

BMJ Open Retrospective observational study of temporal trends and outcomes of hepatitis B screening in patients receiving rituximab

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ABSTRACT

Objective Hepatitis B reactivation (HBr) is strongly associated with rituximab therapy. Guidelines advise hepatitis B screening and use of preventive nucleoside analogue (NA) in patients at risk. In this study, we examined screening trends, post-screening interventions and outcomes in patients receiving rituximab in light of recommendations.

Design Retrospective, observational study.

Setting Single, tertiary care centre in the USA.

Participants Patients receiving rituximab from January 2005 to December 2017.

Primary outcome Trends of hepatitis B screening prior to initiation of rituximab.

Secondary outcome Results of hepatitis B screening, use of preventive NA therapy and HBr incidence.

Results Over 13 years, 2219 patients received rituximab. Screening, with at least hepatitis B core antibody (anti-HBc) prior to the first dose of rituximab, improved from 20% to 97%. Because only 4.5% of patients had a positive anti-HBc, the overall HBr incidence was very low (0.42%). In susceptible patients, the incidence of HBr was 8%. In at-risk patients given preventive NA, 96% remained free of HBr. However, only 23% received a preventive NA and no temporal improvement in compliance was seen. Of those with HBr, 87.5% were hepatitis B surface antigen (HBsAg-)/anti-HBc+.

Conclusions In those treated with rituximab, we demonstrated near-universal anti-HBc screening. Screening unlinked to preventive NA use, in those who are anti-HBc+, is ineffective in reducing HBr. HBr has a high fatality rate. The majority of cases occurred in those who were HBsAg negative. Efforts are needed to educate providers who use rituximab not only to screen for anti-HBc, but to provide preventive NA to those who test positive.

INTRODUCTION

Rituximab therapy poses six times higher odds of hepatitis B reactivation (HBr) compared with chemotherapy regimens that do not contain rituximab in susceptible individuals.¹ The estimated risk of HBr, with rituximab therapy, in patients with hepatitis B surface antigen (HBsAg) positive is 30%–60% and in patients with HBsAg negative and hepatitis B

Strengths and limitations of this study

- Large, retrospective study evaluating the trends of screening over more than a decade.
- Observational data on real-life practices and effect of screening.
- Limited generalisability as this was a single-centre study.
- Unable to assess perceptions or reasons for screening trends.

core antibody (anti-HBc) positive is greater than 10%.² With the use of a nucleoside analogue (NA), HBr can be prevented by 79%–100%.³ The NAs, entecavir and tenofovir are considered superior to lamivudine since they are more potent and have lower rates of resistance.^{3,4}

In 2008, the Center for Disease Control and Prevention (CDC) recommended screening for hepatitis B in patients undergoing treatment with rituximab and in 2013 the Federal Drug Administration (FDA) issued a black box warning to screen for hepatitis B before initial treatment and to monitor for symptoms during and after treatment.^{1,5,6} Over the last decade, the recommendations regarding HBr in patients receiving rituximab have evolved.

The American Association for the Study of Liver Disease (AASLD) first mentioned the risk of rituximab related HBr in their 2007 guidelines.⁷ Routine prophylaxis was recommended in patients with HBsAg+ but not in patients with HBsAg-/anti-HBc+.⁷ Similarly, in 2009, the European Association for the Study of the Liver (EASL) recommended screening for hepatitis B and recommended preventive NA therapy in patients with chronic hepatitis B virus (HBV) (HBsAg+/anti-HBc+) till 12 months after cessation of rituximab.⁸ In contrast, the American Society of Clinical Oncology (ASCO) published a

Provisional Clinical Opinion in 2010 regarding the CDC's 2008 recommendations.⁹ In ASCO's opinion, there was insufficient evidence supporting the CDC recommendations to screen the general population for HBV prior to initiating therapy with rituximab and felt that the consequences of screening and its economic implications had not been fully considered.⁹ Instead, ASCO recommended screening based on clinical judgement and estimated risk of HBV.⁹ A discretionary recommendation was issued to use NA prophylaxis in patients with chronic HBV since there was a dearth of evidence to support it.⁹ In 2015, the American Gastroenterological Association highlighted the increased risk of HBr, not only in patients who were HBsAg+ but HBsAg-/anti-HBc+, and recommended NA prophylaxis in both of the above populations while receiving rituximab therapy.² This was followed by an updated opinion by ASCO in 2015, that recommended universal screening for HBV receiving immunosuppressive therapies and recommended the use of prophylactic NA therapy.¹⁰

