Hepatitis b virus reactivation in patients with occult infection and hematological malignancies submitted to immunosuppressive therapy. A prospective multicenter study

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Abstract

Background: The best strategy of managing patients with occult hepatitis B virus infection (HBsAg negative, anti-HBc antibodies positive with or without anti-HBs antibodies) and hematological malignancies is not defined.

Methods: We prospectively analysed the risk of hepatitis b virus reactivation in 23 of these patients (20 positive for anti-HBs). Eleven patients underwent hematopoietic stem cell transplantation (autologous in 7 cases, allogeneic in 4 cases) while the remaining 12 were treated with immunosuppressive regimens (including rituximab in 8 cases).

Results: During the study no patient presented acute hepatitis. However, three anti-HBc/anti-HBs positive patients submitted to allogeneic hematopoietic stem cell transplantation demonstrated hepatitis B virus reactivation within 12 months from transplant. No one of the remaining patients showed hepatitis B virus reverse seroconversion.

Conclusions: Allogeneic hematopoietic stem cell transplantation is a high risk condition for late hepatitis B virus reactivation in patients with occult infection. Reverse seroconversion seems to be a rare event in anti-HBc/anti-HBs positive patients submitted to autologous hematopoietic stem cell transplantation or systemic chemotherapy with or without rituximab.

Keywords: hepatitis B virus, occult infection, hematological malignancies, immunosuppression, reverse seroconversion
Background

Reactivation of hepatitis B virus (HBV) determining liver injury of different severity, ranging from a subclinical asymptomatic course to severe acute hepatitis and even death, is a very important issue in patients with hematological malignancies [1]. Indeed, HBV related liver injury has been reported to be the third cause of liver disease after graft versus host disease and cytostatic drug hepatototoxicity in these patients [2], and the impact of this problem is outstandingly relevant in Italy where, among patients with B-cell non-Hodgkin's lymphoma, 8.5% have been reported to be positive for hepatitis B surface antigen (HBsAg), and another 41.7% resulted to be positive for hepatitis B core antibody (anti-HBc) with or without hepatitis B surface antibody (anti-HBs) [3]. Accordingly, in the Hematology Department of the Catholic University, among 244 consecutive patients with diffuse large B cell lymphoma observed during the period 2008-2013, 5 resulted to be positive for HBsAg (2%), and 34 for anti-HBc with or without anti-HBs (14%) (unpublished data).

Since effective antiviral therapies are available for HBV, routine screening for the assessment of the individual HBV serological status is mandatory in each patient with oncohematological disease. Universal prophylaxis is well established as an effective treatment to prevent HBV reactivation in HBsAg positive patients according to the present guidelines of the American and European Associations for the Study of Liver Disease [4,5], and has been shown to significantly reduce the rate of HBV related alanine-aminotransferase (ALT) flares, cessations of chemotherapy, liver failure, and deaths in these patients [6].

However, the best strategy of managing HBsAg negative patients with occult HBV infection (anti-HBc positive) is less clear. It is well known that patients with resolved HBV infection (HBsAg negative/anti-HBc positive with or without anti-HBs)
may maintain low level of detectable HBV-DNA in the serum, liver or peripheral-blood mononuclear cells [7], and HBV reactivation with reappearance of HBsAg in the serum (reverse seroconversion) may be detected during and after profound immunosuppressive therapy [8]. In patients with hematological malignancies this risk has been reported to be as high as 12% during conventional chemotherapy, but is probably higher in patients treated with hematopoietic stem cell transplantation (HSCT), in whom it has been reported to range between 14% and 50% [9], or in patients submitted to treatment with monoclonal antilymphocyte B and T antibodies (anti-CD20 and anti-CD52) [7,10].

In this study we prospectively analysed the risk of HBV reactivation in 23 patients HBsAg negative/anti-HBc positive with or without hepatitis B surface antibody and with hematological malignancies who underwent profound immunosuppressive therapy without any prophylactic antiviral treatment. Therefore, the primary objective of our study was the early detection of reverse seroconversion and/or of positive serum HBV-DNA in patients carrying antibodies to HBV in order to prevent acute HBV recurrence; secondary objective was the evaluation of the effectiveness of therapy with nucleoside/nucleotide analogues in the prevention of hepatitis flare.

