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Temporal Trends and Outcomes of Hepatitis B Screening in Patients Receiving Rituximab

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Abbreviations:

Alanine transaminase (ALT)

American Association of the Study of Liver Disease (AASLD)

American Society of Clinical Oncology (ASCO)

Center for Disease Control and Prevention (CDC)

European Association for the Study of the Liver (EASL)

Federal Drug Administration (FDA)

Hepatitis B core antibody (anti-HBc)

Hepatitis B surface antibody (anti-HBs)

Hepatitis B surface antigen (HBsAg)

Hepatitis B reactivation (HBr)

Hepatitis B virus (HBV)

Nucleoside analog (NA)

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Data Sharing: No additional data available

Abstract

Objective:

Hepatitis B reactivation (HBr) is strongly associated with rituximab therapy. Guidelines advise hepatitis B screening and use of preventive nucleoside analogs (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.

Methods:

This is a retrospective study of patients receiving rituximab, from January 2005 to December 2017 at a tertiary care center. Results of hepatitis B testing, use of a preventive NA and HBr outcomes were recorded.

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 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.

Strengths and Limitations

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

Key words:

Hepatitis B reactivation; CD20 monoclonal antibodies; prevention of hepatitis B reactivation, Rituximab, Hepatitis B

Introduction

Rituximab therapy poses 6 times higher odds of Hepatitis B reactivation (HBr) compared to chemotherapy regimens that do not contain rituximab in susceptible individuals.[1] The estimated risk of HBr, with rituximab therapy, in hepatitis B surface antigen (HBsAg) positive patients is 30-60% and in HBsAg negative and hepatitis B core antibody (anti-HBc) positive patients is greater than 10%.[2] With the use of a nucleoside analog (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 HBsAg+ but not in HBsAg-/anti-HBc+ patients.[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 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, ASCO updated the opinion and recommended universal screening for HBV receiving immunosuppressive therapies and recommended the use of prophylactic NA therapy.[10]

Management of HBsAg-/anti-HBc+ patients, has been ambiguous. In 2012, EASL was one of the first associations to detail the management for HBsAg-/anti-HBc+ patients.[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 HBsAg-/anti-HBc+ patients receiving immunosuppressive medications.[1, 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 nucleoside analogs (NA), preferentially entecavir and tenofovir, for prophylaxis prior to rituximab therapies and continued for 12 to 18 months after discontinuation of rituximab.[4, 13] Figure 1 demonstrates a timeline for screening recommendations pertaining to rituximab.

Many centers have reported disappointing adherence 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 center 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 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; ≥2 log10 increase or ≥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 standardized nomenclature proposed at a conference on "Reactivation of Hepatitis B", in 2013, organized by the American Association for the Study of Liver Diseases.[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 ± standard deviation, median [25^{th}, 75^{th} percentiles] or frequency (percent). This study was approved by the Institutional Review Board at the Cleveland Clinic.

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 percent were male, 84.6% Caucasian and the average age at starting therapy was 58 ± 16 years. The most common prescribing specialty was oncology-hematology (70.8%) for the treatment of a lymphoma/leukemia (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.

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 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 leukemia 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 3 (37.5%), persistent in 4 (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 2 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 3 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 to 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 Groups 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 vs Group A (33.3% vs 4.5%, p= 0.003). Conversely, the proportion of preventive NA use was lower in Group B (33%) compared to 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 couple of 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 abti-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. 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 one year.[4, 13] Our data shows that 2 (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. It is possible that we may have not recognized all cases of HBr 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 anti HBc+ patients 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.

Figure Legends

Figure 1: Demonstrates a timeline for screening recommendations pertaining to rituximab

Figure 2: Screening results in patients tested for hepatitis B prior to starting rituximab

Figure 3: Trends in screening prior to receiving rituximab. 3a: Trends of anti-HBc testing prior to the first dose of rituximab. 3b: Trends of preventive nucleoside analog use in patients at risk of hepatitis B reactivation prior to the start of rituximab therapy

Figure 4: Screening results in patients tested for hepatitis B after starting rituximab

Figure 5: Days from first dose of rituximab to reactivation and hepatitis B related mortality

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Tables:

