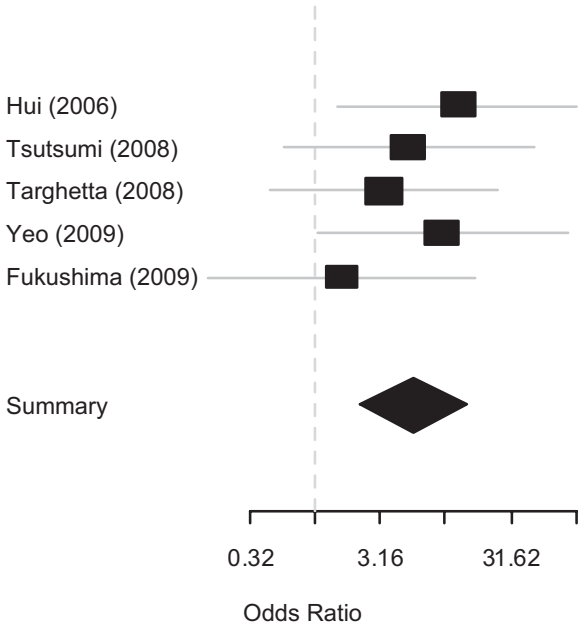
[a]Zero of 10 HBV reactivation for pts with lamivudine prophylaxis versus 4/15 (27%) without antiviral prophylaxis.
[b]Acute liver events defined by acute elevation of liver enzymes, abnormal liver biopsy diagnostic of hepatitis or liver necrosis, hepatic encephalopathy, or demonstration of active viral DNA replication by PCR.
[c]One of 4 that received prophylaxis died versus 1/8 without prophylaxis.
[d]Four of 5 (80%) that received lamivudine with HBV reactivation versus 8/10 (80%) without prophylaxis with HBV reactivation.
NHL, non-Hodgkin's lymphoma; HBV Hepatitis B virus; DLBCL, diffuse large B-cell lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; NR, not reported.

MedWatch system. Over a 12-year period, 183 cases of rituximab-associated HBV-R were reported through the medical literature and 118 cases to the FDA. From literature case reports, 55% of patients experienced liver failure, while the associated mortality rate was 48%. In addition, from case series that had an associated nonrituximab-treated control group, a significant increase in rituximab-associated HBV-R was documented. In interpreting these observations, several factors should be considered.

Increasing evidence has linked rituximab to viral infections including herpes simplex virus, cytomegalovirus, and JC virus [15, 56]. In February 2006, the rituximab label was changed to include information for NHL patients who developed serious viral infections after rituximab treatment [57]. However, the incidences and characteristics of these infections, including risk factors, remain to be elucidated. In addition, the pathophysiology of rituximab-induced viral infections is unclear. The mechanism underlying HBV-R following rituximab treatment is likely more complex than simple B-cell depletion. B-lymphocytes may stimulate cellular immune responses, both to auto-antigens and foreign antigens [58]. Further, Stasi et al. [59] demonstrated following rituximab treatment that significant changes occur in T-lymphocyte activity, including increased Th1/Th2 and Tc1/Tc2 ratios, increased expression of Fas ligand on Th1 and Th2 cells, and expansion of oligoclonal T cells. A role for the importance of B-lymphocytes in HBV-R may also be in part related to reduction of anti-HBV antibodies (i.e. HBsAb+) caused by rituximab and the associated host immunity balance. Tsutsumi et al. [39] showed that despite serum immunoglobulin levels remaining constant through treatment, anti-HBV surface antibody titers significantly decreased with rituximab therapy.

In our data, we found that among HBcAb(+) cases series with an associated nonrituximab-treated control group, there was a more than fivefold higher rate of HBV-R for patients who received rituximab-based therapy. It should also be noted that only one HBV case series was prospective; in that study, Yeo et al. [49] found a HBV-R rate of 25% among HBcAb(+) lymphoma patients, who received rituximab-combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) compared with 0 for CHOP. Given the retrospective nature of most reports and the wide range of HBV-R (3%–45%), it is difficult to make firm recommendations for HBcAb(+) patients. However, in the United States and Europe, it is becoming standard practice to administer antiviral prophylaxis for this patient population [60], although continued prospective studies are needed to clearly delineate the benefit of this strategy.

Controlled data regarding the risk of single-agent rituximab-induced HBV-R in HBsAg(+) or the added risk of rituximab to chemotherapy in this patient population are sparse. Only one of the available five HBsAg(+) case series included a control group treated without rituximab; in that study, Tsutsumi et al. [53] showed that 16% of patients



Study	Rituximab-treated Events	Total	No rituximab Events	Total	Risk ratio M-H, Fixed, 95% CI
Hui et al, 2006[28]	7	88	1	145	12.44 [1.50, 102.94]
Tsutsumi et al, 2008[30]	4	25	0	22	5.24 [0.56, 48.65]
Targhetta et al, 2008[29]	2	74	2	245	3.38 [0.47, 24.38]
Yeo et al, 2009[31]	5	25	0	25	9.37 [1.03, 85.29]
Fukushima et al, 2009[27]	2	32	0	16	1.60 [0.15, 16.66]
Total (95% CI)		**244**		**453**	**5.64 [2.18, 14.54]**
Total events	20		3		
Heterogeneity: Chi^2= 2.12, df=4 (p=0.7145)					
Test for overall effect: Z= 3.65 (p=0.0003)					

