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Hepatitis B Virus Reactivation and Efficacy of Prophylaxis with Lamivudine in Patients Undergoing Allogeneic Stem Cell Transplantation

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Patients previously infected with hepatitis B virus (HBV) undergoing an allograft and recipients from HBV carrier donors are at risk of posttransplant viral reactivation. The role of prophylaxis with lamivudine remains unclear. One hundred seventeen patients, with a median age of *52 years (20-67 years)*, with various hematologic malignancies transplanted between 1999 and 2007 entered the study. Eighty-seven recipients negative for HBV surface antigen (HBsAg), antihepatitis B core antigen antibodies (anti-HBc), and HBV-DNA with HBsAg and HBV-DNA negative donors were defined as at low risk of HBV reactivation, whereas all the remaining 30 patients were defined as at high risk. Patients at high risk transplanted in 2005 or after received lamivudine to prevent HBV reactivation as per the Italian guidelines by the Associazione Italiana per lo Studio del Fegato (AISF). Patients at low risk did not experience HBV reactivation/hepatitis. Among the recipients at high risk, 11 of 25 anti-HBc positive, those HBsAg positive (2 of 2) or negative but transplanted from HBsAg positive donors (3 of 3) were treated with lamivudine. None of these developed HBV reactivation/hepatitis after a median follow-up *of 40 months (17-55 months). H*epatitis developed in 3 anti-HBc positive untreated patients conditioned with a reduced-intensity regimen. Hepatitis B was not observed in recipients at low risk, transplanted from HBsAg negative/anti-HBc positive or negative donors. Lamivudine was effective in controlling reactivation in: HBsAg positive recipients, in patients transplanted from HBsAg positive donors and in HBsAg negative/antiHBc positive recipients, who showed a significant risk of reactivation if not given prophylaxis (NCT 00876148).

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INTRODUCTION

Hepatitis B virus (HBV) reactivation after allogeneic stem cell transplantation (SCT) is a well-known complication not only in HBV surface antigen (HBsAg) carriers, but also in patients with resolved HBV infection [1]. Furthermore, for HBV negative recipients, donors not previously exposed to HBV infection are generally preferred to HBsAg positive or HBV exposed donors [2]. Although poorly characterized, the mechanisms through which the reactivation of latent viral infection occurs is likely to involve a 2-stage process [3]. First, it is widely assumed that in recipients of an allograft previously exposed to HBV, the impaired cellular immunity because of the underlying disease and its treatments can cause viral replication that may lead to fulminant hepatitis. The second stage occurs following the withdrawal of the cytotoxic or immunosuppressive agents and the restoration of the immune function that may result in the T cell immune-mediated destruction of the infected hepatocytes. This phase of immune-reconstitution is usually characterized by clinical hepatitis with transient elevation of alanine aminotransferase (ALT), possible jaundice, and development of constitutional symptoms.

The management of HBV in allogeneic transplantation has changed after the introduction in clinical practice of nucleoside analogs such as lamivudine, capable of inhibiting HBV replication and of reducing viral load. Recently, lamivudine has been administered

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as either prophylaxis or treatment of HBV hepatitis [4-7]. However, its role is still controversial with regard to: (1) prophylaxis in HBsAg negative patients with antibodies against HBV core antigen (anti-HBc), (2) risk of posttransplant hepatitis from HBsAg positive or anti-HBc positive donors, (3) optimal duration of lamivudine prophylaxis, and (4) possible occurrence of drug resistance.

Most published studies on posttransplant HBV reactivation/hepatitis refer to transplants following conventional myeloablative conditioning regimens, whereas reduced-intensity conditioning (RIC)/non-myeloablative (NMA) conditioning regimens have increasingly been used in the past 5-10 years. Therefore, less toxic conditioning regimens are currently more commonly offered to heavily pretreated or older patients with comorbidities. However, the risk of HBV reactivation has not been fully evaluated yet in medically unfit patients [8,9].

Here, we report our experience on HBV reactivation and on the use of lamivudine as prophylaxis in patients considered at risk of HBV reactivation (NCT 00876148).

DESIGN AND METHODS

Patients

One hundred seventeen Caucasian patients who underwent an allograft between 1999 and 2007 at the Bone Marrow Transplant Unit of the University of Torino, Torino, Italy, were included in this retrospective study. Another 6 patients were excluded because HBV serology was not available. Patient characteristics are summarized in Table 1. Eighty-six transplants were from an HLA-identical sibling donor and 31 from an unrelated donor. Three patients received a second allograft from the same donor for disease progression and were included in the study since the first allograft.

