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Hepatitis B virus reactivation in HBsAg-negative, anti-HBc-positive patients receiving immunosuppressive therapy: a systematic review

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Abstract

Background The optimal management of HBsAg-negative, anti-HBc-positive patients who receive immunosuppression remains unclarified. We systematically reviewed the available data on potential predictors of the risk of hepatitis B virus (HBV) reactivation in such patients.

Methods A literature search identified 55 studies with 3640 HBsAg-negative, anti-HBc-positive patients who received immunosuppressive regimens.

Results HBV reactivation was reported in 236 (6.5%) patients. The pooled HBV reactivation rates did not differ between patients with detectable or undetectable HBV DNA in studies with hematological diseases or regimens containing rituximab, but it was higher in patients with detectable than in those with undetectable HBV DNA who were taking rituximab-free regimens (14% vs. 2.6%; risk ratio [RR] 12.67, 95%CI: 95%CI 2.39-67.04, P=0.003) or had non-hematological diseases, although the latter was not confirmed by sensitivity analysis (RR 8.80, 95%CI 0.71-109.00, P=0.09). The pooled HBV reactivation rates were lower in patients with positive than in those with negative anti-HBs in studies with hematological (7.1% vs. 21.8%; RR 0.29, 95%CI 0.19-0.46, P<0.001) or non-hematological (2.5% vs. 10.7%; RR 0.28, 95%CI 0.11-0.76, P=0.012) diseases, and rituximab-containing (6.6% vs. 19.8%; RR 0.32, 95%CI 0.15-0.69, P=0.003) or rituximab-free (3.3% vs. 9.2%; RR 0.36, 95%CI 0.14-0.96, P=0.042) regimens.

Conclusions The risk of HBV reactivation is high; therefore, anti-HBV prophylaxis should be recommended in HBsAg-negative, anti-HBc-positive patients with hematological diseases and/or rituximab-containing regimens, regardless of HBV DNA and anti-HBs status. In contrast, patients with non-hematological diseases or rituximab-free regimens have a low risk of HBV reactivation and may not require anti-HBV prophylaxis if they have undetectable HBV DNA and positive anti-HBs.

Keywords Chronic hepatitis B infection, antiviral therapy, lamivudine, entecavir, tenofovir

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Introduction

Although HBsAg-negative, anti-HBc-positive patients have a lower risk of hepatitis B virus (HBV) reactivation compared to HBsAg-positive patients, the prevalence of anti-HBc is higher than that of HBsAg, ranging from 5% in Western to >50% in Far Eastern countries [1-3]. Thus, there are numerically many cases of HBV exacerbations in HBsAg-negative, anti-HBc-positive patients who receive immunosuppressive regimens. Recommendations based mostly on expert opinion state that HBsAg-negative, anti-HBc-positive patients with detectable HBV DNA should be managed similarly to HBsAg-positive patients, while those with undetectable HBV DNA should be followed carefully, with frequent aminotransferases and HBV DNA determinations, or should receive prophylaxis with lamivudine [3]. The type of immunosuppressive regimen seems to affect the probability of HBV reactivation in this setting. In particular, rituximab, an increasingly used anti-CD20 chimeric monoclonal antibody, has been associated with severe HBV reactivations in HBsAg-negative, anti-HBc-positive patients [1].

Recently, the American Gastroenterological Association [4] strongly recommended antiviral prophylaxis in HBsAg-negative, anti-HBc-positive patients treated with B-cell-depleting agents (e.g., rituximab, ofatumumab) because they were considered to be at high risk (>10%) of HBV reactivation. In the same position paper, all the other HBsAg-negative, anti-HBc-positive patients were considered to be at moderate (1-10%) or low (<1%) risk for HBV reactivation [4]. The latter recommendations were considered as weak and based on evidence of moderate quality. In addition, the usefulness of baseline HBV DNA evaluation is not reported, while the document counseled against using anti-HBs to stratify the risk of HBV reactivation [4]. Since literature data are scarce and no strong recommendation has been made, the optimal management of such cases remains controversial.

We systematically evaluated the available data in order to assess the risk of HBV reactivation in HBsAg-negative, anti-HBc-positive patients under immunosuppression in relation to their baseline HBV status (HBV DNA and anti-HBs), as well as the type of underlying primary disease (hematological vs. non-hematological) and immunosuppressive regimen (rituximab-containing vs. rituximab-free).

Materials and methods

Data sources and searches

PubMed and Scopus from January 2006 to February 2015 were searched to identify all medical literature included under the terms "hepatitis B" and "reactivation" or "immunosuppression" or "immunosuppressive therapy". In addition, a manual search of all relevant review articles and of the retrieved original studies was performed.

Study selection

All studies published in English were included if they fulfilled all of the following criteria: 1) they were randomised trials or observational cohort studies; 2) they included adult patients with past HBV infection (i.e., HBsAg-negative, anti-HBc-positive patients) who received immunosuppressive regimens; and 3) there were patients without pre-emptive prophylaxis with nucleos(t)ide analogs (NAs) against HBV reactivation and with available data on the incidence of HBV reactivation. Studies evaluating solid organ transplant anti-HBc-positive recipients were excluded. In each selected study, only patients with a past HBV infection were evaluated, while HBsAg-positive patients were excluded. The only studies analyzed were those that included a comparative evaluation of differences in the risk for HBV reactivation between different groups of patients. The literature search was performed by one author (EC), who screened titles and abstracts and determined which studies could potentially be included. Each study in the list of the preselected papers was independently evaluated by two reviewers (EC, GP) to determine whether it fulfilled all the inclusion criteria.