Management of patients with HBsAg-/anti-HBc+ has been ambiguous. In 2012, EASL was one of the first associations to detail the management for patients with HBsAg-/anti-HBc+.¹¹ EASL recommended NA therapy in HBsAg-/anti-HBc+ with positive HBV DNA and recommended considering NAs in HBsAg-/anti-HBc+ and HBV DNA negative if close monitoring was not assured.¹¹ The AASLD guideline updates in 2009 and 2015 did

not address NA prophylaxis in patients with HBsAg-/anti-HBc+ receiving immunosuppressive medications.^{11,12}

In 2017 and 2018, EASL and AASLD, respectively, published updates on their guidelines regarding HBV and both recommend universal screening with HBsAg and anti-HBc prior to initiating chemotherapy.^{4,13} Moreover, it is recommended to use NA, preferentially entecavir and tenofovir, for prophylaxis prior to rituximab therapies and continued for 12–18 months after discontinuation of rituximab.^{4,13} Figure 1 demonstrates a timeline for screening recommendations pertaining to rituximab.

Many centres have reported disappointing adherence, of 20%–50%, in screening for HBr susceptibility.^{5,14,15} In this study, we look at the adherence to guidelines and report temporal trends of screening, post-screening interventions and outcomes at a tertiary care hospital.

METHODS

Patients who received rituximab from January 2005 to December 2017 at a tertiary care centre were included in this retrospective, observational study. Patients were included if they had received at least one dose of rituximab at age 18 or above. The pharmacy database was used to identify consecutive patients that received rituximab in the study time frame.

Data collected included demographics, duration of rituximab therapy, indications and prescriber specialty

Evolution of Recommendations Related to HBV Screening and Nucleoside Analog Prophylaxis in Patients Receiving Rituximab.