As part of the pretransplant workup, all patients and donors were evaluated, within 1 month from transplant, for presence of HBsAg, antibodies against HBsAg (anti-HBs), anti-HBc, hepatitis C virus (anti-HCV); hepatitis B e antigen (HBeAg) and antibodies against HBeAg (anti-HBe), and hepatitis D virus (anti-HDV) in HBsAg positive individuals; serum HBV-DNA (COBAS Amplicor HBV Monitor Test, Roche Diagnostics, Switzerland; threshold level 60 IU/mL up to June 2005; COBAS AmpliPrep/COBAS TaqMan HBV Test, threshold level 12 IU/mL from July 2005 onward) was invariably evaluated at baseline in all patients and donors. Liver function tests (LFT) included ALT (reference values 8-40 UI/L), aspartate aminotransferase (AST) (reference values 8-40 UI/L), gamma-glutamyl transpeptidase (reference values 10-50 UI/L), alkaline phosphatase (reference values 53-128 UI/L), total (reference values 0.2-1.01 mg/dL), and fractionated bilirubin, prothrombin time (International Normalized Ratio), partial thromboplastin time, fibrinogen, D-dimer, and antithrombin. All tests were performed with commercially available kits (AUSRIA II and HBe Kit; Abbott Laboratories, North Chicago, IL; AB AUK 3, Sorin Biomedica, Saluggia, VC, Italy; Ortho Diagnostic System, Milan, Italy). Given the Caucasian origin of all the HBsAg positive donors and recipients included in the study, the absence of pretransplant chronic liver disease and of previous treatments with nucleoside or nucletide analogs, HBV genotype and mutants were not evaluated in accordance with our national guidelines [7,10,11].

The study was approved by the institutional review board of our Institution (NCT 00876148).

Risk Categories and Lamivudine Prophylaxis

The recipients negative for serum HBsAg, anti-HBc, and HBV-DNA who were transplanted from HBsAg and HBV-DNA negative donors (regardless of their anti-HBc status) were defined as "naïve" and considered at low risk of posttransplant HBV reactivation/hepatitis. HBV reactivation has been reported in this group [12,13]; however, in our study, they were defined as naïve given that recipients who lack HBV serum markers are infrequently carriers of an occult HBV infection, which is likely to reactivate [13]. For the same reason, HBsAg and HBV-DNA negative donors are very unlikely to transmit the infection, whereas the rate of HBV transmission from anti-HBc-positive donors of solid organs, different from the liver, is very low [7,14]. Low-risk patients did not receive any HBV prophylaxis throughout the study.

All HBV carriers defined as HBsAg positive and/or anti-HBc positive recipients, or recipients with HBsAg positive donors, regardless of the presence/absence of other HBV serum markers, were regarded as at high risk of HBV reactivation. Overall, 14 anti-HBc positive recipients transplanted in 2004 or before (phase 1) did not receive any prophylaxis (Table 2) whereas, when transplanted in 2005 or later (phase 2), in light of the recommendations by the Associazione Italiana per lo Studio del Fegato (A.I.S.F.) [7], anti-HBc positive recipients were treated with lamivudine. Overall, of the 61 recipients transplanted in phase 2, 16 (2 HBsAg positive recipients, 3 HBsAg negative recipients with HBsAg positive donors and 11 HBsAg negative/anti-HBc positive recipients) received lamivudine prophylaxis.

Lamivudine was given at 100 mg/day from conditioning up to 12-18 months after discontinuation of all immunosuppressive drugs [7,15]. Patients off immunosuppression but on chemotherapy for disease relapse were maintained on lamivudine prophylaxis.

Table 1. Patient characteristics

No. of patients	117
Median age at transplant, years (range)	52 (20-67)
Median follow-up, months (range)	42 (14-111)
Male/Female	55/62
Disease	
Multiple myeloma	61
Acute myelogenous leukemia/RAEB	18
Chronic lymphocytic leukemia	14
Lymphoma	15
Chronic myeloproliferative disease	7
Chronic myelomonocytic leukemia	1
Aplastic anemia	1
Conditioning regimens	
Conventional	
Cyclophosphamide-TBI (1200 cGy)	6
Busulfan-Cyclophosphamide	8
Cyclophosphamide-ATG	1
Reduced intensity	
Thiothepa-Cyclophosphamide	16
Melphalan-Fludarabine-TBI (200 cGy)	5
Busulfan-Melphalan	2
Non-myeloablative	
TBI (200 cGy) ± Fludarabine	75
TLI-ATG	4
GVHD prophylaxis	
Cyclosporine+methotrexate	33
Cyclosporine+mycophenolate mofetil	84
Donor Type	
Related	86
Unrelated	31
Stem cell source	
Peripheral blood / Bone marrow	114 / 3
Patients previously treated with anti-CD20 monoclonal antibody	18

RAEB indicates refractory anemia with excess of blasts; TBI, total body irradiation; ATG, Antithymocyte globulin; TLI, total lymphoid irradiation.