Data extraction and quality assessment

Data extraction from the finally selected papers was carried out by two authors (EC, PC) according to a predefined form. Any queries regarding data extraction were arbitrated by discussion with another author (GP). Data extracted for selected studies included country and center(s), date of publication, type of study, sample size, age, sex, HBV status before initiation of immunosuppression regarding anti-HBs positivity and HBV DNA detectability, underlying primary disease (hematological or not), type of immunosuppressive regimen (rituximab or not), follow-up period, number of patients with HBV reactivation, administration of NAs after HBV reactivation, and final outcome. A pilot data extraction form was tested and revised. We categorized the included studies as randomized controlled trials (RCTs), prospective or retrospective cohort studies. The Cochrane Collaboration's tool for assessing the risk of bias in RCTs [5] and the Newcastle Ottawa Scale [6] were used to assess the quality of the included randomized and nonrandomized studies, respectively.

Data synthesis and analysis

The outcome of interest involved HBV reactivation in two separate groups: patients with or without hematological disease and patients receiving rituximab-containing or rituximab-free regimens. The pooled rate of HBV reactivation (p_i) was estimated by the inverse variance method, transforming to logits using the equation $lp_i=\log(p_i/[1-p_i])$ with the corresponding variance being $1/(N_i \times p_i \times [1-p_i])$, where p_i represents the estimated probability from the study and N_i represents the corresponding reference population at baseline. Pooled logit estimates and their 95% confidence intervals (CI) were back-transformed to probabilities by the inverse logit transformation $p_i=e^{lpi}/(e^{lpi}+1)$, where e is the base of the natural logarithm [7].

Meta-analysis aims to synthesize the outcomes of each included study into one weighted average to estimate the intervention effect, along with 95%CI to assess the statistical significance. Risk ratios (RR) were calculated for the predefined outcomes and studies were weighted against the natural logarithm of the variance of RR. Random-effects meta-analysis was chosen in advance as the analysis method, to incorporate the assumption that the true effect varies across studies. In cases of zero responders, zero was replaced by 0.5, and the number of participants was corrected accordingly. Funnel plots were produced to visually inspect for publication bias and were assessed using the modified Harbord's test for outcomes when there were ≥10 studies available [8,9].

Heterogeneity was examined visually in the forest plots and its extent was estimated using the I^2 measure, as proposed by Higgins *et al* [10], as low (I^2=25-49%), moderate (I^2=50-74%) and high (I^2≥75%). All analyses were performed using STATA, version 12.0. We considered P<0.05 (two-sided) as significant.

Results

In total, 1120 articles were initially identified from the literature search, but only 58 studies [11-68] fulfilled the inclusion criteria. Six studies, two from a single center in China [32,66], two from a single center in Japan [22,67] and two from Turkey [51,68], had overlapping study periods; in these cases, only the more recent study from each center was included [22,32,51]. Thus, 55 studies with a total of 3640 HBsAg-negative, anti-HBc patients were included in our analysis [11-65]. Study and patient characteristics are presented in Table 1. There was only one RCT [34], 25 prospective [11,13,15,18-23,26,27,29,30,32,35,41,42,47,55-57,60,63-65], 2 prospective/retrospective [17,37], and 27 retrospective cohort studies [12,14,16,24,25,28,31,33,36,38-40,43-46,48-54,58,59,61,62]. The RCT and 26 (48%) of the 54 nonrandomized studies were of low quality.

HBV reactivation under immunosuppressive regimens

HBV reactivation was detected in 6.5% (236/3640) of HBsAg-negative, anti-HBc-positive patients who received immunosuppressive regimens during a median follow up of 24 months (range: 12-49). The definition of HBV reactivation was based on HBsAg reappearance and/or HBV DNA increase (with elevated levels of aminotransferases in 4 studies [27,42,47,54]). The rates of HBV reactivation ranged from 0-85.7% in 22 studies that defined reactivation as both HBsAg reappearance and HBV DNA increase [11-13,20,23,24,26,31-33,36,37,40,42,44,46-48,51,54,56,63], from 0-19.6% in 12 studies that defined reactivation as HBsAg reappearance alone [14,17,19,28,38,39,41,43,45,49,55,62], and from 0-17.9% in 16 studies that defined reactivation as an increase in HBV DNA alone [15,16,18,22,25,27,29,30,34,35,52,53,57,59,60,65]. No definition of HBV reactivation was provided in 5 studies that included 306 patients [21,50,58,61,64].

HBV reactivation occurred during immunosuppressive therapy in 58 patients (between 30 and 300 days after the initiation of immunosuppressive therapy) and after the cessation of immunosuppression in 48 patients (between 14 and 670 days after immunosuppression discontinuation) [12,15,16,28,32,37,40,44,45,48,53-56,59,64,65]. No data regarding the timing of HBV reactivation were provided for 130 patients.