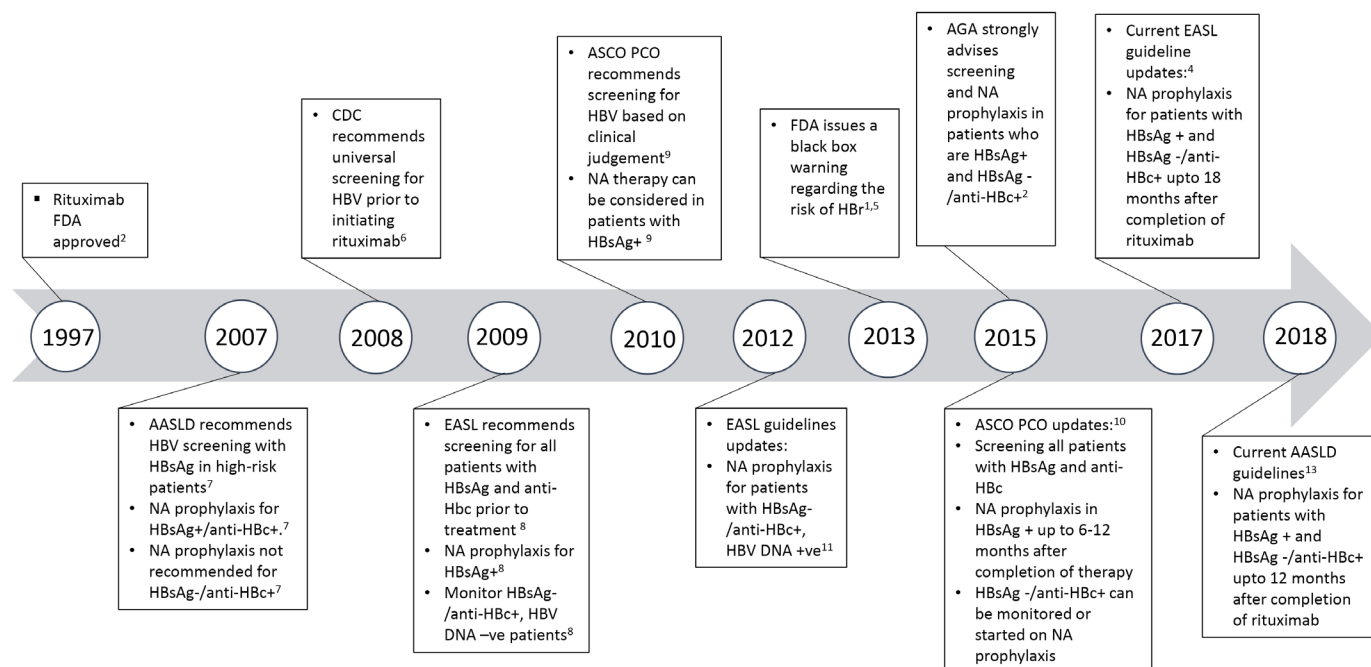


Figure 1 Timeline of screening recommendations pertaining to rituximab. AASLD, American association of the study of liver disease; AGA, American gastroenterological association; anti-HBc, hepatitis B core antibody; ASCO, American society of clinical oncology; CDC, center for disease control and prevention; EASL, European association for the study of the liver; FDA, federal drug administration; HBr, hepatitis B reactivation; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NA, nucleoside analogue; PCO, provisional clinical opinion.

for rituximab. Date and results of hepatitis B testing were recorded. Testing for hepatitis B included viral serologies: HBsAg, anti-HBc and hepatitis B surface antibody (anti-HBs). Medical records were individually reviewed to confirm testing for hepatitis B. Post-screening actions were recorded as none or use of a NA. Outcomes of screening recorded were change in HBsAg status and change in HBV DNA levels. Outcomes of HBr were death, persistence (continued HBsAg or HBV DNA positivity) or resolution (loss of HBsAg positivity).

HBr was defined as HBsAg reverse seroconversion and/or change in HBV DNA: positive; $\geq 2 \log_{10}$ increase or $\geq 100\,000$ IU/mL.³ Preventive NA therapy was a prescription of a NA, in a patient at risk of HBr, prior to HBr. Patients with anti-HBc with or without HBsAg were considered at risk of HBr and considered eligible to receive NA prior to starting and post completion of rituximab therapy. The above definitions were adopted from the standardised nomenclature proposed at a conference on 'Reactivation of Hepatitis B', in 2013, organised by the AASLD.³

Cochran-Armitage trend tests were used to assess trends across the years. Analysis was done using SAS. A $p < 0.05$ was considered statistically significant. Data are presented as mean \pm SD, median (25th, 75th percentiles) or frequency (%).

Patient and public involvement

This was a retrospective, chart review study therefore no direct patient involvement was required. There was no public involvement.

RESULTS

Patient characteristics

We identified 2219 patients who received rituximab from 2005 to 2017. Fifty-six per cent were men, 84.6% Caucasian and the average age at starting therapy was 58 ± 16 years. The most common prescribing specialty was oncology-haematology (70.8%) for the treatment of a lymphoma/leukaemia (63.8%). The median duration of rituximab therapy was 107 (21, 562) days and the median days from anti-HBc testing to receiving rituximab was 17 (3, 361) days.

Group A: patients screened prior to rituximab with at least anti-HBc

Sixteen hundred and sixty-three patients were tested for hepatitis B prior to starting rituximab. Out of these, 1584 (95%) were tested for anti-HBc. Figure 2 depicts screening results for patients screened prior to rituximab. Figure 3A illustrates the trends of anti-HBc testing, prior to receiving rituximab over the study period.

