A Danish nationwide questionnaire study of hepatitis B virus screening before immunosuppressive therapy

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ABSTRACT

INTRODUCTION: Difficulty in identifying patients who are at risk for hepatitis B virus (HBV) reactivation makes it important to screen for HBV before initiating immunosuppressive therapy. The aim of this study was to investigate screening procedures for HBV infection before initiation of immunosuppressive therapy and to explore HBV treatment strategies.

METHODS: All Danish units of haematology, oncology, dermatology, rheumatology and gastroenterology using immunosuppressive agents were invited to fill out a questionnaire for The Danish Database for Hepatitis B and C.

RESULTS: A total of 28 (53%) of the 53 included units answered the questionnaire; of which 25 (89.3%) had a guideline regarding screening for HBV serological markers prior to immunosuppressive therapy, but only ten (37%) had a guideline that is in line with the joint guidelines from the national Danish Societies of Infectious Diseases and Gastroenterology and Hepatology. Nineteen (76%) units had a strategy regarding treatment for reactivation before initiating immunosuppressive therapy in case of positive HBV serology. It was not possible to determine the number of HBV reactivations as this was not registered in the ICD-10 system. The Danish Medicines Agency had one report of reactivation.

CONCLUSIONS: A minority of the units had screening guidelines for HBV reactivation that were in line with the guidelines of the national scientific societies. Screening in accordance with these recommendations should be a goal for all Danish units in order to prevent HBV reactivation.

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Hepatitis B virus (HBV) infection is a major global health problem: approximately 240 million individuals are chronically infected, and according to the World Health Organization (WHO) approximately 686,000 individuals die annually due to hepatitis B [1]. Reactivation of HBV infection is a well-known complication in patients receiving immunosuppressive therapy [2]. HBV reactivation is characterised by rising serum HBV DNA levels followed by rising alanine transaminase. The increase in HBV replication frequently occurs within weeks or months after immunosuppression, but sometimes it occurs even within the treatment period. Immune reconstitution days or weeks after dose reduction or finished treatment may lead to a flare-up of hepatitis B manifested as hepatocellular injury due to alanine transaminase elevation [3]. The clinical presentation of the disease is highly variable ranging from a subclinical, asymptomatic course to fulminant hepatitis, liver failure and death [3]. Reactivation is observed in different settings and can therefore be difficult to diagnose. It is associated with the use of monoclonal antibodies, chemotherapy, steroids and immunosuppression in the context of solid organ transplantation [4-6]. Reactivation is most commonly observed in patients receiving chemotherapy for haematological malignancies [7], but it is also frequent in patients treated for diseases in the specialities of dermatology, rheumatology, gastroenterology, oncology and nephrology [8]. Prophylactic anti-viral therapy has been shown to be effective in preventing HBV reactivation [9, 10]. Nevertheless, inconsistency in guideline recommendations and the lack of HBV screening before the initiation of immunosuppressive treatment have led to successive reports of fatal reactivation [11].

As a result of the increasing use of aggressive immunosuppressive agents, a growing number of international migrants, and the difficulty of identifying patients in HBV high-risk groups, HBV reactivation has also become a growing problem in low-endemic countries.

The aim of this study was to investigate screening procedures for HBV infection before the initiation of immunosuppressive therapy, and to explore the use of strategies for further treatment in patients with a HBV serology indicating ongoing or previous HBV infection who are undergoing immunosuppressive therapy in a HBV-low-endemic country, such as Denmark.

METHODS

From March to May 2014, all Danish units in the specialities of haematology, oncology, dermatology, rheumatology and gastroenterology were identified through medinfo.dk and the SKS browser (the Healthcare Classification System – a collection of International, Nordic and Danish classifications). The units were included in the

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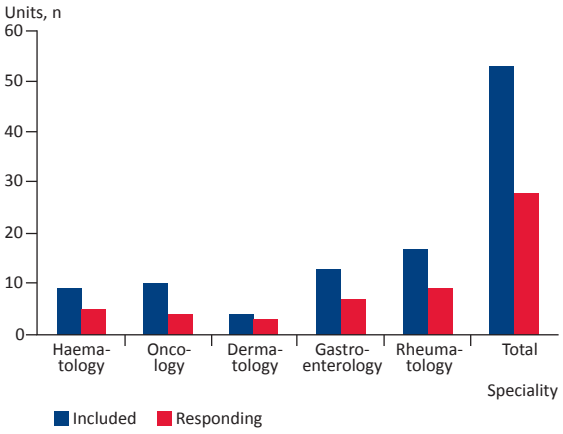
FIGURE 1

Distribution of units that chose to answer the questionnaire, grouped by medical speciality.



study owing to their use of immunosuppressive agents on a daily basis (e.g. alemtuzumab, azathioprine, cyclophosphamide, steroids, methotrexate, rituximab and TNF inhibitors).