HBV reactivation in patients with or without hematological diseases

The total pooled rate of HBV reactivation was significantly higher in patients with detectable than in those with undetectable serum baseline HBV DNA: 18.8% (95%CI 11.8-28.7) vs. 5.7% (95%CI 3.2-9.8); RR 4.27 (95%CI 1.45-12.56); P=0.008; I^2=31.3%, P for heterogeneity=0.149 (Fig. 1). Evidence of bias was found in HBV DNA comparisons for HBV reactivation risk by visual inspection of funnel plots and by Harbord's modified test (P=0.019).

The total pooled rate of HBV reactivation was also lower in patients with positive than in those with negative anti-HBs: 5.2% (95%CI 3.5-7.6) vs. 17.0% (95%CI 12.5-22.6); RR 0.29 (95%CI 0.19-0.44), P<0.001; I^2=0%, P for heterogeneity=0.993 (Fig. 2). Visual inspection of funnel plots and Harbord's modified test found no evidence of bias in anti-HBs comparisons for HBV reactivation risk (P=0.212).

The pooled rate of HBV reactivation was 10.9% (95%CI 7.8-14.9) in studies including patients with hematological and 3.6% (95%CI 2.2-5.7) in studies including patients with non-hematological diseases. Since no individual study included patients from both groups, no appropriate conclusion could be drawn regarding the RR for HBV reactivation in patients with hematological diseases compared to those with non-hematological diseases.

Comparing patients with detectable and undetectable serum baseline HBV DNA, the pooled rate of HBV reactivation was significantly higher in studies with non-hematological diseases: 14.2% (95%CI 6.9-26.9) vs. 2.0% (95%CI 1.1-3.6); RR 20.59 (95%CI 3.34-126.94), P=0.001; I^2=0%, P for heterogeneity=0.788 [18,20,29,32]. However, it was only numerically higher in studies with hematological diseases: 21.9% (95%CI 12.9-34.7) vs. 11.3% (95%CI 6.3-19.5); RR 2.33 (95%CI 0.69-7.83), P=0.173; I^2=30.5%, P for heterogeneity=0.195 [15,17,34,35,44,47,56] (Fig. 1, 3). In order to explore the wide 95%CIs, we conducted a sensitivity analysis excluding studies with uncertainty in estimates. Patients with detectable rather than undetectable baseline HBV DNA had a numerically higher risk for HBV exacerbation in studies with non-hematological diseases: RR 8.80 (95%CI 0.71-109.00), P=0.090 I^2=0%, P for heterogeneity=0.965 [18,20]. However, there was no difference in studies with hematological patients: RR 0.96 (95%CI 0.32-2.89), P=0.938; I^2=0%, P for heterogeneity=0.795 [15,34,35,44,56].

Likewise, the pooled rate of HBV reactivation was lower in patients with positive than in those with negative anti-HBs in studies with hematological—7.1% (95%CI 4.4-11.2) vs. 21.8% (95%CI 15.3-30.1); RR 0.29 (95%CI 0.19-0.46), P<0.001, I^2=0%, P for heterogeneity=0.862 [15-17,25,28,32,34-

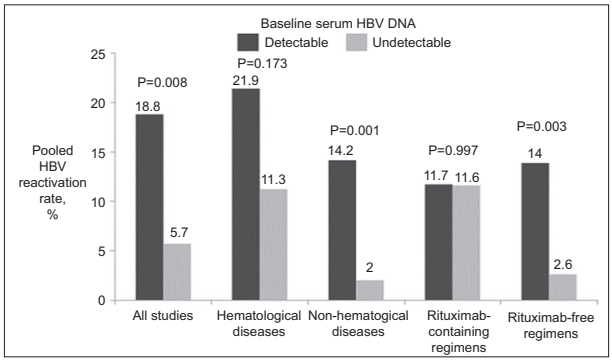

Figure 1 Pooled rates of hepatitis B virus (HBV) reactivation in different subgroups of HBsAg-negative, anti-HBc-positive patients in relation to their baseline serum HBV DNA detectability

Table 1 Published studies regarding reactivation of hepatitis B virus (HBV) infection in HBsAg-negative, anti-HBc-positive patients receiving immunosuppressive therapy