Figure 1. Forest plot of case series assessing the risk of HBV reactivation in lymphoma patients treated with rituximab-based therapy compared with nonrituximab controls.

treated with rituximab alone or rituximab/chemotherapy experienced HBV-R compared with 0 patients who received chemotherapy alone. In chemotherapy-related HBsAg(+) studies, the antiviral agent lamivudine has been associated with a significant reduction in chemotherapy-associated HBV-R-related mortality to <5% to 10% compared with 60% to 70% without prophylaxis [9, 11]. Tsutsumi et al. [53] found that 0 of 10 HBsAg(+) rituximab-treated patients given lamivudine had HBV-R compared with 4 of 15 rituximab-treated patients not given prophylaxis. However, we recently reported that prophylactic lamivudine did not decrease the risk of HBV-R in rituximab-treated HBsAg(+) patients, although total patient numbers were small (n = 15) [61]; however, of the four of five HBsAb(+) patients treated with rituximab-based therapy without prophylaxis who experienced HBV reactivation, three of the four occurred after withdrawal of antiviral prophylaxis (duration of prophylaxis: median 2 months after last rituximab dose). An important consideration is the optimal length of antiviral prophylaxis. Several groups advocate continuation of antiviral therapy for at least 6 months following the last cycle of chemotherapy and longer after rituximab [62]. Although with extended use of antiviral therapy, lamivudine resistance is a growing area of concern (up to 30%–35%) [40,42,45,63]. Newer, more potent antivirals with much lower rates of HBV resistance, such as adefovir and tenofovir, should be examined.

It was interesting that over the same period where 183 unique cases were published in peer-reviewed medical literature, only 118 cases were reported to the FDA. Of note, all serious adverse events (such as HBV-R) that occur in United States, as well as ex-United States, are required to be reported to the FDA. FDA AERS is a passive surveillance system with

associated limitations including underreporting, reporting bias, and data completeness. Indeed, we found that cases published in the medical literature were highly superior in data quality compared with FDA reports. Case reports in the FDA database need to be interpreted cautiously as not all cases are systemically validated. Furthermore, the FDA AERS data do not provide true incidence or prevalence information due to lack of information of number of patients exposed. This limits analyses to validated data mining signal detection techniques [27–29]. Nevertheless, it should be acknowledged that the FDA AERS system is worldwide in its scope for drugs approved in the United States and it often provides important safety signals.

Some limitations of our analysis should be noted. The number of HBV-R occurrences depicted here are likely an underestimation of the true incidence. It is difficult to accurately estimate the incidence of rituximab-associated HBV-R among persons with NHL in part due to incomplete reporting of reactivation cases among rituximab-treated patients and incomplete data on the number of unique patients with lymphoid malignancies who have received rituximab. On the other hand, HBV-R cases with morbid/fatal complications are more likely to be reported. Additionally, an interpretation has been that HBV-R occurs mostly in endemic HBV areas (e.g. Hong Kong and Taiwan) [55, 64, 65]. Rates are not as high, but recent data from urban USA centers show that ~10% of all cancer patients treated with immunosuppressive therapy have past or active HBV infection [66, 67]. The retrospective nature of the majority of rituximab-associated HBV-R cases also makes definitive conclusions difficult regarding incidence and mortality. However, given the results of the meta-analysis and the fact that nearly one-third of HBV-R in case reports occurred >6 months after the last rituximab dose, which is an unusual occurrence with chemotherapy alone, supports the likelihood of a real effect of rituximab-mediated HBV-R. 'Delayed' HBV-R (i.e. >6 months) may in part be explained by the long half-life of rituximab, whereby serum levels (and B-cell suppression) may be detected in patients for >6 months [68], while other factors may also be involved (e.g. immunoglobulins and T-cell immunity).

In conclusion, rituximab therapy may increase the risk of developing HBV-R and associated liver failure and death in HBcAb(+) and HBsAg(+) patient populations. As rituximab continues to gain more indications of use (including non-malignant indications) and newer monoclonal CD20 antibodies become clinically available (e.g. ofatumumab), it is important that clinicians and patients be aware of the potential for HBV-R. In the absence of prospective data, it is advisable that patients with HBV infection [HBsAg(+) or HBcAb(+)], who receive rituximab-based therapy receive concomitant antiviral prophylaxis and for at least 9 months after the last rituximab dose. It is critical, however, that prospective studies of antibody-induced HBV-R continue as many unanswered questions remain (i.e. risk of HBV-R with single-agent rituximab; the ideal type, length, and benefit of antiviral prophylaxis, especially in HBsAg(+) populations; identification of additional risk factors (e.g. co-infection with hepatitis C, D, and/or E viruses [69, 70]); and mechanisms of rituximab-associated HBV-R). Finally, increased efforts should be given toward post-marketing drug surveillance and the timely dissemination of data to practicing physicians.

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disclosure

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