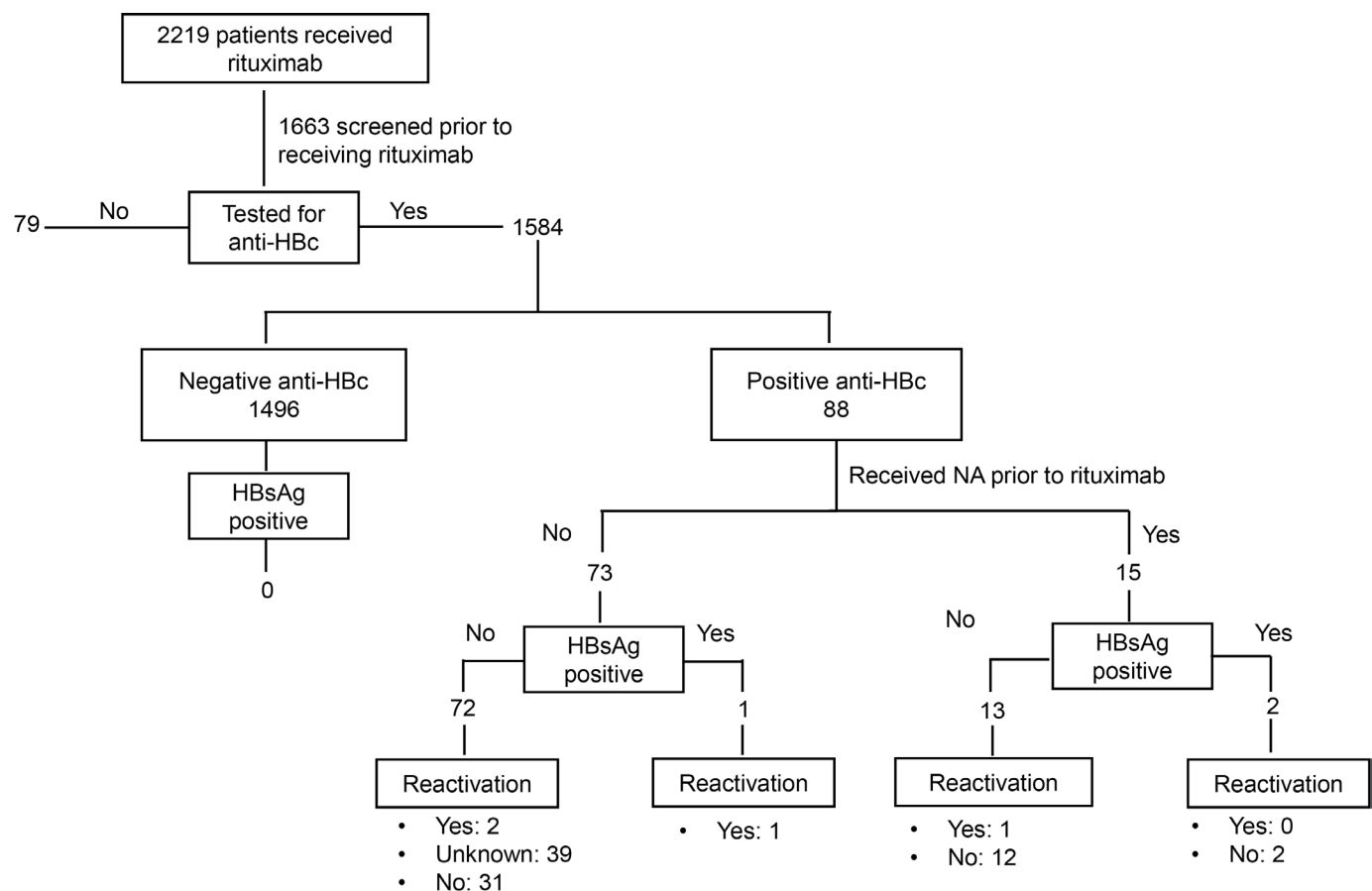


Figure 2 Screening results in patients tested for hepatitis B prior to starting rituximab. Anti-HBc, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; NA, nucleoside analogue.