Phone calls to the above-mentioned hospital units identified the email addresses of the head physicians of the departments. A questionnaire consisting of eleven questions was created and emailed to all head physicians of the included units on behalf of the Danish Database for Hepatitis B and C (DANHEP) [12]. The questionnaire was accompanied by an introductory letter explaining the issue of HBV reactivation associated with the use of immunosuppressive agents. E-mails with questionnaires and introductory letters were initially sent in the beginning of June 2014 and then twice more, the latest in November 2014. If a unit did not return the questionnaire by the end of November 2014, unit staff was politely asked by phone to participate in the study. It was decided to keep the participating units anonymised and to refer only to the medical speciality of the units.

As part of this study, we attempted to determine the exact number of reactivations, but this was unfortunately not possible because the units included in the study had not registered the number of reactivations through the International Classification of Diseases, tenth edition (ICD-10) system. We therefore contacted the Danish Medicines Agency (the supreme pharmaceutical authority in Denmark), who used their database to determine that there had been only one report of reactivation of HBV as a side effect to immunosuppressive therapy.

According to Danish legislation on research ethics, the approval of the Research Ethics Committee was not needed as this was a questionnaire-based study. This study was based on questionnaires answered by hospital departments rather than individual patients.

Trial registration: not relevant.

RESULTS

A total of 59 potential units were traced of which six were excluded: four because they were not offering treatment relevant to the current study, and two because they were unable to answer the questionnaire due to technical problems. In total, 53 units were included.

Of these 53 units, nine were haematology units, ten were oncology units, four were dermatology units, 13 were gastroenterology units and 17 were rheumatology units.

Of the 53 units approached, 28 (53%) chose to participate in the study, of which five (18%) were haematology units, four (14%) were oncology units, three (11%) were dermatology units, seven (25%) were gastroenterology units and nine (32%) were rheumatology units (**Figure 1**).

Of the 25 approached but not participating units (47%), four were haematology units (16%), six oncology units (24%), one was a dermatology unit (4%), six were gastroenterology units (24%) and eight were rheumatology units (32%).

A total of 25 (89%) of the participating units had a guideline on screening of HBV serological markers before the initiation of immunosuppressive therapy. It must be expected that if a unit has guidelines on screening for HBV, these guidelines will be followed by the specialists working at that unit. Only ten (36%) of the guidelines were in line with the joint guidelines from the Danish Society of Infectious Diseases and the Danish Society of Gastroenterology and Hepatology (hereafter: "national societies"), which recommend screening for HBsAg, anti-HBs and anti-HBc before initiation of immunosuppressive therapy in Denmark [13].

Regarding the measurement of specific HBV serological markers (question answered by 27 units), four (15%) units screened for HBsAg only; ten (37%) units screened for HBsAg, anti-HBs and anti-HBc; one (4%) unit screened for HBV-DNA and anti-HBc; three (11%) units screened for HBsAg and anti-HBc; five (18%) units screened for HBsAg and anti-HBs; and four (15%) units (all oncology units) did not provide screening for any HBV serological markers before the initiation of immunosuppressive therapy.

Of the responding units, 25 (89%) answered the question regarding "a strategy" on further treatment of patients with positive HBV serological markers (positive HBsAg, anti-HBc or anti-HBs in non-vaccinated individuals) during and after immunosuppressive therapy. A total of 19 (76%) of these units had a strategy for further

treatment. A "strategy" included either a unit-approved guideline describing the treatment and prophylaxis of the patient with antiviral therapy during and after the immunosuppressive therapy or a guideline directing the patient to a department of infectious diseases or medical gastroenterology for further treatment and anti-viral prophylaxis.

DISCUSSION

In this nationwide Danish questionnaire study, we revealed that the majority (89%) of the 28 participating units did follow HBV screening procedures before the initiation of immunosuppressive therapy; 89% is a relatively high share, but only ten (37%) of these units had a guideline that was in line with the recommendations published by the national societies. A future goal should therefore be that all units in Denmark follow the same national screening procedures before initiating immunosuppressive therapy to ensure the best possible treatment for the patients. This could be improved by additional collaboration between the national scientific societies that use these immunosuppressive agents.