Follow-up

LFT and viral DNA load of patients at high risk were carried out monthly for the first 3 months, and complete HBV serologic tests at 3 and 6 months post-transplant or as clinically indicated. Complete HBV serologic tests were carried out every 6 months in patients at low risk or at the onset of LFT abnormalities.

HBV reactivation in HBV carriers was defined as an HBV-DNA level higher than 20,000 IU/mL and in patients originally HBsAg negative as reemergence of HBsAg (reverse seroconversion) after gradual loss of anti-HBs antibodies [7]. Hepatitis flare was defined as an increase of serum ALT levels higher than 1.5-fold of baseline, with a significant viral breakthrough from baseline (at least 20,000 IU/mL) [13-17]. Moreover, during hepatitis flare, workup for differential diagnoses of posttransplant hepatic complications included serologic tests and polymerase chain reaction (PCR) assays for hepatitis A virus, hepatitis C virus, cytomegalovirus, Epstein-Barr virus, herpes simplex virus types 1 and 2, human herpesvirus 6, parvovirus B19 and adenovirus; serologic tests for aspergillum and toxoplasma; abdominal ultrasound; drug toxicities, iron overload, and signs and symptoms of graft-versus-host disease (GVHD) and sinusoidal obstructive syndrome. Liver biopsy was not performed routinely [18]. Liver GVHD was diagnosed as per standard criteria [19,20] and defined as LFT abnormalities (alkaline phosphatase $\geq 2 \times$ upper limit of normal, AST or ALT $> 3 \times$ upper limit of normal or total serum bilirubin ≥ 1.6 mg/dL) not because of other causes and responsive to immunosuppressive drugs.

Statistical Analysis

Incidence of GVHD between patients exposed or not exposed to HBV and incidence of hepatitis between patients treated with lamivudine or not treated were compared by the Fisher's Exact Test. Clinical outcomes were calculated with the method of Kaplan-Meier and analyzed with the "log rank" test. Statistical analyses were obtained with the SPSS software (SPSS Inc. and Microsoft Corporation, Chicago, IL). A P value $<.05$ was considered statistically significant.

RESULTS

Survival

Overall, after a median follow-up of 42 (range: 14-111) months, 54 (46%) of the patients were alive, whereas 31 (26%) died from disease progression, 27 (23%) from transplant-related toxicity, 2 (2%) from a second malignancy, 1 (1%) of acute myocardial infarction. Median time to death was 9 months (range: 1-96). No HBV-related death was observed.

Liver GVHD and HBV

Among the 23 patients who developed grade II-III acute liver GVHD (aGVHD), 1 had received the graft from an HBsAg-positive donor, 1 was an HBsAg positive patient, and 5 were anti-HBc positive. The remaining 16 had no serologic evidence of prior HBV exposure. Liver GVHD incidence was not influenced by pretransplant HBV exposure ($P=.6$).

Lamivudine Prophylaxis, HBV Reactivation, and Outcome

Eighty-seven patients at low risk of HBV reactivation were not given lamivudine prophylaxis and did not develop hepatitis B. Of note, none of the 5 naïve patients of this group who received a transplant from anti-HBc positive donors experienced hepatitis, and only 1 of the 5 became anti-HBc positive during follow-up.

Among the 30 patients at high risk of HBV reactivation (25 HBsAg negative/anti-HBc positive; 3 HBsAg negative from HBsAg positive donors; 2 HBsAg positive recipients), lamivudine prophylaxis was given to the 16 who were transplanted in 2005 or later, for a median duration of 19 months (range: 8–42). The other 14 HBsAg negative/anti-HBc positive

Table 2. Virological characteristics and clinical outcome of high risk recipients

	Prophylaxis	No prophylaxis
No. of patients	16	14
Sex (Male/Female)	7/9	8/6
Age, years (range)	56 (29-64)	52 (40-63)
Diseases	MM 6 / CLL 4 AML-RAEB 3 NHL 1 / CML 1 CMML 1	MM 10 AML-RAEB 3 CLL 1
Myeloablative conditioning	1	0
GVHD prophylaxis		
CsA-MMF	9	14
CsA-MTX	7	0
Pre-transplant HBV serology	No. of Patients	No. of Patients
HBsAg +	2	0
Anti-HBc +	15	14
Anti-HBs +	10	7
HBV DNA (IU/mL) +	1 (19.500)	0
Post-transplant HBV serology		
HBsAg +	1§	2
Anti-HBc +	12	12
HBV-DNA (IU/mL) +	1§ (1.400.000)	2 (>10^8; 71.700)
HBV hepatitis	1§	2
Median follow-up (range)	40 months (17-55)	85 months (59-111)
Alive	8	2
Donor HBV serology		
HBsAg +	3	0
Anti-HBc +	7	3
Anti-HBs +	5	3
HBV-DNA (IU/mL) +	2 (121; 762)	0
HBV prophylaxis	0	0