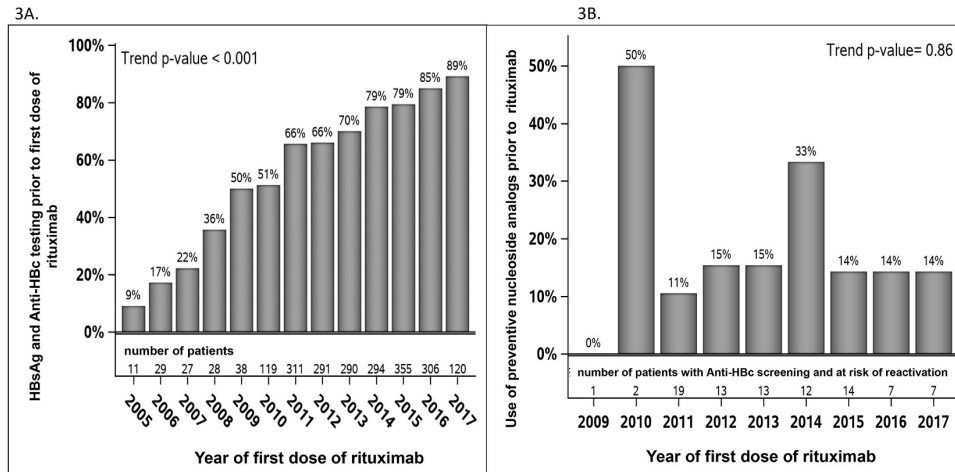


Figure 3 Trends in screening prior to receiving rituximab. (A) Trends of anti-HBc testing prior to the first dose of rituximab. (B) Trends of preventive nucleoside analogue use in patients at risk of hepatitis B reactivation prior to the start of rituximab therapy. Anti-HBc, hepatitis B core antibody; HBsAg, hepatitis B surface antigen.

Group B: patients screened after receiving rituximab with at least anti-HBc

Figure 4 depicts screening results of patients screened for hepatitis B after receiving rituximab. In the patients that tested negative for anti-HBc, 97% tested negative for HBsAg and 3% were not tested for HBsAg. In the group, not tested for anti-HBc, 74% were not tested for HBsAg either and 26% tested negative for HBsAg. Two patients in group B were started on preventive NA therapy after screening.

Table 1 shows a comparison between group A and group B.

Post-screening actions

In total, 4.5% patients were positively identified as at risk of HBr. Three patients tested positive for HBsAg and anti-HBc and the remaining were HbsAg-/anti-HBc+. Twenty-three (23%) of patients at risk of HBr were prescribed a preventive NA: 15 prior to starting rituximab; and 8 after at least one dose of rituximab. The median days from NA start to

