Patients treated with rituximab are poorly screened for hepatitis B infection: Data from a low-incidence country

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ABSTRACT

Background & Aims: Patients with chronic or resolved hepatitis B are at risk of hepatitis B reactivation (HBVr) when treated with high-risk immunosuppressive therapy such as rituximab. Therefore, international guidelines recommend HBV screening prior to rituximab treatment and subsequent antiviral prophylaxis among patients with a (resolved) infection. In this study, we evaluated the adherence to those recommendations.

Methods: This is a retrospective multicentre study including patients treated with rituximab between 2000-2021. Performance of correct screening was assessed, defined as the measurement of hepatitis B surface antigen (HBsAg) and hepatitis B core antibodies (anti-HBc). Next, initiation of antiviral prophylaxis and HBVr rate among patients with a chronic or resolved HBV infection was studied.

Results: We enrolled 3,176 patients of whom 1,448 (46%) were screened correctly. Screening rates differed significantly between academic and non-academic hospitals; respectively 65% vs 32% (p<0.001). In addition, screening rates differed across specialties and improved throughout the years; from 32% before 2012 to 75% after 2020 among academic prescribers, versus 1% to 60% among non-academic prescribers (both p<0.001). Antiviral prophylaxis was initiated in 58% vs 36% of the patients with a chronic or resolved HBV infection. Seven patients experienced HBVr, including one fatal liver decompensation.

Conclusions: Many patients treated with rituximab were not correctly screened for HBV infection and antiviral prophylaxis was often not initiated. Although screening rates improved over time, rates remain suboptimal. With the increasing number of indications for rituximab and other immunosuppressive agents these findings could raise awareness among all medical specialties prescribing these agents.

1. Introduction

Hepatitis B virus infection (HBV) is considered a global health threat as it is associated with liver decompensation, liver cirrhosis and primary liver cancer [1]. Worldwide, approximately 269 million individuals have a chronic active hepatitis B infection [1,2]. In the Netherlands, the prevalence of chronic hepatitis B has been estimated at 0.2-0.4%, and approximately 3.5% of the population has a resolved hepatitis B infection [3-5]. Since most HBV infections progress asymptomatically, many patients are unaware of their infection. However, both active and quiescent infections can re-activate in the setting of immunosuppressive or cytotoxic treatment [6].
The anti-CD20 monoclonal agent rituximab is considered a high risk immunosuppressive agent [6-8]. The risk for hepatitis B viral reactivation (HBVr) is 9% among patients with a resolved HBV infection and up to 80% among chronic hepatitis B (CHB) patients when treated with rituximab [9,10]. An HBVr can result in severe and even fatal complications such as symptomatic hepatitis, liver failure, and death. However, HBVr can be prevented using antiviral prophylaxis such as nucleos(t)ide analogues (NAs) [10-12].

It is therefore, according current national and international guidelines, recommended to screen patients who start high-risk immunosuppressive therapy [13-15]. A correct screening includes testing for both hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B core antigen (anti-HBc) to identify both patients with a chronic (HBsAg positive) and resolved (HBsAg negative, anti-HBc positive) infection. In addition, antiviral prophylaxis is recommended for patients with either a chronic or resolved hepatitis infection if treated with rituximab [13,14].

Nevertheless, findings from several studies suggest that screening might be performed sub optimally (Supplementary Table) [16-21]. In the Netherlands, a low endemic country, data on the screening rates among patients treated with high risk immunosuppressive agents are lacking. We therefore aimed to study (1) hepatitis B screening performance in patients treated with rituximab, (2) management of patients with a resolved or chronic hepatitis B infection, and (3) the number of patients that experienced hepatitis B reactivation.

2. Materials and methods

2.1. Study design and patient population

This is a retrospective, observational, multicentre cohort study in the area of Rotterdam, the Netherlands, including one large tertiary academic hospital and four non-academic hospitals. Adult patients who received rituximab between 2000 and 2021 were identified by hospital pharmacy records. Patients were excluded if rituximab was initiated in a different hospital. Data was retrieved from medical notes and laboratory records of each participating hospital. This study was conducted according to the principles outlined in the 1964 Declaration of Helsinki and its later amendments. The original study protocols have been approved by the medical ethical committees. No patients consent was obtained for the study due to its retrospective design and to prevent selection bias as many patient were deceased.