None of the oncology units participating in this study screened for HBV markers before the initiation of immunosuppressive therapy. This could be because the Danish Society of Clinical Oncology has been influenced by The American Society for Clinical Oncology (ASCO), which in 2010 published a clinical opinion stating that there is insufficient evidence on this subject to determine the benefits and harms of universal screening for HBV in cancer patients receiving immunosuppressive therapy. Physicians should, nevertheless, be careful with "high-risk" patients [14]. It is difficult, however, to be careful when suspected risk factors of HBV infection are not always apparent. In addition, the patient may not know the risk factors or even remember high-risk behaviour and, furthermore, the provider may not ask about risk factors or not even be aware of them [2]. However, in 2015 ASCO published a new clinical opinion recommending that medical providers screen for HBV before starting anti-CD20 therapy or haematopoietic cell transplantation. Additionally, they should also screen patients with risk factors for HBV infection [15].

In general, there is inconsistency between guideline recommendations in this area. The European Association for the Study of the Liver, the Asian-Pacific Association for the Study of the Liver and The US Centers for Disease Control and Prevention recommend universal HBV screening prior to initiation of immunosuppressive therapy, whereas the American Association for the Study of Liver Diseases and the National Comprehensive Cancer Network recommend screening of patients with risk factors [8].

Denmark is an HBV-low-endemic country with an estimated HBV prevalence of 0.24% [12]. The majority of HBV infected individuals in Denmark are immigrants [16]. However, cases with a fatal outcome of reactivation also do occur in native Danish individuals with no suspected risk factors for HBV infection. This shows that although a country is low endemic regarding HBV infections and the majority of infected individuals are immigrants, it is still not possible to determine exactly which patients are at "high risk" of experiencing HBV reactivation. Thus, a screening strategy directed towards high-risk persons, e.g., patients migrated from HBV-endemic countries to Denmark, is insufficient. In addition, providers may often forget to ask about risk factors as HBV is rarely encountered in native Danes. Therefore, universal screening for HBV markers is the first critical step towards prevention. As recently presented by Perrillo et al in JAMA, a barrier to universal HBV screening is the misperception that HBV reactivation rarely occurs in Western countries, and that all who are HBV-infected have recognisable risk factors [2]. Together with inconsistent guideline recommendations in this area, these barriers play a part in the continuous occurrence of HBV reactivation due to failure to screen patients for HBV before initiating immunosuppressive therapy. This is unfortunate as HBV reactivation is easily prevented with prophylactic antiviral therapy, which does not interact with medications used for immunosuppressive therapy.

Another reason to support universal HBV screening is the possible interruption of chemotherapy that may follow from reactivation, and which may potentially lead to a poorer cancer therapy-related outcome [17].

A total of 19 (68%) of the responding 28 units had a guideline on further treatment and prophylaxis of patients with positive HBV serological markers – including referring the patient to a department of infectious diseases or a department of medical gastroenterology for further evaluation and treatment. In the present study, we did not investigate prophylactic antiviral procedures in departments of infectious diseases; thus, it was not possible to determine whether lamivudine, tenofovir or entecavir were used as first-line prophylactic antiviral therapy in Denmark. Today, entecavir or tenofovir is recommended as first-line treatment [18, 19].

It is not clear for how long antiviral therapy should be continued. In patients receiving rituximab, reactivation can occur late, which is the reason why the European Association for the Study of the Liver (EASL) recommends continuing antiviral prophylaxis during and up to 12 months after the completion of immunosuppressive therapy [18]. Very few of the participating units had a guideline on the duration of prophylactic antiviral therapy, and none of the Danish Societies representing the five types of units included had any recommendations regarding this issue.

A strength of this study is that we reached out to the entire relevant healthcare sector to gather information regarding HBV screening before the initiation of immunosuppressive therapy, but it should be noted that only 28 (53%) of the contacted units chose to respond. Moreover, only 25 of 28 (89%) participating units had a screening guideline. We do not know why so many units chose not to participate, but we presume this might be due to competing demands for the physicians' time. Furthermore, it is difficult to know if the specialists actually adhere to the guidelines set forth by the units [20].

According to The Danish Medicines Agency, there had been only one report of HBV reactivation notified as a side effect to immunosuppressive therapy. Nevertheless, The Danish Medicines Agency concluded that far from everything is reported to them, including rare side effects such as HBV reactivation.

CONCLUSIONS

This nationwide questionnaire study demonstrated that in an HBV-low-endemic country such as Denmark, very few units have guidelines that are in line with the joint guidelines of the national scientific societies of infectious diseases and gastroenterology and hepatology, and not all units have a treatment strategy for HBV reactivation.

It is important to increase physicians' awareness of HBV reactivation and to implement universal screening for HBV before the initiation of immunosuppressive therapy both in high-endemic and in low-endemic countries, because of the potential severity of reactivation and the efficiency of prophylactic antiviral therapy.

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