Study [1st author, year (Ref no)]	Category of study	Quality of study*	Patients, n	Age, years, (mean/ median)	Male sex, n	Underlying disease	Mean follow-up, months	Immunosuppressive therapy	Anti-HBs (+)/ HBV DNA (+), n	HBV reactivation, n (%)
Hui, 2006 [47]	PS	8	152	60	NA	Hematological	12	88 rituximab, 64 others	122/17	7 (5)
Li, 2007 [46]	RS	5	11	NA	NA	Hematological	NA	Rituximab	NA/NA	5 (45)
Knoll, 2007 [56]	PS	5	7	NA	5	Hematological	NA	NA	7/3	6 (85.7)
Targhetta, 2008 [45]	RS	5	319	62	NA	Hematological	NA	74 rituximab, 245 others	NA/NA	4 (1)
Matsue, 2009 [36]	RS	7	22	58.6	NA	Hematological	33	NA	18/NA	6 (27)
Fukushima, 2009 [37]	RS/PS	8	48	67.4	26	Hematological	14	32 rituximab, 16 others	NA/0	2 (4)
Ferraro, 2009 [38]	RS	5	42	60.9	NA	Hematological	NA	NA	NA/NA	6 (14)
Hammond, 2009 [39]	RS	6	61	51	43	Hematological	NA	10 rituximab, 51 others	52/0	12 (20)
Yeo, 2009 [44]	RS	7	46	63	NA	Hematological	NA	21 rituximab, 25 others	30/1	5 (11)
Charpin, 2009 [42]	PS	7	21	57.7	15	Rheumatic	27	anti-TNF agents	21/NA	0
Vassilopoulos, 2010[11]	PS	6	19	NA	NA	Rheumatic	NA	anti-TNF agents	NA/NA	0
Ji, 2010 [25]	RS	8	88	NA	50	Hematological	22	43 rituximab, 45 others	65/NA	1 (1)
Caporalli, 2010 [26]	PS	7	67	57.3	26	Rheumatic	43	anti-TNF agents	28/0	0
Loras, 2010 [27]	PS	7	79	51	NA	Gastrointestinal	13	NA	NA/NA	1 (5)
Matsue, 2010 [28]	RS	8	56	71	37	Hematological	26	Rituximab	37/NA	5 (9)
Pei, 2010 [40]	RS	8	95	66	51	Hematological	12	Rituximab	NA/NA	4 (4)
Francisci, 2010 [41]	PS	5	56	NA	NA	Hematological	NA	NA	43/3	3 (5)
Çeneli, 2010 [51]	RS	8	20	48	NA	Hematological	15	Others	12/0	2 (10)
Giaccone, 2010 [43]	RS	7	11	55	NA	Hematological	NA	NA	NA/0	2 (18)
Ramos, 2010 [49]	RS	6	71	49	42	Hematological	47	NA	NA/NA	8 (11)
Cassano, 2011[12]	RS	6	62	54	NA	Dermatological	49	anti-TNF agents	50/0	1 (2)
Urata, 2011[29]	PS	8	135	62.3	NA	Rheumatic	12	83 others, 52 anti-TNF agents	85/0	7 (5)
Tamori, 2011 [30]	PS	8	45	59	6	Rheumatic	23	Others	36/1	1 (2)

(Contd...)

Table 1 *(Continued)*

Study [1st author, year (Ref no)]	Category of study	Quality of study*	Patients, n	Age, years, (mean/ median)	Male sex, n	Underlying disease	Mean follow-up, months	Immunosuppressive therapy	Anti-HBs (+)/ HBV DNA (+), n	HBV reactivation, n (%)
Sugauchi, 2011 [31]	RS	7	166	NA	NA	Hematological	NA	138 rituximab, 28 NA	NA/NA	4 (2)
Koo, 2011 [32]	PS	7	62	67.2	37	Hematological	32	Rituximab	33/0	2 (3)
Lan, 2011 [33]	RS	6	70	50	8	Rheumatic	NA	anti-TNF agents	58/4	1 (1)
Cheung 2011[35]	PS	7	10	67.2	6	Hematological	17	4 rituximab, 6 others	3/7	1 (10)
Vigano, 2011 [55]	PS	5	50	46	NA	Hematological	17	NA	44/NA	6 (12)
Kato, 2011 [57]	PS	5	35	NA	NA	Rheumatic	25	NA	NA/NA	6 (17)
Hagiwara, 2012 [53]	RS	6	27	NA	NA	Solid cancer	NA	Others	NA/NA	2 (7)
Tan, 2012 [21]	PS	7	188	NA	NA	Rheumatic	20	Others	NA/4	2 (1)
Mori, 2012 [22]	PS	5	62	73	NA	Rheumatic	NA	14 others, 48 anti-TNF agents	43/0	0
Peng, 2012 [23]	PS	6	43	59	NA	Solid cancer	NA	Others	30/NA	4 (9)
Matsui, 2013 [16]	RS	8	59	67.9	NA	Hematological	21	NA	39/NA	4 (7)
Kim, 2013 [17]	RS-PS	8	257	NA	NA	Hematological	NA	232 rituximab, 25 others	188/3	19 (7)
Chiu, 2013 [18]	PS	5	3	53	3	Dermatological	NA	anti-TNF agents	2/NA	0
Oh, 2013 [65]	PS	6	67	65.7	NA	Various diseases	NA	Rituximab	NA/1	2 (3)
Saitta, 2013 [19]	PS	5	44	60	13	Solid cancer	NA	Others	20/4	0
Papa, 2013 [20]	PS	5	22	42	NA	Gastrointestinal	NA	anti-TNF agents	NA/NA	0
Huang, 2013 [34]	RCT	low quality†	39	69	28	Hematological	19	Rituximab	25/15	7 (18)
Morisco, 2013 [24]	RS	5	4	NA	NA	Gastrointestinal	NA	anti-TNF agents	NA/NA	1 (25)
Elkady, 2013[48]	RS	5	18	34.4	26	Hematological	NA	Others	NA/NA	5 (28)
Laurenti, 2013 [50]	RS	6	7	51	4	Rheumatic	NA	anti-TNF agents	6/NA	0
Biondo, 2014[13]	PS	7	20	63	7	Rheumatic	45	anti-TNF agents	14/0	0
Ye, 2014 [51]	RS	8	50	NA	NA	Rheumatic	12	anti-TNF agents	40/NA	0
Mikulska, 2014 [14]	RS	7	137	45	84	Hematological	12	33 rituximab, 104 others	124/NA	14 (10)
Hsu, 2014 [15]	PS	8	150	61	NA	Hematological	27	Rituximab	116/5	17 (11)
Masarone, 2014 [54]	RS	6	96	64.4	57	Hematological	NA	48 rituximab, 48 others	NA/96	10 (10.4)

(Contd...)