2.2. Outcomes

The main outcome was the proportion of correctly performed HBV screenings in patients who started rituximab treatment. Correct screening was defined as the measurement of both HBsAg and anti-HBc within one year prior to and one month after start of rituximab treatment. Patients were categorised as correctly screened, unscreened, and incorrectly screened. Incorrectly screened patients were divided into subgroups; 1) HBsAg only, 2) anti-HBs or HBV DNA only, and 3) not screened one year prior or one month after start of rituximab treatment.

Secondary outcome included the initiation of antiviral prophylaxis (i.e. NAs) at the start of rituximab treatment in patients with evidence of a chronic hepatitis B [HBsAg(+)] or resolved hepatitis B [HBsAg(-) but anti-HBc(+)] infection. Next, we studied the number of patients that experienced hepatitis B reactivation (HBVr), defined as alanine aminotransferase (ALT) increase in combination with an elevated HBV DNA level (unknown DNA baseline: ≥10,000 IU/mL or known HBV DNA baseline: ≥2 log increase), and/or HBsAg seroreversion within prior HBsAg negative patients.

2.3. Statistical analysis

Results are presented as mean (± standard deviation [SD]), numbers (in percentages), and medians (with interquartile range [IQR]). Associations between screening performance and prescribers or hospital type (academic vs non-academic) were studied using Chi-square test. To study the screening rates over time, year of rituximab was categorised as screening before 01.01.2012 (<2012), 01.01.2012 – 31.12.2014 (2012-2015), 01.01.2015 – 31.12.2017 (2015-2018), 01.01.2018 – 31.12.2019 (2018-2020), and after 01.01.2020 (>2020). Etiological multivariable analysis was used to study risk factors for screening failure [22,23], including sex, ethnicity, hospital type (academic versus non-academic), setting (outpatient clinic versus hospitalised patients), and year of rituximab treatment. Differences were considered as statistically significant if p<0.05. Statistical analysis was performed using IBM SPSS for Windows, version 25.0 (SPSS Inc., Chicago, Illinois, USA). Graph Pad Prism version 5 for Windows (GraphPad Software, San Diego, California, USA) was used for graphical representation of the results.

3. Results

3.1. Study population

In total 3,176 patients were included; 1,290 academic and 1,886 non-academic. The patient characteristics are displayed in Table 1. High volume rituximab prescribers included haematologists (61.0%), and low volume prescribers included neurologists (2.8%), ophthalmologists (2.7%), pulmonologists (0.9%), dermatologists (0.3%), and gastroenterologists (0.3%). Patients received rituximab predominantly in outpatient care setting (94.6%). Haematological malignancies (58.0%) were the most common indications for rituximab.

3.2. HBV screening performance was suboptimal and differed significantly between academic and non-academic hospitals, and between rituximab prescribers

Overall, 1,448 patients (45.6%) were screened correctly and 959 patients (30.2%) were never screened (Fig. 1). In addition, 308 patients (9.7%) were screened for HBsAg only, 10 patients for anti-HBc only (0.3%), and 34 patients (1.1%) were screened for other HBV serological markers (i.e. anti-HBs or HBV DNA only). Another 417 patients (13.1%) were screened correctly, but not within the predefined period (Fig. 1). The screening rates differed significantly between academic and non-academic hospitals; screenings were performed correctly in 65.0% versus 32.3% of the patients in respectively academic and non-academic hospitals (Fig. 1; p<0.001). In addition, screening rates differed between rituximab prescribers (Fig. 2), with highest rates among academic rheumatologists but lowest rates among non-academic rheumatologists.

3.3. Screening rates improved over time, but remain suboptimal

The screening rates improved over time; from 31.9% before 2012 to 75.1% after 2020 in the academic hospital, and from respectively 1.2% to 59.5% in non-academic hospitals (Fig. 2, p<0.001). When data were stratified on prescriber, screening rates also improved over time (<2018 versus >2018; Fig. 3).

Findings were consistent in multivariable analysis, which demonstrated that hospital type (academic versus non-academic; OR 4.30, 95% CI 3.62 – 5.11, p<0.001) and year of rituximab treatment (OR 1.41, 95% CI 1.37 – 1.46, p<0.001) were significantly associated with screening performance, but not sex, ethnicity, or setting (outpatient clinic versus hospitalised patients). No difference was observed when screening rates were stratified for race; correct screening among 45/45/40% of the Caucasian/North African or Middle East/Asian patients.