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[c]
Male	895(56.5)	100(55.2)	
Ethnicity			0.65[c]
Caucasian	1,326(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[a]
Provider specialty			<0.001[c]
Oncology-Hematology	1,072(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[c]
Lymphoma/Leukemia	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[b]
At risk of HBr	88(5.6)	12(6.6)	0.55[c]
Use of prophylactic NA	21(1.3)	2(1.1)	0.99[d]
	N=88	**N=12**	
Reactivation status in anti-HBc positive	4(4.5)	4(33.3)	0.003[c]
	N=24	**N=6**	
Preventive NA use in those that received an NA	21(87.5)	2(33)	0.005[d]
	N=4	**N=4**	
Outcomes of HBr			0.99[b]
Death	2(50.0)	1(25.0)	
Persistence	2(50.0)	2(50.0)	
Resolved	0(0.0)	1(25.0)	

ULN: upper limit of normal, HBr: hepatitis B reactivation, NA: nucleoside analog

Statistics presented as Mean ± SD, Median [P25, P75] or N (column %).

p-values: a=ANOVA, b=Kruskal-Wallis test, c=Pearson's chi-square test, d=Fisher's Exact test.

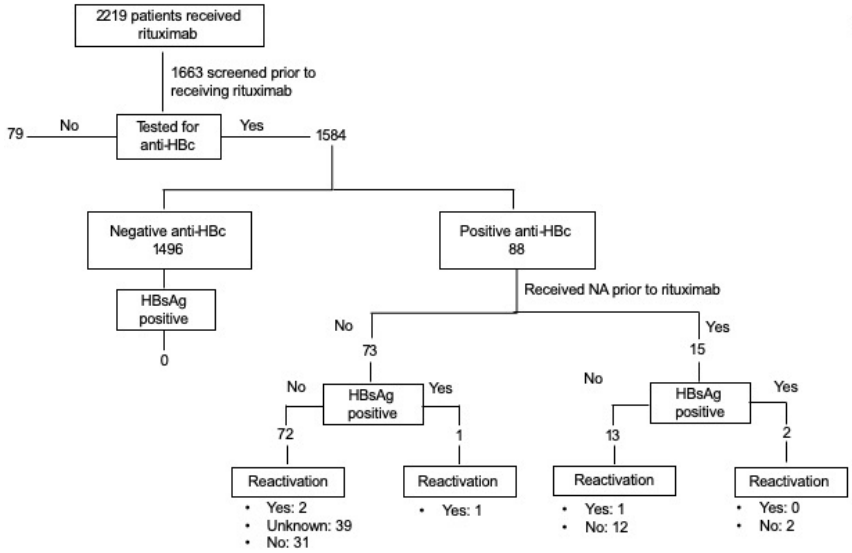

Figure 1

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Figure 2a

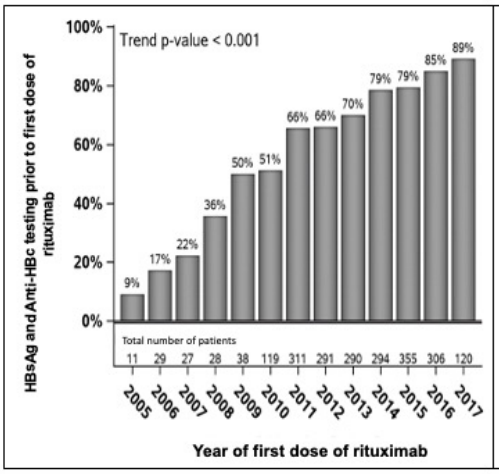
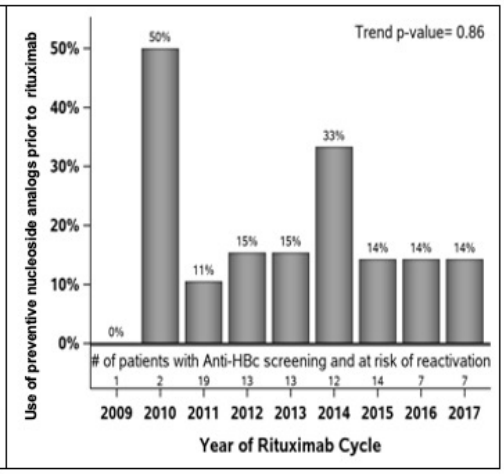