Table 1 *(Continued)*

Study [1st author, year (Ref no)]	Category of study	Quality of study*	Patients, n	Age, years, (mean/ median)	Male sex, n	Underlying disease	Mean follow-up, months	Immunosuppressive therapy	Anti-HBs (+)/ HBV DNA (+), n	HBV reactivation, n (%)
Navarro, 2014 [58]	RS	7	13	62.1	NA	Dermatological	28.6	anti-TNF agents	8/NA	0 (0)
Nakamura, 2014 [59]	RS	7	57	64	10	Rheumatic	18	anti-TNF agents	46/NA	3 (5.2)
Tamori, 2014 [60]	PS	6	49	60	27	Hematological	NA	30 rituximab, 19 others	NA/NA	8 (16.3)
Nakamoto, 2014 [61]	RS	6	35	NA	NA	Hematological	NA	NA	27/NA	4 (11.4)
Balanti, 2014 [62]	RS	5	25	63.2	NA	Rheumatic	NA	anti-TNF agents	24/0	0 (0)
Seto, 2014 [64]	PS	8	63	NA	25	Hematological	24	Rituximab	NA/0	26 (41)
Barone, 2015 [63]	PS	8	179	57.3	75	Rheumatic	NA	14 rituximab, 165 anti-TNF agents	NA/0	0 (0)

*The Newcastle Ottawa Scale (NOS) was used to assess the quality of nonrandomized studies. In NOS, a 9-score system, studies scored ≥7 were considered as high-quality. The Cochrane Handbook for Systematic Reviews of Interventions was used to assess the quality of the included randomized study (low quality if ≥4 domains had uncertain risk of bias or if 1 domain had a high risk of bias). †The RCT was of low quality because 3 domains (selection bias, performance bias and detection bias) were of high risk of bias

TNF, tumor necrosis factor; Others, other than rituximab or TNF immunosuppressive/chemotherapy agents; RCT, randomized controlled trial, PS, prospective cohort study; RS, retrospective cohort study; NA, not available

36,39,41,44,47,51,55,61]—or non-hematological—2.5% (95%CI 1.5-4.6) vs. 10.7% (95%CI 5.7-19.0); RR 0.28 (95%CI 0.11-0.76) P=0.012; I^2=0%, P for heterogeneity=0.987 [13,18,19,22,23,26,30 ,33,42,50,52,58,59,62]—diseases (Fig. 2, 4).

HBV reactivation with or without rituximab

The pooled rate of HBV reactivation was numerically higher in patients treated with rituximab-containing than in those with rituximab-free regimens: 9.7% (95%CI 6.3-14.6) vs. 4.1% (95%CI 2.8-6.1); RR 1.80 (95%CI 0.99-3.28), P=0.056; I^2=0%, P for heterogeneity=0.849 (Fig. 5). Both groups had numerically close mean durations of follow up (20±12 vs. 22±10 months). The directions of the results were similar even when the rates of HBV reactivation were evaluated separately in prospective—RR 4.91 (95%CI 0.93-26.09), P=0.062 [35,47,63]—and retrospective—RR 1.49 (95%CI 0.74-2.98), P=0.265 [14,25,39,44,45,54]-studies.

HBV reactivation developed after the cessation of immunosuppression in 26 (42%) of 62 patients receiving rituximab-containing regimens (range: 14-409 days) and 6 (32%) of 19 patients receiving rituximab-free regimens (range: 90-300 days). No conclusions could be drawn because of the lack of available data concerning the incidence of HBV reactivation in patients: a) receiving rituximab-containing regimens for hematological vs. non-hematological diseases; or b) receiving rituximab alone vs. rituximab in combination with other regimens, particularly steroids.

The pooled rate of HBV reactivation was significantly higher in patients with detectable than in those with undetectable baseline serum HBV DNA treated with rituximab-free regimens: 14.0% (95%CI 7.5-24.7) vs. 2.6% (95%CI 1.2-5.3); RR 12.67 (95%CI 2.39-67.04), P=0.003; I^2=0%, P for heterogeneity=0.599 [18,20,29,32,34]. However, no such difference was seen in patients treated with rituximab-containing regimens: 11.7% (95%CI 6.5-20.2) vs. 11.6% (95%CI 5.0-24.7); RR 1.00 (95%CI 0.25-3.97), P=0.997; I^2=0%, P for heterogeneity=0.412 [15,34,65] (Fig. 1).