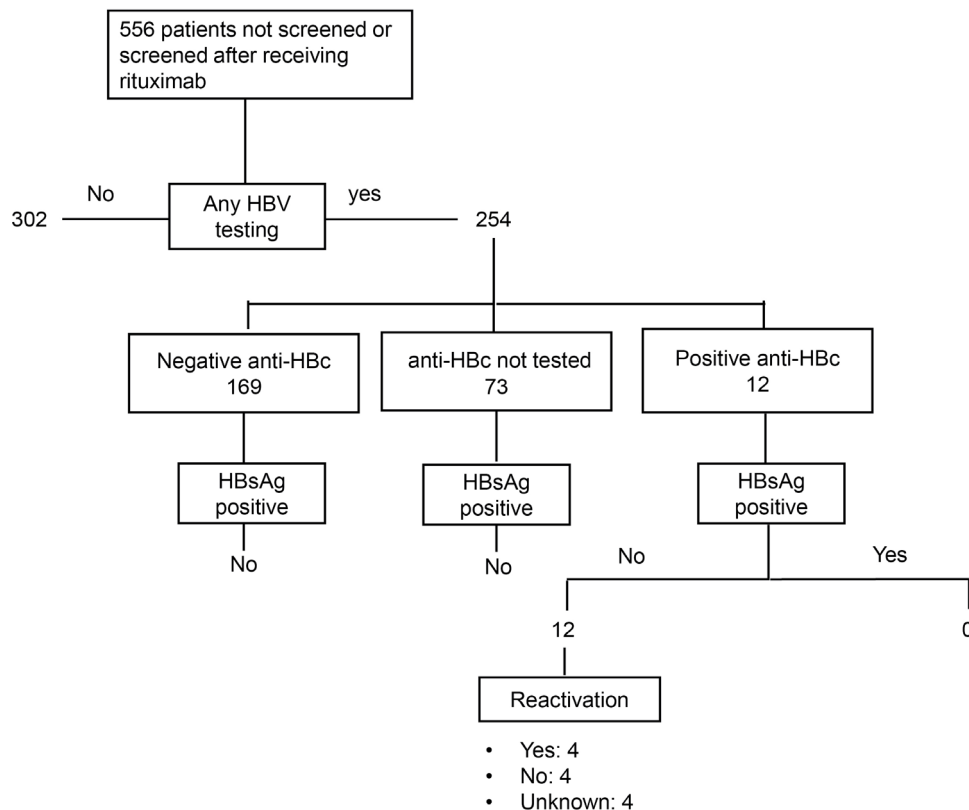


Figure 4 Screening results in patients tested for hepatitis B after starting rituximab. Anti-HBc, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

Table 1 Comparison between group A and group B

Characteristic	Group A, n (%)	Group B, n (%)	P value
	N=1584	N=181	
Gender			0.75‡
Male	895 (56.5)	100 (55.2)	
Ethnicity			0.65‡
Caucasian	1326 (83.7)	148 (81.8)	
African-American	174 (11.0)	26 (14.4)	
Asian	12 (0.76)	1 (0.55)	
Hispanic or Latino	30 (1.9)	2 (1.1)	
Other/unknown	42 (2.7)	4 (2.2)	
Age at first dose of rituximab (years)	57.5±15.7	55.5±14.6	0.11*
Provider specialty			<0.001‡
Oncology-Haematology	1072 (67.7)	120 (66.3)	
Rheumatology	268 (16.9)	49 (27.1)	
Transplant	150 (9.5)	3 (1.7)	
Other	94 (5.9)	9 (5.0)	
Indication for rituximab			<0.001‡
Lymphoma/leukaemia	974 (61.5)	106 (58.6)	
Autoimmune disease	178 (11.2)	24 (13.3)	
Glomerulonephritis	22 (1.4)	0 (0.0)	
Vasculitis	191 (12.1)	38 (21.0)	
Other	219 (13.8)	13 (7.2)	
Days from screening to first dose of rituximab	25 (6, 494)	-442 (-1367, -26)	<0.001†
At risk of HBr	88 (5.6)	12 (6.6)	0.55‡
Use of prophylactic NA	21 (1.3)	2 (1.1)	0.99§
	N=88	N=12	
Reactivation status in anti-HBc positive	4 (4.5)	4 (33.3)	0.003‡
	N=24	N=6	
Preventive NA use in those that received an NA	21 (87.5)	2 (33)	0.005§
	N=4	N=4	
Outcomes of HBr			0.99†
Death	2 (50.0)	1 (25.0)	
Persistence	2 (50.0)	2 (50.0)	
Resolved	0 (0.0)	1 (25.0)	

Statistics presented as mean±SD, median (P25, P75) or N (column %).

*ANOVA.

†Kruskal-Wallis test.

‡Pearson's χ^2 test.

§Fisher's exact test.

Anti-HBc, hepatitis B core antibody; HBr, hepatitis B reactivation; NA, nucleoside analogue; ULN, upper limit of normal.

rituximab was 4 (0, 32) and the median duration of use was 306.5 (174, 733) days. Entecavir (70%) was the most commonly prescribed NA. **Figure 3B** illustrates the trends of preventive NA use in patients at risk of HBr prior to the start of rituximab therapy.