3.4. Management of patients with a chronic or resolved hepatitis B infection

Among the 2,183 patients with available HBV serology, 12 patients (0.6%) with a resolved or chronic hepatitis B infection. Next, we studied the number of patients with a chronic (HBsAg positive) and resolved (HBsAg negative, anti-HBc positive) infection. In addition, antiviral prophylaxis is recommended for patients with either a chronic or resolved hepatitis infection if treated with rituximab [13,14].
Abbreviations

non-academic patients (29.1%; p

started in 31 of the 70 academic patients (44.3%) and in 16 of the 55

among HBsAg(-) but anti-HBc(+). A recent survey, conducted among Dutch oncologists

to follow a standardized protocol [26]. However, although current (inter)national

to hepatitis B core antigen; anti-HBs, antibodies to hepatitis B surface antigen; HBV, hepatitis B virus.

In total, seven patients experienced HBVr, including four chronic hepatitis B patients and three patients with a resolved HBV infection (Fig. 4). Of those, two patients experienced hepatic decompensation, of whom one patient died. Among the seven patients with an HBVr, five (71.4%) had an haematological disease. None of the patients who received antiviral prophylaxis experienced HBVr.

4. Discussion

Hepatitis B reactivation (HBVr) is a severe complication among patients with a chronic or resolved hepatitis B infection treated with high risk immunosuppressive agents such as rituximab [10]. In this multi-centre study, including one large academic hospital and four non-academic hospitals in the Netherlands, we demonstrated that screening rates were suboptimal. In seven patients lack of antiviral prophylaxis resulted in HBVr, including one fatal liver decompensation. This stresses the importance of insight in screening performances and HBVr risk to raise more awareness on this issue.

Current international guidelines for hepatitis B are comprehensive regarding screening on HBV markers for patient with high risk immunosuppressive agents [13–15]. For instance, the current guideline of the European Association for the Study of the Liver (EASL) published in 2017 [13] and the previous EASL guideline (published in 2012) [24] raised attention on this topic. In line with the publication of those guideline updates we observed that the screening rates improved significantly after 2012 and 2018. Our findings are in line with a study, performed in the USA, which demonstrated that testing for anti-HBc and HBsAg increased from 9% to 87% from 2005 to 2017 [25].

Despite the recommendations of those guidelines we observed that hepatitis B screening is not consistently practiced. A possible explanation is that physicians from low endemic countries have limited knowledge about hepatitis B, because they rarely treat patients with an hepatitis B infection. In addition, physicians prescribing high risk immunosuppressive agents, for instance haematologists or rheumatologists, might be unaware of the international hepatitis B guidelines and consult subsequently only guidelines that are published by their medical association(s). A recent survey, conducted among Dutch oncologists showed that only 27% of the respondents indicated to follow a standardized protocol [26]. However, although current (inter)national guidelines (for instance for rheumatoid arthritis and B cell lymphoma) address the risk of HBV reactivation they are unclear on how to screen patients or how to manage patients with resolved or chronic hepatitis B infection [27–31].

Our results showed a significant difference in screening rates between academic and non-academic hospitals. Several factors could