In contrast to baseline HBV DNA status, anti-HBs seropositivity affected the risk of HBV reactivation regardless of rituximab therapy. In particular, the pooled rate of HBV

Figure 2 Pooled rates of hepatitis B virus (HBV) reactivation in different subgroups of HBsAg-negative, anti-HBc-positive patients in relation to their baseline anti-HBs status

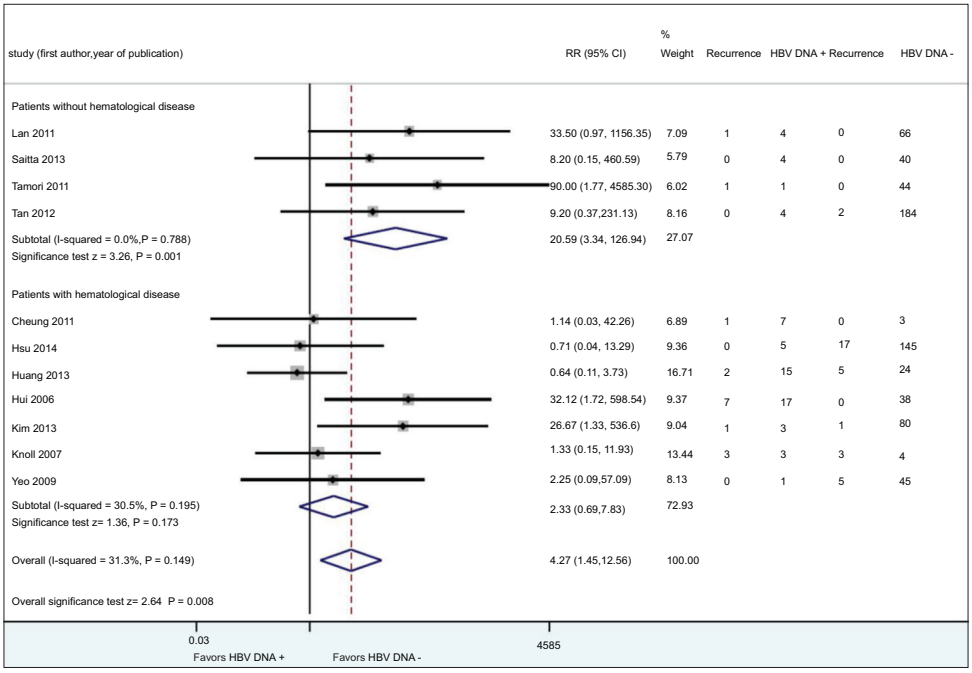

Figure 3 Forest plots of rates of hepatitis B virus (HBV) reactivation between HBsAg-negative, anti-HBc-positive patients with detectable and undetectable HBV DNA in studies with or without hematological diseases
RR, relative risk; 95%CI, 95% confidence interval

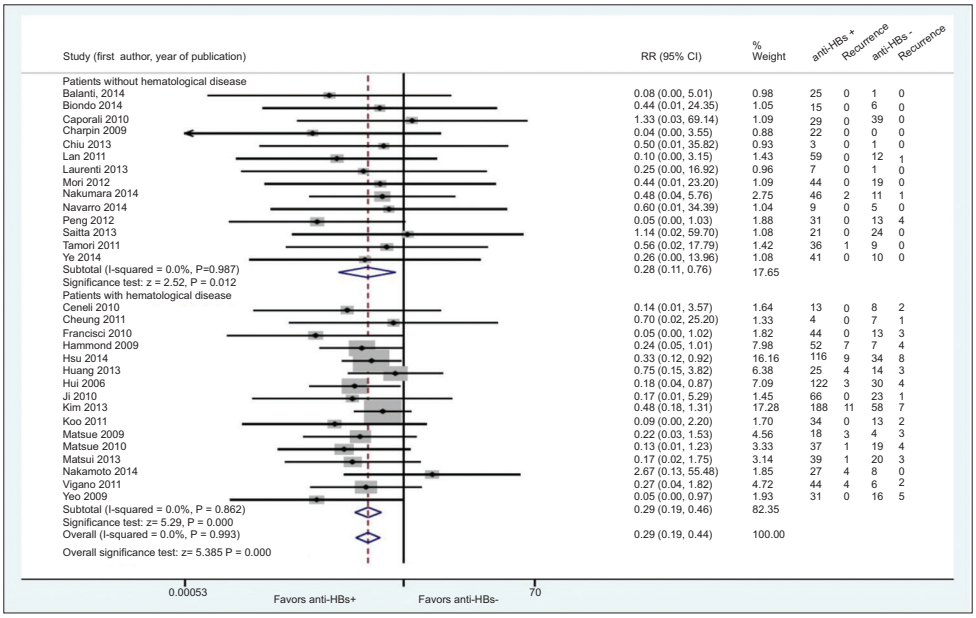

Figure 4 Forest plots of rates of hepatitis B virus (HBV) reactivation between HBsAg-negative, anti-HBc-positive patients with positive and negative anti-HBs in studies with or without hematological diseases
RR, relative risk; 95%CI, 95% confidence interval

reactivation was lower in patients with than in those without anti-HBs treated with rituximab-containing—6.6% (95%CI 2.9-14.4) vs. 19.8% (95%CI 15.6-24.7); RR 0.32 (95%CI 0.15-0.69), P=0.003; I^2=0%, P for heterogeneity=0.736 [15,25,28,32,34,35]—or rituximab-free regimens—3.3% (95%CI 2.0-5.5) vs. 9.2% (95%CI 5.3-15.4); RR 0.36 (95%CI 0.14-0.96), P=0.042; I^2=0%, P for heterogeneity=0.988 [12,17,18,24,22,25,29,32,34,49,51,57,58,61] (Fig. 2).