**Methods**

Patients were consecutively enrolled in this prospective study between December 2007 and December 2008 in three Italian Hematology Departments (Università Cattolica del Sacro Cuore, Rome and Campobasso; Istituti Fisioterapici Ospedalieri, Rome). Informed consent was obtained from each patient and the procedures
followed were in accordance with the ethical guidelines of the Helsinki Declaration of 1975, as revised in 2008.

All the patients who were scheduled for treatment with anticancer therapy and/or HSCT for a lymphoproliferative or myeloproliferative disease were screened for the present study and had serum HBsAg, anti-HBs and anti-HBc IgG determined. All the HBsAg-negative patients found to be positive for anti-HBc were enrolled in the study, independently of the anti-HBs status. At the time of enrollment all patients were checked for co-infection with hepatitis C virus (HCV), and human immunodeficiency virus (HIV), and underwent serum assay of hepatitis b e antigen (HBeAg), hepatitis b e antibody (HBeAb), HBV-DNA and routine laboratory parameters assessing liver and kidney function. During the period of immunosuppressive therapy and for 18 months thereafter every three months complete HBV serum markers, including anti-HBc IgM and HBV-DNA serum level, were measured. In case of HBsAg reverse seroconversion (reappearance of serum HBsAg) with detectable HBV-DNA level, we started antiviral therapy with nucleoside/nucleotide analogues.

Twenty-eight anti-HBc positive/HBsAg negative patients were enrolled in the study. Two patients discontinued the study because they preferred to refer to another Hematology Department, while three patients died after the enrolment due to hematological disease progression, and could not complete the study. Among the 23 evaluable patients, there were 13 men and 10 women with a median age of 60 years (range 43-79 years) (Table 1). Twenty patients (87%) were positive for anti-HBs, (11 anti-HBe positive, 9 anti-HBe negative), while 3 (13%) were anti-HBs negative (1 anti-HBe positive, and 2 anti-HBe negative). All the patients had undetectable HBV-DNA serum level and the serum HBV-DNA load was determined throughout the
study by quantitative reverse transcriptase polymerase chain reaction (COBAS AmpliPrep/COBAS TaqMan HBV test, Roche Diagnostics, Switzerland, threshold level 12 IU/mL). None of the patients tested positive for antibody to HIV. All the patients but 3 had negative serum assay for anti-HCV antibodies, and two of them were also HCV-RNA positive. The patients had various hematological malignancies, with lymphoma being the most frequent disease; three patients had Hodgkin lymphoma and 14 non-Hodgkin lymphoma (5 mantle cell, 5 diffuse large B cell, 3 follicular, 1 peripheral T-cell); the other patients had multiple myeloma (two cases), chronic lymphocytic leukemia (two cases), acute myeloid leukaemia (one case) and myelodysplastic syndrome (refractory anemia with excess of blasts type 2) (one case). They were submitted to various treatment regimens according to the different hematological disease, In particular, among the 12 patients submitted to immune suppression without HSCT, the treatment regimen included rituximab in 9 patients. Furthermore, when considering the 11 patients undergoing HSCT, 7 received autologous transplant and 3 allogeneic transplant, while the remaining patient underwent both autologous and allogeneic transplant (Table 1). Indeed, all but one HSCT patients had detectable antibodies to HBsAg with serum levels ranging from 34 to 1000 IU/mL (mean 230.5 IU/mL). All the stem cell donors for patients submitted to allogeneic HSCT tested negative for HBV serum markers.

Follow-up for the post-immunosuppression period was calculated from the date of last administration of chemotherapy or date of HSCT. The median follow-up, was 35 months (range 18-45 months).