MM indicates multiple myeloma; CLL, chronic lymphocytic leukemia; AML-RAEB, acute myelogenous leukemia-refractory anemia with excess of blasts; NHL, non Hodgkin lymphoma; CML, chronic myelogenous leukemia; CMML, chronic myelomonocytic leukemia; GVHD, graft-versus-host disease; CSA, cyclosporine; MMF, mycophenolate mophetil; MTX, methotrexate; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; Anti-HBc, anti-hepatitis B core antibodies; Anti-HBs, anti-hepatitis B surface antigen antibodies.
§developed after early lamivudine discontinuation.

patients transplanted in or before 2004 did not receive any prophylaxis.

Lamivudine was well tolerated in all but 1, who discontinued the drug because of severe nausea. Among these 16 patients, 3 died from disease progression during treatment. According to the scheduled prophylaxis [7] and at the time of this analysis, lamivudine has been stopped 12-18 months after the discontinuation of all immunosuppressive drugs in 4 patients, and, following the withdrawal, none of them experienced HBV reactivation after a median time of 12 months (range: 1-19).

Three patients with HBsAg positive donors (HBeAg, anti-HBe, and anti-HDV negative), of whom 2 were also positive for HBV-DNA, were given lamivudine and none developed HBV reactivation or hepatitis (Table 3). During follow-up, all remained HBsAg and anti-HBs negative, with undetectable HBV-DNA, and only 1 became anti-HBc positive. The 2 HBV-DNA-positive donors were treated for 1 month prior to transplant with lamivudine at 100 mg/day and became negative at the time of granulocyte colony stimulating factor (G-CSF) mobilized peripheral blood stem cell (PBSC) collection. One recipient developed liver aGVHD 24 months after transplant and was still on immunosuppression and lamivudine prophylaxis at the time of last contact; another discontinued all immunosuppressive drugs 13 months after transplant and stopped lamivudine 13 months later without any signs of HBV reactivation; finally, the third recipient stopped immunosuppressive therapy 8 months posttransplant because of leukemic progression, and died from the disease 18 months posttransplant while on lamivudine.

The 2 HBsAg positive recipients (HBeAg, anti-HBe, and anti-HDV negative) became HBsAg negative 13 and 3 months posttransplant, respectively, while on lamivudine (Table 3). One patient developed mild liver GVHD 4 months posttransplant; nevertheless, discontinued all immunosuppression 6 months posttransplant and lamivudine 15 months later, without evidence of HBsAg reverse seroconversion, whereas the other was still on prophylaxis at the time of last contact.

Overall, 3 of 117 patients developed HBV hepatitis at 4, 15, and 29 months posttransplant, diagnosed in the light of ALT levels and serology. All 3 patients were anti-HBc positive and HBsAg negative before transplant; their donors were HBsAg negative and only 1 anti-HBc positive (Table 4). Two patients were not given prophylaxis because transplanted before 2005 and 1 discontinued it prematurely because of intolerance. The latter was HBsAg negative, anti-HBc and anti-HBs positive, underwent 2

Table 3. Virological characteristics and clinical outcome of HBsAg positive/negative pairs

	HBsAg negative recipients / positive donors			HBsAg positive recipients / negative donors	
	Recipient 1	Recipient 2	Recipient 3	Recipient 4	Recipient 5
Sex	Male	Female	Female	Male	Female
Age (years)	54	61	28	38	58
Disease	MM	AML	CML	MM	MM
Myeloablative conditioning	No	No	Yes	No	No
GVHD prophylaxis					
CsA-MMF	+	–	–	+	+
CsA-MTX	–	+	+	–	–
Pre-transplant recipient HBV serology					
HBsAg	–	–	–	+	+
Anti-HBc	–	+	+	+	+
Anti-HBs	+	+	+	–	–
HBV-DNA (IU/mL)	–	–	–	–	19.500
HBV prophylaxis	Yes	Yes	Yes	Yes	Yes
Post-transplant recipient HBV serology					
HBsAg	–	–	–	–	–
Anti-HBc	+	+	+	+	+
Anti-HBs	+	+	+	+	+
HBV-DNA (IU/mL)	–	–	–	–	–
HBV hepatitis	No	No	No	No	No
Follow-up (months)	43	18	40	26	35
Outcome	Alive	Dead °	Alive	Alive	Alive
Donor HBV serology					
HBsAg	+	+	+	–	–
Anti-HBc	+	+	+	–	+
Anti-HBs	–	–	–	+	+
HBV-DNA (IU/mL)	–	121	762	–	–
Donor HBV prophylaxis	No	Yes	Yes	No	No