Figure 2b



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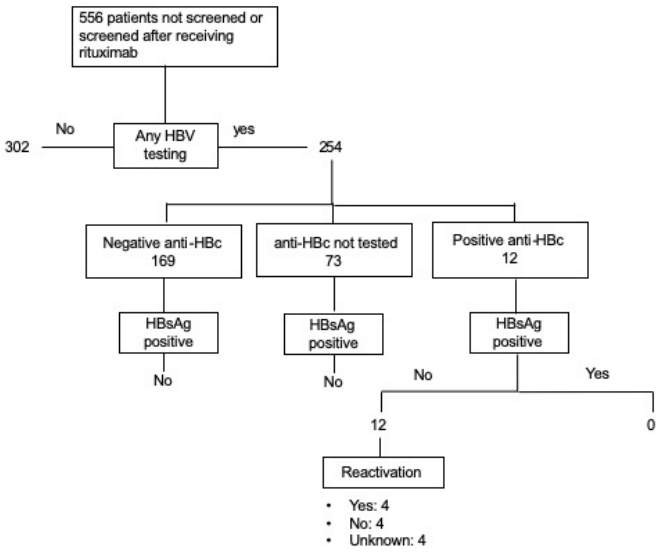

Figure 3

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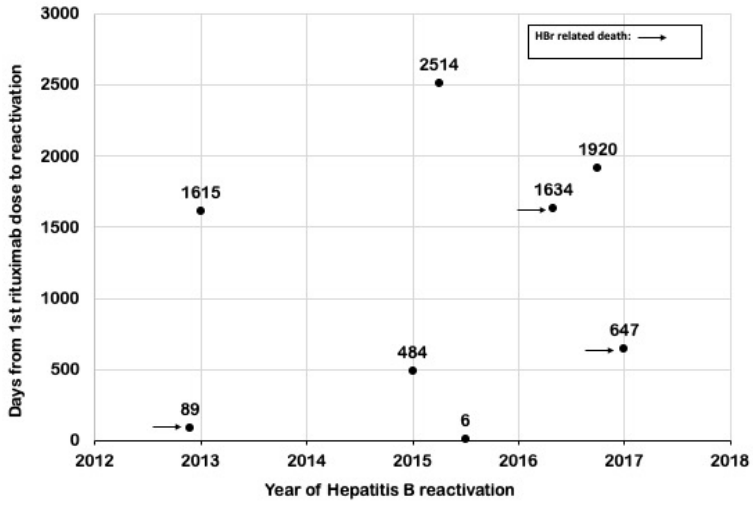
Figure 5



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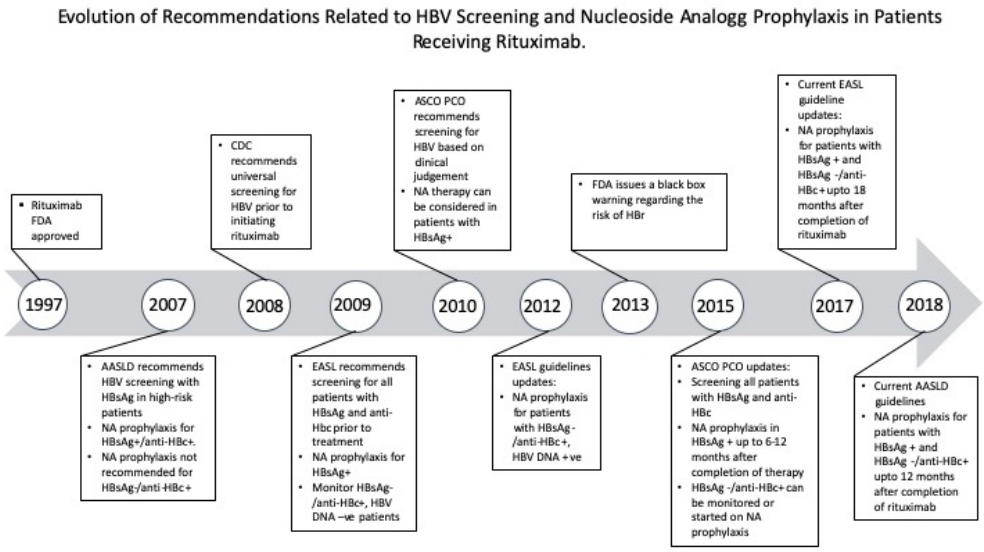

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A Retrospective Observational Study of Temporal Trends and Outcomes of Hepatitis B Screening in Patients Receiving Rituximab

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Abbreviations:

Alanine transaminase (ALT)

American Association of the Study of Liver Disease (AASLD)

American Society of Clinical Oncology (ASCO)

Center for Disease Control and Prevention (CDC)

European Association for the Study of the Liver (EASL)

Federal Drug Administration (FDA)

Hepatitis B core antibody (anti-HBc)

Hepatitis B surface antibody (anti-HBs)

Hepatitis B surface antigen (HBsAg)

Hepatitis B reactivation (HBr)

Hepatitis B virus (HBV)

Nucleoside analog (NA)

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Competing Interest: None declared.