Results
During the course of the study no patient presented HBV hepatitis, defined as increased serum alanine aminotransferase exceeding three times the upper normal value or an increase of more than 100 U/l when compared to baseline pre-chemotherapy value associated to HBV reactivation with evidence of HBsAg reverse seroconversion (the reappearance of HBsAg) with an increase in HBV-DNA level when compared with baseline value in the absence of acute infection with hepatitis A or C viruses or other systemic infection [11]. However, three anti-HBc/anti-HBs positive patients showed HBV reactivation with reappearance of HBsAg in the serum and detectable HBV-DNA without a relevant increase of serum ALT level (Table 2). These pts, were affected by acute myeloid leukaemia, multiple myeloma and myelodysplastic syndrome (refractory anemia with excess of blasts type 2), respectively. All of them had undergone allogeneic HSCT (pt 2 was previously treated with unsuccessful autologous HSCT), and virus reactivation was detected 8, 10 and 9 months after HSCT, respectively.

The patients tested positive for anti-HBs prior to the start of haematological therapy, and pts 1 and 2 were also anti-HBe positive. In particular, pt 1 had a high title of anti-HBsAg (439.5 mUI/ml), while pts 2 and 3 had an intermediate title (34.5 and 52.6 mU/ml). At the time of HSCT, anti-HBs title was significantly reduced in patient 1 (17.9 mUI/ml), undetectable in patient 2, and slightly decreased in patient 3.

After the detection of HBV reactivation, all three patients were effectively treated with entecavir 0.5 mg once daily with progressive decrease of serum HBV-DNA and ALT level. Patient 1 died 30 months after the allogeneic HSCT due to recurrence of acute myeloid leukemia; at that time she still showed low serum level of HBV-DNA. Six months after the beginning of therapy with entecavir, patient 2 showed loss of HBsAg, undetectable HBV-DNA, and reappearance of anti-HBs;
these viral findings were still present on March 2012, 43 months after the allogeneic
HSCT when the patient died because of respiratory failure complicating graft versus
host disease. Finally, patient 3 died 33 months after the allogeneic HSCT because
of recurrent mielodysplastic syndrome; at that time the patient showed undetectable
serum level of HBV-DNA and normal serum ALT.

Among the anti-HBs patients without HBV reactivation, one patient showed a
transient loss of anti-HBs whereas HBV-DNA remained negative, and another one
showed anti-HBe loss maintaining detectable anti-HBs. As regards the 3 anti-HBs
negative patients, one patient underwent autologous HSCT and two an
immunosuppressive regimen, including rituximab in one case; no change of the
HBV serological status was detected in all of them.

Discussion and conclusions
In our prospective study, we evaluated HBV reactivation in patients with
hematological malignancies, who are HBsAg negative/anti-HBc positive with or
without anti-HBs, undergoing intensive immunochemotherapy including rituximab
and/or HSCT. To our knowledge, there is only one prospective study evaluating the
risk of HBV reactivation in HBsAg negative/antiHBc positive patients with or without
anti-HBs submitted to intensive immunosuppressive regimens including rituximab
[12]. Then, this is the second prospective study evaluating HBV reactivation in this
setting of patients but it is the first in which a small cohort of HSCT pts has been
included in the analysis.

The therapeutic approach to HBsAg negative/anti-HBc positive patients
receiving immunosuppressive therapy is controversial: Lok et al did not recommend
routine antiviral prophylaxis with nucleoside or nucleotide analogues for these
individuals [4], while, according to the guidelines of the European Association for the Study of the Liver, HBsAg-negative patients with positive anti-HBc antibodies and undetectable HBV-DNA in the serum who receive chemotherapy and/or immunosuppression should be followed carefully by means of ALT and HBV-DNA testing performed at 1-3 month interval and treated with antiviral therapy upon confirmation of HBV reactivation before ALT elevation [5]. On the contrary, universal antiviral prophylaxis has been proposed for all anti-HBc positive patients undergoing therapy for haematological malignancies [13], or exclusively in patients with detectable HBV-DNA [5,9], or in patients who need to be treated with intense immunosuppressive regimens (such as chemotherapy with fludarabine, dose-dense regimens, HSCT, autologous myeloablative transplant, induction in acute leukaemia, and use of monoclonal antibodies) [10].

Onco-hematological pts with an occult HBV infection exposed to intensive immunosuppression without prophylaxis have a reactivation risk ranging from 3% to 25% according to available data [2,14]. In HSCT patients the HBV reverse seroconversion usually occurs as a delayed event and may have relevant clinical consequences since reconstitution of immunity after tapering or withdrawal of cytotoxic therapy may trigger immune-mediated injury of infected hepatocytes leading to acute hepatitis with a clinical picture ranging from subclinical transaminase elevation, to jaundice or fulminant liver failure and death [15].