Reactivation

HBr was identified in 0.4% of those receiving rituximab (8% of those at risk). Reactivation occurred in one

(12.5%) patient who was HBsAg+/anti-HBc+ and in 7 (87.5%) who were HBsAg-/anti-HBc+. In those that reactivated, 87.5% were not prescribed preventive NA. Of those at risk and given NA prophylaxis, 96% remained free of HBr. One case of HBr occurred in a patient prescribed a preventive NA prior to starting rituximab. Reactivation was identified 1503 days after the last dose of rituximab when he presented with relapsed chronic lymphocytic

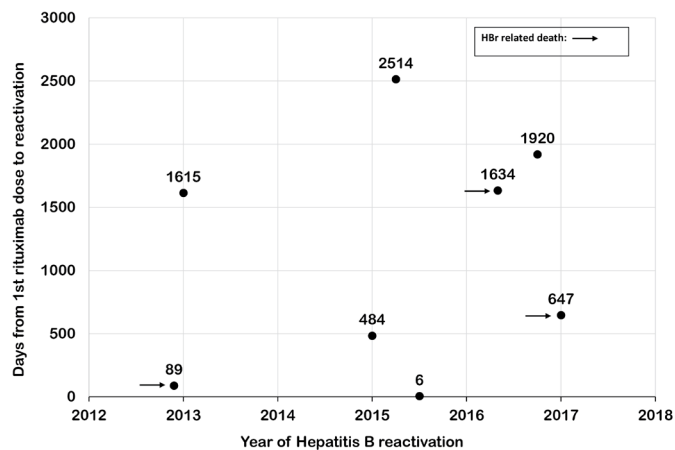


Figure 5 Days from first dose of rituximab to reactivation and hepatitis B related mortality. HBr, hepatitis B reactivation.

leukaemia after being lost to follow for several years. The status of HBr was unknown in 49 patients as repeat serologic testing was unavailable. Repeat testing, either HBV DNA levels and/or HBsAg serology, was done in 43 patients and no reactivation was identified.

All patients at risk and not prescribed NA prophylaxis tested negative for HBsAg and were either anti-HBc+/anti-HBs+ or anti-HBc+/anti-HBs-. Of these, 9% had HBr, status of HBr was unknown in 49% and repeat serologic testing in 42% was negative.

While HBr was rare, it was fatal in three (37.5%), persistent in four (50%) and resolved in one (12.5%). The median time from starting rituximab to identification of reactivation was 1131 (286, 1777) days. The median time from the last dose of rituximab to identification of HBr was 59 (–66, 812) days. HBr was identified greater than 18 months after the last dose of rituximab in two patients. Two patients continued to receive rituximab even after reactivation and were started on a NA; the infection persisted in these patients. The median duration of rituximab in those who reactivated was 342 (34, 1249) days. The three fatalities from HBr occurred in patients that were HBsAg–/anti-HBc+ on initial screening. **Figure 5** illustrates, in a graph, the time-to-reactivation from the first dose of rituximab. The rate of HBr in the intervals 2005–2008, 2009–2014 and 2013–2017 was 0%, 0.26% and 0.44%, respectively.

DISCUSSION

Our study describes the real-life practices and outcomes of hepatitis B screening in patients receiving rituximab for oncologic and non-oncologic conditions over a 13-year period. We found evolution of near-universal hepatitis B screening; a rate much higher than other reported series.^{5,16} Testing for anti-HBc and HBsAg increased from 9% to 87% from 2005 to 2017. The rate of increase in screening was highest 2008–2014 which correlates with recommendations and awareness of HBr. During this time period, at our institute, no automatic clinical reminder had been implemented and the steady rise in screening

rates was a consequence of prescriber awareness and adherence to guidelines and warnings issued.

Comparison of group A and group B revealed no statistically significant difference in the prevalence of patients at risk of HBr. In group A, 5.6% were at risk of HBr and in group B 6.6%, $p=0.55$. However, the incidence of HBr was higher in group B versus group A (33.3% vs 4.5%, $p=0.003$). Conversely, the proportion of preventive NA use was lower in group B (33%) compared with group A (87.5%), $p=0.005$. Of note, 87.5% of HBr was in patients not prescribed a preventive NA. These findings illustrate that timely screening and use of preventive NA was associated with a decrease in the incidence of HBr, in our cohort.