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Table 1

<table>
<thead>
<tr>
<th>Patient characteristics.</th>
<th>Academic (N=1,290)</th>
<th>Non-academic (N=1,886)</th>
<th>Total (N=3,176)</th>
</tr>
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<tbody>
<tr>
<td><strong>Age at start rituximab</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(years; median, IQR)</td>
<td>57 (45–66)</td>
<td>66 (56–74)</td>
<td>63 (51–71)</td>
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<tr>
<td><strong>Sex</strong> (male; n,%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>73 (5.7)</td>
<td>20 (1.1)</td>
<td>93 (2.9)</td>
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<tr>
<td>Asian</td>
<td>26 (2.0)</td>
<td>21 (1.1)</td>
<td>47 (1.5)</td>
</tr>
<tr>
<td>North African/Middle East</td>
<td>35 (2.7)</td>
<td>84 (4.5)</td>
<td>119 (3.7)</td>
</tr>
<tr>
<td>Other</td>
<td>16 (1.2)</td>
<td>47 (2.5)</td>
<td>63 (2.0)</td>
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<tr>
<td><strong>Prescriber</strong> (n,%)</td>
<td></td>
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<tr>
<td>Haematologist</td>
<td>610 (47.3)</td>
<td>1,325 (70.3)</td>
<td>1,935 (60.9)</td>
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<tr>
<td>Internist</td>
<td>307 (23.4)</td>
<td>1,154 (61.0)</td>
<td>1,461 (46.2)</td>
</tr>
<tr>
<td>Rheumatologist</td>
<td>86 (6.7)</td>
<td>314 (16.6)</td>
<td>399 (12.6)</td>
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<td>Pulmonologist</td>
<td>26 (2.0)</td>
<td>4 (0.2)</td>
<td>30 (0.9)</td>
</tr>
<tr>
<td>Neurologist</td>
<td>73 (5.7)</td>
<td>17 (0.9)</td>
<td>90 (2.8)</td>
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<td>Dermatologist</td>
<td>80 (6.2)</td>
<td>19 (1.0)</td>
<td>99 (3.1)</td>
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<td>Ophthalmologist</td>
<td>80 (6.2)</td>
<td>7 (0.4)</td>
<td>87 (2.7)</td>
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<tr>
<td>Gastro-enterologist</td>
<td>10 (0.8)</td>
<td>1 (0.1)</td>
<td>11 (0.3)</td>
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<tr>
<td><strong>Clinical setting</strong> (n,%)</td>
<td></td>
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<tr>
<td>Outpatient care</td>
<td>1,140 (88.4)</td>
<td>1,863 (98.8)</td>
<td>3,003 (96.4)</td>
</tr>
<tr>
<td>Hospitalized patients (non-ICU)</td>
<td>139 (10.8)</td>
<td>21 (1.1)</td>
<td>160 (5.0)</td>
</tr>
<tr>
<td>Hospitalized patients (ICU)</td>
<td></td>
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<tr>
<td><strong>Indication</strong> (n,%)</td>
<td></td>
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<tr>
<td>Haematological malignancies</td>
<td>574 (44.5)</td>
<td>1,268 (67.2)</td>
<td>1,842 (58.0)</td>
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<tr>
<td>Thrombocytopenia</td>
<td>25 (1.9)</td>
<td>30 (1.6)</td>
<td>55 (1.7)</td>
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<tr>
<td>Anaemia</td>
<td>10 (0.8)</td>
<td>28 (1.5)</td>
<td>38 (1.2)</td>
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<tr>
<td>Vasculitis</td>
<td>150 (11.6)</td>
<td>103 (5.5)</td>
<td>253 (8.0)</td>
</tr>
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<td>Rheumatoid arthritis</td>
<td>62 (4.8)</td>
<td>309 (16.4)</td>
<td>371 (11.7)</td>
</tr>
<tr>
<td>Renal disorders</td>
<td>69 (5.3)</td>
<td>63 (3.3)</td>
<td>132 (4.2)</td>
</tr>
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<td>Autoimmune diseases</td>
<td>147 (11.4)</td>
<td>51 (2.7)</td>
<td>198 (6.2)</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>40 (3.1)</td>
<td>1 (0.1)</td>
<td>41 (1.3)</td>
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<td>Transplantation-related</td>
<td>66 (5.1)</td>
<td>0 (0.0)</td>
<td>66 (2.1)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>147 (11.4)</td>
<td>33 (1.7)</td>
<td>180 (5.7)</td>
</tr>
<tr>
<td><strong>Year of rituximab treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2012</td>
<td>47 (3.6)</td>
<td>242 (12.8)</td>
<td>289 (9.1)</td>
</tr>
<tr>
<td>2012–2015</td>
<td>174 (13.5)</td>
<td>284 (15.1)</td>
<td>458 (14.4)</td>
</tr>
<tr>
<td>2015–2018</td>
<td>476 (36.9)</td>
<td>507 (26.9)</td>
<td>983 (31.0)</td>
</tr>
<tr>
<td>2018–2020</td>
<td>404 (31.3)</td>
<td>557 (29.5)</td>
<td>961 (30.3)</td>
</tr>
<tr>
<td>&gt;2020</td>
<td>189 (14.7)</td>
<td>296 (15.7)</td>
<td>485 (15.3)</td>
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</tbody>
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*a Haematological malignancies included lymphoma, leukemia, and monoclonal gammopathy of undetermined significance (MGUS). Thrombocytopenia included thrombocytopenia eci, Immune thrombocytopenic purpura (ITP) and Thrombotic thrombocytopenic purpura (TTP). Anaemia included hemoglobinopathy, autoimmune anaemia. Vasculitis included granulomatosis with polyangiitis (Morbus Wegener) and other vasculitis-related diseases. Renal disorders included nephrotic syndrome, glomerulonephritis. Autoimmune disorders included systemic lupus erythematosus (SLE), anti-synthetase syndrome, anti-phospholipid syndrome, and Morbus Graves.