Data Sharing: All data relevant to the study are included in the article or uploaded as supplementary information

Abstract

Objective: Hepatitis B reactivation (HBr) is strongly associated with rituximab therapy. Guidelines advise hepatitis B screening and use of preventive nucleoside analogs (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 center in the United States of America

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 nucleoside analog 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 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.

Strengths and Limitations

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

Key words:

Hepatitis B reactivation; CD20 monoclonal antibodies; prevention of hepatitis B reactivation, Rituximab, Hepatitis B

Introduction

Rituximab therapy poses 6 times higher odds of Hepatitis B reactivation (HBr) compared to chemotherapy regimens that do not contain rituximab in susceptible individuals.[1] The estimated risk of HBr, with rituximab therapy, in hepatitis B surface antigen (HBsAg) positive patients is 30-60% and in HBsAg negative and hepatitis B core antibody (anti-HBc) positive patients is greater than 10%.[2] With the use of a nucleoside analog (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 HBsAg+ but not in HBsAg-/anti-HBc+ patients.[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 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 HBsAg-/anti-HBc+ patients, has been ambiguous. In 2012, EASL was one of the first associations to detail the management for HBsAg-/anti-HBc+ patients.[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 HBsAg-/anti-HBc+ patients receiving immunosuppressive medications.[1, 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 nucleoside analogs (NA), preferentially entecavir and tenofovir, for prophylaxis prior to rituximab therapies and continued for 12 to 18 months after discontinuation of rituximab.[4, 13] Figure 1 demonstrates a timeline for screening recommendations pertaining to rituximab.

Many centers have reported disappointing adherence, of 20% to 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 center 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 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; ≥2 log10 increase or ≥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 standardized nomenclature proposed at a conference on "Reactivation of Hepatitis B", in 2013, organized by the American Association for the Study of Liver Diseases.[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 ± standard deviation, median [25th, 75th percentiles] or frequency (percent). This study was approved by the Institutional Review Board at the Cleveland Clinic.

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 percent were male, 84.6% Caucasian and the average age at starting therapy was 58 ± 16 years. The most common prescribing specialty was oncology-hematology (70.8%) for the treatment of a lymphoma/leukemia (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.

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 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 leukemia 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 3 (37.5%), persistent in 4 (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 2 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 3 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 to 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 Groups 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 vs Group A (33.3% vs 4.5%, p= 0.003). Conversely, the proportion of preventive NA use was lower in Group B (33%) compared to 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 one year.[4, 13] Our data shows that 2 (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 anti HBc+ patients 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.

Figure Legends

Figure 1: Timeline of screening recommendations pertaining to rituximab

Figure 2: Screening results in patients tested for hepatitis B prior to starting rituximab

Figure 3: Trends in screening prior to receiving rituximab. 3a: Trends of anti-HBc testing prior to the first dose of rituximab. 3b: Trends of preventive nucleoside analog use in patients at risk of hepatitis B reactivation prior to the start of rituximab therapy

Figure 4: Screening results in patients tested for hepatitis B after starting rituximab

Figure 5: Days from first dose of rituximab to reactivation and hepatitis B related mortality

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Tables:

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[c]
Male	895(56.5)	100(55.2)	
Ethnicity			0.65[c]
Caucasian	1,326(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[a]
Provider specialty			<0.001[c]
Oncology-Hematology	1,072(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[c]
Lymphoma/Leukemia	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[b]
At risk of HBr	88(5.6)	12(6.6)	0.55[c]
Use of prophylactic NA	21(1.3)	2(1.1)	0.99[d]
	N=88	**N=12**	
Reactivation status in anti-HBc positive	4(4.5)	4(33.3)	0.003[c]
	N=24	**N=6**	
Preventive NA use in those that received an NA	21(87.5)	2(33)	0.005[d]
	N=4	**N=4**	
Outcomes of HBr			0.99[b]
Death	2(50.0)	1(25.0)	
Persistence	2(50.0)	2(50.0)	
Resolved	0(0.0)	1(25.0)	

ULN: upper limit of normal, HBr: hepatitis B reactivation, NA: nucleoside analog

Statistics presented as Mean ± SD, Median [P25, P75] or N (column %).

p-values: a=ANOVA, b=Kruskal-Wallis test, c=Pearson's chi-square test, d=Fisher's Exact test.