Outcomes of patients with HBV reactivation

Data regarding outcomes were provided in 174 (73.8%) of 236 patients with HBV reactivation, while data regarding antiviral therapy after the onset of HBV reactivation were available for 148 (85%) of these 174 patients: 23 remained untreated and 125 were treated with NAs (entecavir: 56, lamivudine: 59, adefovir±lamivudine: 4, entecavir or lamivudine:

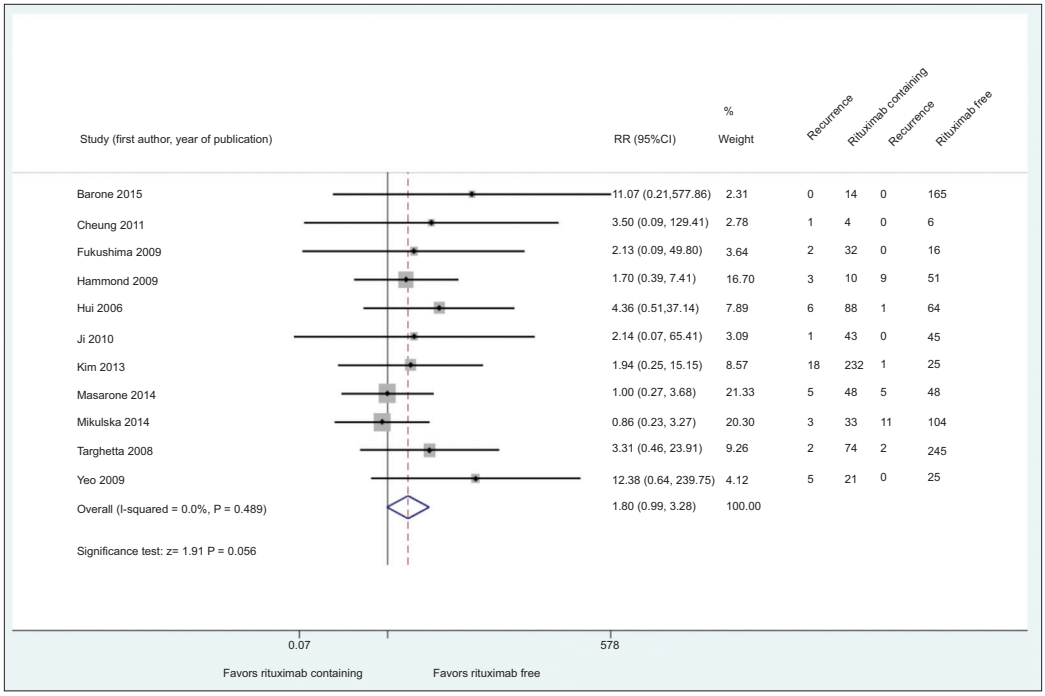

Figure 5 Forest plots of rates of hepatitis B virus (HBV) reactivation between HBsAg-negative, anti-HBc-positive patients treated with and without rituximab-containing regimens
RR, relative risk; 95%CI, 95% confidence interval

6) [12,15-17,21,23-25,27-41,44-48,51,54,65]. Twenty-two (14.9%) of the 148 patients died: 7/23 (30.4%) patients who remained untreated and 15/125 (12%) patients treated with NAs. Finally, 2 (3.5%) of 56 patients and 10 (17%) of 59 patients who received entecavir and lamivudine, respectively, for HBV reactivation died during the follow-up period [12,15-17,21,23-25,28-30,32-39,44,45,47,51,54].

Discussion

In this systematic review of more than 3600 HBsAg-negative, anti-HBc-positive patients who received immunosuppressive therapy we confirmed that patients treated with rituximab-containing regimens have a higher risk for HBV reactivation, compared to those receiving rituximab-free regimens: 9.7% vs. 4.1%; RR 1.80 (95%CI 0.99-3.28). No relevant studies were identified and therefore no conclusions could be drawn concerning the new generations of anti-CD20 monoclonal antibodies (e.g., ofatumumab, veltuzumab), developed recently. The pooled rates of HBV reactivation were 10.9% in patients with hematological diseases and 3.6% in patients with non-hematological diseases, but no direct statistical comparison could be drawn between these two groups because of limitations in the available data.

The detectability of baseline HBV DNA had no impact on the risk of HBV reactivation in patients at high risk due to the underlying disease or the immunosuppressive regimens. In particular, the pooled rates of HBV reactivation were similar in patients with detectable or undetectable HBV DNA treated with rituximab-containing regimens or having hematological diseases. In contrast, patients with detectable, compared to those with undetectable baseline HBV DNA had a higher risk for HBV reactivation if they were treated with rituximab-free regimens (14.0% vs. 2.6%; RR 12.67, P=0.003) or had non-hematological diseases (14.2% vs. 2%; RR 20.59, P=0.001), although the latter difference became insignificant in the sensitivity analysis (P=0.090). Practically, it could be suggested that in HBsAg-negative, anti-HBc-positive patients with non-hematological disease, or treated with rituximab-free regimens, HBV DNA evaluation is useful for stratification of the risk for HBV reactivation. However, in those who have hematological disease or are treated with rituximab-containing regimens, anti-HBV prophylaxis seems to be necessary in all cases, regardless of baseline HBV DNA status.