Abbreviations: ICU, intensive care unit.

(0.5%) were HBsAg(+); 111 patients (5.1%) were HBsAg(-) but anti-HBc (+), and two patients were anti-HBc(+) without known HBsAg status (0.1%; p < 0.008). In addition, the number of patients receiving antiviral prophylaxis increased over time, from 27.1% before 2018 to 47.0% after 2018 (p = 0.057); an increase from 50.0% to 66.7% among HBsAg(+) patients (p = 0.565), and 25.0% to 45.8% among HBsAg(-) but anti-HBc(+) patients (p = 0.035).
Some specialties have (had) access to computerized screening tools while others did not have this access. Secondly, there is a possibility that within the same institution some specialties have (had) access to computerized screening tools while others did not have this access. First, awareness of HBV reactivation might be higher among medical specialists that prescribe rituximab more frequently and routinely. However, it is remarkable that in this study high-volume prescribers did not necessarily perform screening more adequately compared to low-volume prescribers. Secondly, there is a possibility that within the same institution some specialties have (had) access to computerized screening tools while others did not have this access. Adequate screening can prevent HBV reactivation and potentially fatal outcomes by administering antiviral prophylaxis. Current guidelines from the European and American associations for liver diseases therefore recommend antiviral prophylaxis over monitoring of HBV DNA, HBsAg and/or ALT levels among patients treated with rituximab. However, we observed that many patients with a resolved or chronic hepatitis B did not receive antiviral prophylaxis. Although the administration of antiviral agents increased after 2018 many patients still did not receive adequate management. This resulted in seven HBVr, of whom one patient developed fatal liver decompensation. Therefore, all patients starting on high risk immunosuppressive agents who have evidence of a (resolved) hepatitis B infection should be treated in collaboration with a hepatologist or infectious disease specialist.

It should be noted that not only rituximab has been listed as high risk immunosuppressive agent, also anthracycline derivatives and high dose corticosteroids (prednisone > 20 mg per day for >4 weeks) are considered high risk agents. Those patients should also be screened for HBV serology and treated with antiviral prophylaxis if they are HBsAg positive or anti-HBc positive (HBsAg-negative). Pre-emptive therapy (screening for HBsAg and HBV DNA every 1-3 months during and after immunosuppression) is recommended among patients receiving agents with a moderate or low risk of HBV reactivation. Moderate risk agents includes tumour necrosis factor (TNF)-α inhibitors, cytokine inhibitors and integrin inhibitors, tyrosine kinase inhibitors and moderate dose of corticosteroids (prednisone < 20 mg for ≥4 weeks). Low risk agents include low dose corticosteroids and traditional immunosuppression such as azathioprine, 6-mercaptopurine, and methotrexate. Antiviral prophylaxis should be started among HBsAg positive patients. However, each clinician could consider also starting antivirals in anti-HBc positive only patients, as these agents are inexpensive, have limited side effects, and are very effective in preventing HBVr. Our study included a large cohort of patients that were treated with rituximab in one tertiary and four non-academic hospitals in a time period of 20 years. However, some limitations should be acknowledged. First, the number of HBVr can be an underestimation, since HBVr can occur >6 months after last rituximab infusion, and some of the included patients started rituximab treatment in 2020 or 2021. Also, we were not able to assess the incidence of HBVr among patients who were not screened. Since rituximab is often combined with cytotoxic agents which can cause toxic hepatitis, it is unknown what could have caused a possible rise in ALT (or even liver failure) among those without any HBV serology/HBV DNA measurements. In addition, there will be patients with unknown toxicity of rituximab probably due to an unknown HBVr. Another issue not addressed in this study is the use of electronic tools for screening which could have affected screening results per medical specialty. Furthermore, we defined correct screening as the measurement of both HBsAg and anti-HBc, in line with the current international guidelines. However, it could be debated that the patients who were screened for anti-HBc only could be considered as correctly screened since both patients with an active and resolved HBV infection (both anti-HBc positive) have an indication for antiviral prophylaxis. Nevertheless, with the limited number of patients in our cohort who were screened for anti-HBc only, screening rates will remain suboptimal when contribut to the discrepancy in screening performance between academic and non-academic hospitals, and between prescribers. First, awareness of HBVr might be higher among medical specialists that prescribe rituximab more frequently and routinely. However, it is remarkable that in this study high-volume prescribers did not necessarily perform screening more adequately compared to low-volume prescribers. Secondly, there is a possibility that within the same institution some specialties have (had) access to computerized screening tools while others did not have this access. Adequate screening can prevent HBV reactivation and potentially fatal outcomes by administering antiviral prophylaxis. Current guidelines from the European and American associations for liver diseases therefore recommend antiviral prophylaxis over monitoring of HBV DNA, HBsAg and/or ALT levels among patients treated with rituximab. However, we observed that many patients with a resolved or chronic hepatitis B did not receive antiviral prophylaxis. Although the administration of antiviral agents increased after 2018 many patients still did not receive adequate management. This resulted in seven HBVr, of whom one patient developed fatal liver decompensation. Therefore, all patients starting on high risk immunosuppressive agents who have evidence of a (resolved) hepatitis B infection should be treated in collaboration with a hepatologist or infectious disease specialist.