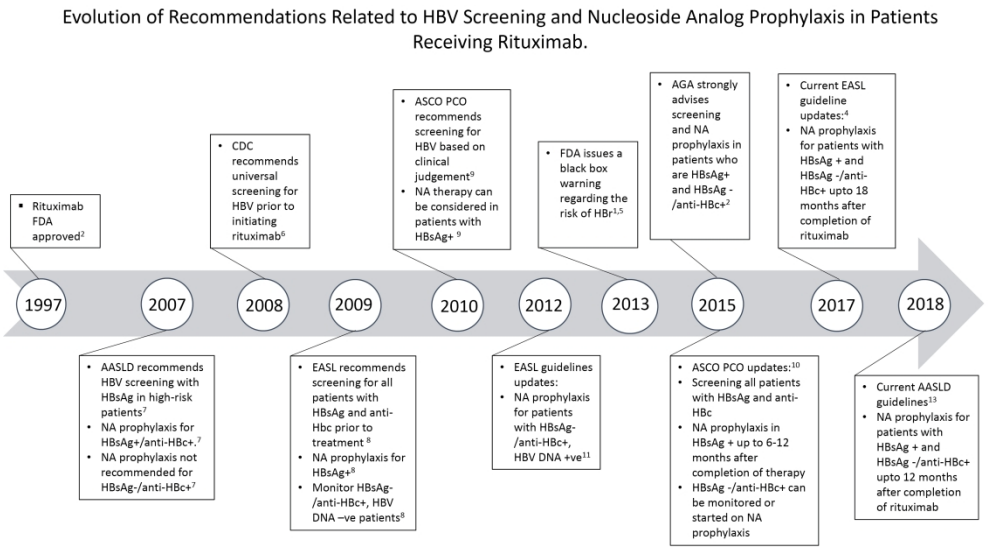

Figure 1
Timeline of screening recommendations pertaining to rituximab

338x190mm (300 x 300 DPI)

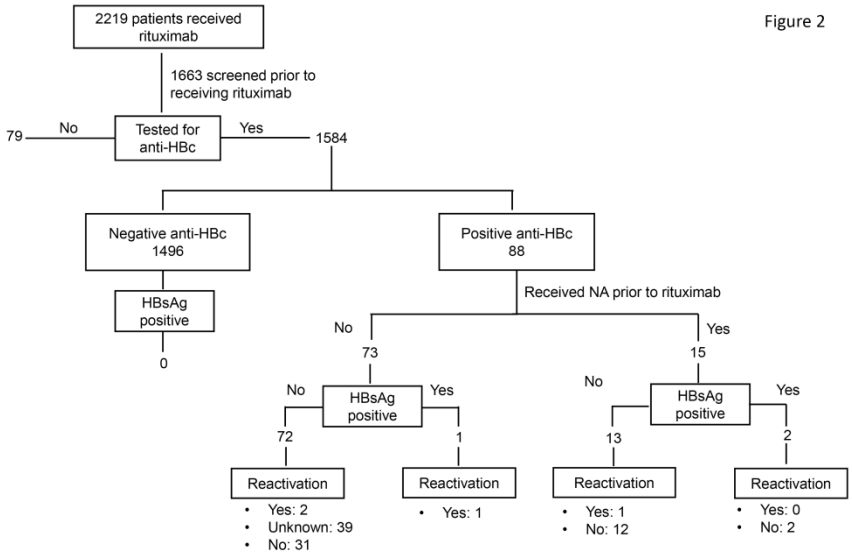

Figure 2
Screening results in patients tested for hepatitis B prior to starting rituximab