Although the current statement recommends against using anti-HBs status to guide antiviral prophylaxis [4], we found that positive compared to negative anti-HBs at baseline was associated with a significantly lower risk for HBV reactivation in all patient subgroups: those with hematological (7.1% vs. 21.8%, RR 0.29, 95%CI 0.19-0.46, P<0.001) or non-hematological diseases (2.5% vs. 10.7%, RR 0.28, 95%CI 0.11-0.76, P=0.012), and under rituximab-containing (6.6% vs. 19.8%, RR 0.32, 95%CI 0.15-0.69, P=0.003) or rituximab-free (3.3% vs. 9.2%, RR 0.36, 95%CI 0.14-0.96, P=0.042) regimens. This analysis was based on baseline anti-HBs status and not on baseline anti-HBs levels or their possible reduction during immunosuppression therapy, given the very limited literature data available. Based on these findings, and taking into account the impact of baseline HBV DNA, it could be suggested that anti-HBV prophylaxis seems to be necessary, irrespectively of baseline HBV DNA or anti-HBs status, in patients who have hematological disease or

are under rituximab-containing regimens. On the other hand, in patients with non-hematological diseases under rituximab-free regimens, antiviral prophylaxis should be recommended in those with detectable baseline HBV DNA, regardless of anti-HBs status, but is not required in those with undetectable HBV DNA and positive anti-HBs. The decision for anti-HBV prophylaxis may be individualized in patients with non-hematological diseases under treatment with rituximab-free regimens and have undetectable HBV DNA and negative anti-HBs.

An interesting finding was that HBV reactivation developed in 26 (42%) of 62 patients receiving rituximab-containing regimens between 14 and 409 days after the cessation of immunosuppression and in 6 (32%) of 19 patients receiving rituximab-free regimens between 90 and 300 days after the end of immunosuppression. Thus, clinicians should continue to follow these patients closely for long after the completion of immunosuppression/chemotherapy, avoiding early discontinuation of possible anti-HBV prophylaxis.

The clinical presentation of HBV reactivation may vary from asymptomatic to acute liver failure and death [1]. Indeed, higher mortality has been reported in HBsAg-negative, anti-HBc-positive compared to HBsAg-positive patients, perhaps related to underestimation of the risk for HBV reactivation and the delay in diagnosis [1]. Thus, early diagnosis and prompt treatment initiation are crucial for the effective management of such cases not under anti-HBV prophylaxis. Of the 236 patients with HBV reactivation included in our review, 148 received NAs (mainly lamivudine or entecavir). The mortality rate was relatively high (15%), but the cause of death was not always clearly associated with the HBV reactivation, particularly in those who had hematological diseases or bone marrow transplantation. As might be expected, among the patients with HBV reactivation, mortality was 30% for those who remained untreated and 12% for those who received antiviral therapy. In addition, among the patients who received antiviral therapy for HBV reactivation, the mortality was 17% for those treated with lamivudine and 3.5% for those treated with entecavir. Although these data do not come from RCTs and direct comparison is not possible, it seems clinically more appropriate to use a high genetic barrier agent, like entecavir or tenofovir, whenever HBV reactivation is diagnosed. On the other hand, such data regarding antiviral therapy after HBV reactivation seem insufficient to justify a change in the current recommendation for the use of lamivudine as prophylaxis for HBsAg-negative, anti-HBc-positive patients who require immunosuppression, provided that serum HBV DNA is undetectable.

In conclusion, our findings favor the use of anti-HBV prophylaxis in HBsAg-negative, anti-HBc-positive patients with hematological diseases and/or under rituximab-containing regimens, regardless of their baseline anti-HBs and serum HBV DNA status. Antiviral prophylaxis should be given in HBsAg-negative, anti-HBc-positive patients with non-hematological diseases who are taking rituximab-free regimens and have detectable baseline HBV DNA, irrespectively of their anti-HBs status, but is not required in those with undetectable HBV DNA and positive anti-HBs. Since HBV reactivation often occurs after the completion of the immunosuppressive/chemotherapy courses, clinicians should continue anti-HBV prophylaxis and/or the follow up of such patients for at least 12 months after the discontinuation of immunosuppression. An agent with a high genetic barrier may be used in order to better optimize the management of HBV reactivations occurring in HBsAg-negative, anti-HBc-positive patients.

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Summary Box

What is already known:

- HBsAg-negative, anti-HBc-positive patients have a lower risk of hepatitis B virus (HBV) reactivation compared to HBsAg-positive patients, but the prevalence of anti-HBc is higher than that of HBsAg
- Antiviral prophylaxis is strongly recommended in HBsAg-negative, anti-HBc-positive patients treated with B-cell-depleting agents
- The usefulness of baseline anti-HBs evaluation remains controversial

What the new findings are:

- The use of anti-HBV prophylaxis is recommended in HBsAg-negative, anti-HBc-positive patients with hematological diseases and/or under rituximab-containing regimens, regardless of their baseline anti-HBs and serum HBV DNA status
- Antiviral prophylaxis is not required in HBsAg-negative, anti-HBc-positive patients with non-hematological diseases who receive rituximab-free regimens and have undetectable HBV DNA and positive anti-HBs
- The decision for anti-HBV prophylaxis may be individualized in patients with non-hematological diseases treated with rituximab-free regimens who have undetectable HBV DNA and negative anti-HBs
- Since HBV reactivation often develops after the completion of the immunosuppressive/chemotherapy courses, clinicians should continue anti-HBV prophylaxis and/or the follow up of such patients for at least 12 months after discontinuation of immunosuppression

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