The overall percentage of reactivation in our study group of anti-HBc positive patients was 12%, but if we consider only patients submitted to HSCT this rate increased to 27.3%. In particular, the risk of HBV reactivation appeared to be substantially higher in patients undergoing allogeneic HSCT (3/4, 75%) compared to patients treated with autologous HSCT (0/7).
The rate of HBV reactivation in allogeneic HSCT in our study was higher than that reported in recent retrospective series in which it ranged from 12% to 21.4% while risk factors for HBV reactivation were reported to be chronic onco-hematological disease, duration of chemotherapy regimens before HSCT and younger age at transplantation [15-17]. Our results should be interpreted with caution considering the limited number of patients evaluated; however, taking into account the prospective design of the study, a great accuracy in the diagnosis of reactivation was possible. Indeed, the periodic evaluation at 3-month interval allowed us to detect HBV reactivation in the stage of reverse seroconversion before the occurrence of clinically overt acute HBV hepatitis, that is considered as index event of HBV reactivation in retrospective studies. Interestingly, the presence of anti-HBs did not decrease the risk of HBV reactivation in the setting of allogeneic HSCT since all our patients had initially detectable antibodies to HBsAg.

Conversely, none of the patients undergoing autologous HSCT developed reverse seroconversion, thus confirming that this therapeutic approach entails a lower risk of reactivation at least in patients with anti-HBs positivity. Accordingly, in their retrospective series Ceneli et al reported that only 2/39 (5%) anti-HBc positive patients submitted to autologous HSCT developed HBV reactivation. Eleven of the patients included in that study had multiple myeloma and this disease resulted to be an independent risk factor for HBV reactivation at multivariate analysis [18].

None of our 12 patients submitted to immunosuppressive treatments without HSCT presented a reverse seroconversion throughout the evaluation period even if 9 of them were treated with therapeutic regimens including rituximab. The first retrospective and prospective study on HBV reactivation in malignant lymphoma with occult hepatitis was published by Fukushima et al in 2009 [12]. In the prospective
part of the study they enrolled 24 pts from 2005 to March 2008. HBV reactivation without hepatitis was observed in only one pt (4.1%) who had received intensive chemotherapy including steroid and rituximab. The absence of HBV reactivation in our patients may be related to the high rate of anti-HBs positivity (10/12, 83.3%). Indeed, the partial protective role against reverse seroconversion of anti-HBs in this setting of patients has been demonstrated in large retrospective series. Yeo et al reported on a large series of HBsAg negative/anti-HBc positive pts with diffuse large B cell lymphoma treated with either cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) alone or rituximab plus CHOP (R-CHOP). Acute hepatitis associated to HBV reactivation was observed only in the R-CHOP group (25% of the cases); male sex, absence of anti-HBs and use of rituximab were demonstrated to be predictive of HBV reactivation [11]. More recently, Koo et al found in a series of 62 HBsAg negative/anti-HBc positive pts with lymphoma and treated with rituximab that the overall HBV reactivation hepatitis rate was only 3% and the possible risk factors included advanced age, undetectable anti-HBs and advanced lymphoma at diagnosis. None of the pts tested positive for anti-HBs experienced HBV reactivation [19]. Finally, in a series of 29 patients with B-cell lymphoma treated with rituximab containing regimens, Pei et al showed that anti-HBs was lost in 8/29 cases (27.6%). Interestingly, none of the 10 cases with anti-HBs titers higher than 100 mIU/mL before start of rituximab became negative for anti-HBs; furthermore among the patients with anti-HBs loss, only one experienced HBsAg reappearance in the serum [20].