While the rate of screening has become nearly universal, only 23% of at-risk patients received guideline recommended preventive therapy. No temporal trend was seen in the prescription of preventive NA therapy and it did not mirror hepatitis B screening trends. Moreover, the rate of HBr increased over time even though screening improved. Recommendations pertaining to NA prophylaxis have been evolving through this time period whereas screening recommendations remained consistent and robust. This may explain the discrepancy between screening and preventive NA trends. In our cohort, the majority (98%) of the patients at risk were HBsAg–/anti-HBc+ and it is only in the last few years that guidelines have strongly recommended preventive NAs for patients that test HBsAg–/anti-HBc+.^{4,13}

Figure 1 highlights the frequent amendments and variations to the guidelines. This must have posed a challenge, for practitioners, to follow and remain updated. For instance, in 2010, ASCO's recommendations differed from other guidelines as they did not strongly endorse universal screening or NA prophylaxis.⁹ It was not until 2015 that their opinion changed.¹⁰ In our cohort, the majority indications for rituximab were oncologic however it is undiscernible if ASCO's opinion influenced practice or not.

Current guidelines recommend HBsAg and anti-HBc testing prior to administering rituximab.^{4,13} We found that all patients, identified as at risk for HBr, were positive for anti-HBc. Furthermore, our cohort reflects a low prevalence of hepatitis B, evidenced by the presence of past hepatitis B at around 5% and chronic hepatitis less than 1%.¹³ Therefore, the incidence of acute hepatitis B (HBsAg+/anti-HBc and anti-HBs–) would be very low and in retrospect testing with only anti-HBc would have identified all at-risk patients. It is plausible, that in low prevalence populations, anti-HBc may be sufficient and the most pertinent test required to identify at-risk patients.

Figure 5 illustrates the wide range of days from the first dose of rituximab to reactivation. In our study, HBr was identified as early as 6 days and as late as 6 years from the first dose of rituximab. In the patient, in whom reactivation occurred several years after completion of rituximab was diagnosed with a new malignancy at the time of the HBr and hence HBr

may not be directly related to previous rituximab therapy. However, similar variability was reported, in a study of patients with Non-Hodgkin's lymphoma, in which HBr occurred at 2.7 to 213 weeks after the last cycle of rituximab.¹⁷ This may be explained by the fact that HBr was only identified if repeat HBV testing was performed and therefore, reactivation may have occurred earlier but not detected. On the other hand, a lack of clinical hepatitis may have deterred repeated testing for viral hepatitis. In our cohort, HBr mortality was high and occurred in patients, identified with HBr, months after the first dose of rituximab. It is pertinent to note that all cases of HBr were identified after 2013, the year that the FDA issued a black box warning regarding HBr. In our patients, the majority that reactivated were HBsAg-/anti-HBc+ and the risk of HBr must have been thought to be low. Moreover, with increasing awareness more patients were identified.

The appropriate duration of preventive NA post rituximab is unclear. Current guidelines recommend NA use for 12–18 months (180–540 days) post rituximab followed by surveillance for 1 year.^{4 13} Our data shows that two (25%) developed reactivation more than 540 days after end of treatment. The cost-benefit of continued NA versus surveillance is a suitable topic for further investigation.

The limitations of this study were its retrospective and observational study design which did not allow for an assessment into the reasons for non-adherence to guidelines and likely underestimated the incidence of HBr. It is possible that not all cases of HBr were identified as repeat testing for hepatitis B was required to diagnose HBr and was not routinely conducted in patients at risk.

In conclusion, our study demonstrates near-universal adherence to screening recommendations for hepatitis B prior to rituximab can be achieved. However, screening unlinked to preventive NA use in those who are anti-HBc+, is ineffective in reducing HBr. Use of NA is 96% protective against HBr. Renewed efforts are needed to assure NA treatment is used in patients with anti-HBc+ receiving rituximab. The risk of HBr may be present for a prolonged period of time after the discontinuation of rituximab. More studies are needed to evaluate the risk of HBr, after the discontinuation of rituximab, to risk stratify patients and verify current management strategies.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study was approved by the Institutional Review Board at the Cleveland Clinic.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. All data relevant to the study are included in the article.

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