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redefining the definition of correct screening. Moreover, additional data that was not part of the first data extraction, such as the treatment duration of antiviral prophylaxis among the patients who received antivirals, could not be collected due to protocol regulation restrictions. Next, we observed a significant difference in screening among academic and non-academic hospitals. However, we included only one large academic hospital. It is therefore unknown whether our findings could be translated to other (Dutch) academic hospitals. Also, the included hospitals are located in a multiethnic area of the Netherlands. Therefore, it is unknown whether our findings could be translated to other areas in the Netherlands. However, multivariate analysis demonstrated that ethnicity was not associated with screening performance. Finally, our findings might only be generalizable to other low-endemic countries, although similar HBV screening rates were reported in both low- and higher-risk areas as well [16,18,21].

With an increasing number of indications for rituximab treatment, as well as other high risk immunosuppressive and cytotoxic agents such as TNF-α inhibitors and other biologic agents [36], awareness of risk of HBVr and the importance of HBV screening is necessary among a wide variety of medical specialties. Therefore, both international and national guidelines should be revised and targeted education sessions might improve screening rates, as demonstrated in a study by Dyson et al [37]. In addition, screening rates might also be improved using Information Technology (IT) tools. A computer-assisted reminder system alerting physicians of HBV screening might improve screening rates [38]. Another IT system initiated in a Japanese hospital automatically provided information on HBV screening and status of the patient to the attending physician when prescribing rituximab. Implementation of this system was 100% effective, as all patients were treated according to the hospital’s hepatitis B guidelines [39]. An Electronic Medical Record (EMR) template in which a result of a recent HBV test is required prior to rituximab prescription could be another solution.

In conclusion, many patients treated with rituximab were not adequately screened for the presence of an HBV infection. Although screening rates improved significantly over the years they remain suboptimal. Lack of adequate screening and antiviral prophylaxis impacted patient outcomes and resulted in HBVr in a couple of patients (including one fatal liver decompensation). Our findings could be used to raise awareness among all medical specialties. Reinforcement of current guidelines, ongoing education, and implementation of electronic systems could play a pivotal role in optimising screening rates and subsequent management of patients with hepatitis B treated with rituximab.

**Funding statement**

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**Ethics approval statement**

The original study protocols have been approved by the medical ethical committees and are in line with the Declaration of Helsinki of 1975.

**Author’s contributions**

SB, RH, MS and RdM conducted the study. SB, RH and MS performed statistical analysis. SB and RH made graphic images, interpretation of data and revision of the manuscript. SB and RH wrote the manuscript, which was revised by all authors. All authors reviewed and approved the final manuscript.

**Data availability statement**

Data not available.

**Conflict of interest disclosure**

SB received an unrestricted research grant from Gilead. RdK has received honoraria for consulting/speaking from Gilead, Janssen, echosens, AbbVie, and Norgine and received research grants form Gilead and Janssen. MS has received speaker’s fees and research support from
Roche, Innogenetics, BMS, Gilead and Fujirebio. The other authors report no disclosures.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2022.11.024.

References