In conclusion our study shows that allogeneic HSCT is a high risk condition for late HBV reactivation in patients with occult HBV hepatitis and that in these patients universal antiviral prophylaxis could be advisable and prolonged for at least 12
months after transplant. We did not observe HBV reverse seroconversion in patients submitted to autologous HSCT or systemic chemotherapy including rituximab and then we think that in these patients a close monitoring of anti-HBs and HBsAg performed at 1 month interval could be sufficient to prevent overt hepatitis at least in patients who are anti-HBs positive without detectable serum HBV-DNA at baseline. Larger prospective studies are needed to compare risks and benefits of an observational/early intervention approach versus a general prophylaxis. In patients submitted to periodic virological assessment, we propose to immediately start prophylactic treatment with analogues when anti-HBs disappears and/or HBsAg appears regardless of the serum level of HBV-DNA.

**List of abbreviations:** HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen; anti-HBc: hepatitis B core antibody; anti-HBs: hepatitis B surface antibody; ALT: alanine-aminotransferase; HSCT: hematopoietic stem cell transplantation, HCV: hepatitis C virus, HIV: human immunodeficiency virus; HBeAg: hepatitis b e antigen; HBeAb: hepatitis b e antibody.

**Competing interests:** The Authors declare that they have not competing interests.

**Authors’ contribution:** MP, MB and SH designed the study and drafted the manuscript; GB performed the statistical analysis; LN, MDA, SF, AG, LL, CM, LP, GLR, ST collected the data, participated in the study design and helped to draft the manuscript; SS and RL made a critical revision of the manuscript. All the authors read and approved the final manuscript.
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References


surface antigen: clinically significant or purely "occult"?. Hepatology 2001, 34:194-203.


Table 1: Clinical features of the enrolled patients

<table>
<thead>
<tr>
<th>UPN</th>
<th>Gender</th>
<th>Age (yrs)</th>
<th>Anti-HBs</th>
<th>Anti-HBe</th>
<th>Hematological disease</th>
<th>HSCT</th>
<th>Rituximab (No/Yes)</th>
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</tr>
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<td>positive</td>
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<tr>
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<td>negative</td>
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<td>Yes</td>
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<td>negative</td>
<td>NHL mantle cell</td>
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<tr>
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<td>positive</td>
<td>MM</td>
<td>Autologous</td>
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<tr>
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<td>positive</td>
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</table>

Abbreviations: UPN: unique patient number; HSCT: hematopoietic stem cell transplantation; AML: acute myeloid leukaemia; MM: multiple myeloma; MDS (RAEB type 2): myelodysplastic syndrome (refractory anemia with excess of blasts type 2); CLL: chronic lymphocytic leukemia; NHL: non-Hodgkin lymphoma; DLBCL diffuse large B cell lymphoma; HL: Hodgkin lymphoma;
Table 2: Characteristics of patients with reverse seroconversion

<table>
<thead>
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<th>UPN</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
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<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>HBV markers</td>
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<td>anti-HBs positive</td>
<td>anti-HBs positive</td>
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<tr>
<td></td>
<td>anti-HBe positive</td>
<td>anti-HBe positive</td>
<td>anti-HBe negative</td>
</tr>
<tr>
<td>Anti-HBsAg title at baseline</td>
<td>439.5 mIU/mL</td>
<td>34.5 mIU/mL</td>
<td>52.6 mIU/mL</td>
</tr>
<tr>
<td>Time to reverse seroconversion from HSCT</td>
<td>8 months</td>
<td>10 months</td>
<td>9 months</td>
</tr>
<tr>
<td>HBV-DNA peak</td>
<td>$696 \times 10^6$ UI/mL</td>
<td>$2 \times 10^6$ UI/mL</td>
<td>$116 \times 10^6$ UI/mL</td>
</tr>
<tr>
<td>ALT peak</td>
<td>68 UI/L</td>
<td>101 UI/L</td>
<td>52 UI/L</td>
</tr>
<tr>
<td>Antiviral therapy</td>
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<td>entecavir 0.5 mg once daily</td>
<td>entecavir 0.5 mg once daily</td>
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<tr>
<td>Viral outcome</td>
<td>HBV-DNA1,654 IU/mL</td>
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<td>HBV-DNA negative</td>
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</table>

Abbreviations: UPN: unique patient number; HBV: hepatitis B virus; HSCT: hematopoietic stem cell transplantation; Anti-HBs: antibodies to hepatitis B surface antigen; Anti-HBe: antibodies to hepatitis B e antigen; ALT: alanine-aminotransferase