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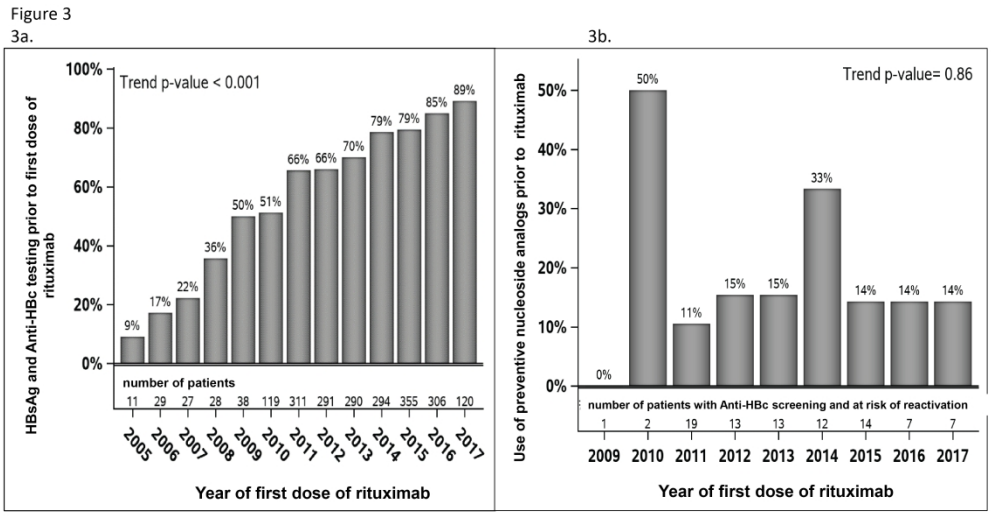

Figure 3
Trends in screening prior to receiving rituximab. 3a: Trends of anti-HBc testing prior to the first dose of rituximab. 3b: Trends of preventive nucleoside analog use in patients at risk of hepatitis B reactivation prior to the start of rituximab therapy

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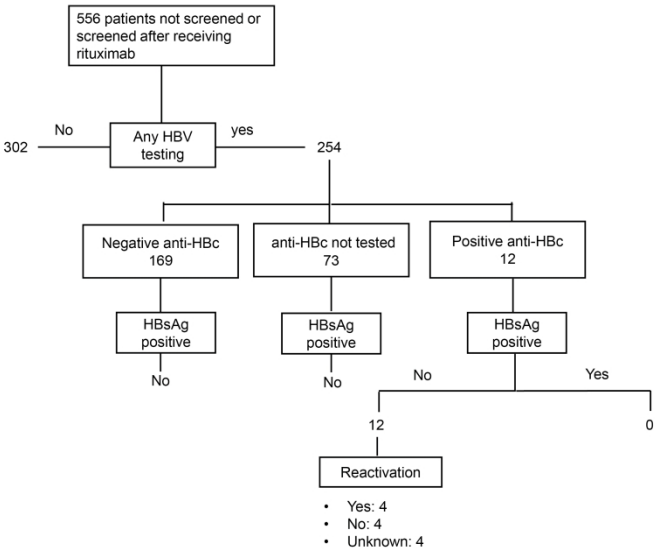

Figure 4

Figure 4
Screening results in patients tested for hepatitis B after starting rituximab

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Figure 5

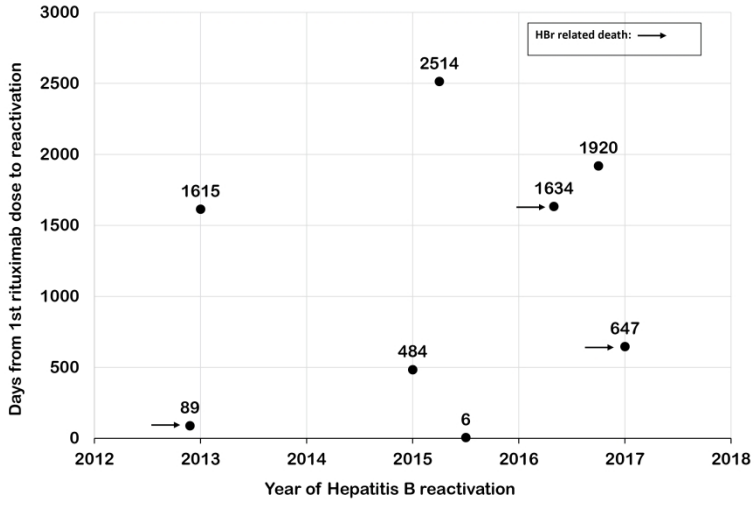

Figure 5
Days from first dose of rituximab to reactivation and hepatitis B related mortality

338x190mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found page 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported page 4
Objectives	3	State specific objectives, including any prespecified hypotheses page 4
Methods		
Study design	4	Present key elements of study design early in the paper page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection page 5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants page 6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable page 6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group page 6
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy page 7
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed page 7
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram page 27
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders page 7
		(b) Indicate number of participants with missing data for each variable of interest page 7
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures page 8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives page 9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias page 11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence page 11
Generalisability	21	Discuss the generalisability (external validity) of the study results page 11
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based page 1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.