HBsAg indicates hepatitis B surface antigen; MM, multiple myeloma; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; GVHD, graft-versus-host disease; CsA, cyclosporine; MMF, mycophenolate mophetil; MTX, methotrexate; HBV, hepatitis B virus; Anti-HBc, anti-hepatitis B core antibodies; Anti-HBs, anti-hepatitis B surface antigen antibodies.

° due to disease progression.

allogeneic transplants from an anti-HBc and anti-HBs positive donor for disease progression and was treated with anti-CD20 monoclonal antibodies in between. Lamivudine was given for 8 months from the time of the first transplant up to 1 month postsecond transplant. HBV reactivation (HBsAg positive, ALT 1205 IU/L, HBV DNA 1,400,000 IU/mL) occurred 7 months after lamivudine had been discontinued. However, the drug was well tolerated when used for treating HBV hepatitis.

Hepatitis was successfully treated in all with lamivudine at 100 mg/day though adefovir was added in 1 patient 16 months later because of biochemical and virologic breakthrough (ALT 87 U/L, HBV DNA 298,000 UI/mL) [11]. One patient died from disease progression during maintenance treatment.

Overall, between patients given and not given lamivudine, there was no difference in overall survival (OS).

DISCUSSION

HBV reactivation represents a well-known problem in hematologic malignancies. It is reported that HBsAg positive patients with lymphoma, in particular, are at higher risk of HBV reactivation after chemotherapy [7,21,22]. In Italy, the prevalence of HBsAg among these patients was reported as higher than 8% [22], more than 7-fold the actual rate in the general population (~1%) [23]. A high prevalence of HBsAg negative/anti-HBc positive status among patients with non-Hodgkin lympohoma was also described (41.5%) [22]. Furthermore, the increasing use of intense myelosuppressive therapies, including transplants and monoclonal antibodies [8,24,25], combined with a profound immunodeficiency related to the underlying disease [26-28], confer additional risks. Despite the fact that HBV reactivation has been increasingly observed after allogeneic transplantation, with an incidence of 50% or more for susceptible individuals [29,30], very few data have been published regarding the impact of RIC/NMA conditioning regimens [8,9] and the role of prophylaxis with lamivudine in HBsAg negative but anti-HBc positive patients [31].

Our retrospective analysis on 117 patients transplanted before and after the clinical introduction of lamivudine showed interesting results as to the risk of hepatitis B in "naïve" and anti-HBc positive recipients, the risk of transmission from anti-HBc positive donors, and the efficacy of lamivudine in HBsAg positive or anti-HBc positive recipients, and in recipients with HBsAg positive donors.

Table 4. Virological characteristics and clinical outcome of Anti-HBc positive recipients (25 patients)

	Prophylaxis (n=11)		NO Prophylaxis (n=14)	
	Donor Anti-HBc POS (n=3)	Donor Anti-HBc NEG (n=8)	Donor Anti-HBc POS (n=3)	Donor Anti-HBc NEG (n=11)
Sex (M/F)	2 / 1	3 / 5	3 / 0	5 / 6
Median age (years)	56 (55 - 58)	56 (53 - 64)	56 (46 - 59)	55 (40 - 63)
Disease	MM 1 / AML 1 CLL 1	CLL 3 / MM 2 AML 1 NHL 1 / CML 1	MM 3	MM 7 / AML 3 CLL 1
Myeloablative conditioning	1	0	0	0
GVHD prophylaxes				
CsA-MMF	1	5	3	11
CsA-MTX	2	3	0	0
Recipient pre-transplant HBV serology				
HBsAg +	0	0	0	0
Anti-HBc +	3	8	3	11
Anti-HBs +	1	6	1	7
HBV-DNA (IU/mL) +	0	0	0	0
Recipient post-transplant HBV serology				
HBsAg +	1	0	0	2
Anti-HBc +	3	4 (2 NA)	1 (1 NA)	9
HBV-DNA (IU/mL) +	1 (1.400.000)	0	0	2 (>10^8; 71.700)
HBV hepatitis	1§	No	No	2
Median follow-up (range)	47 months (41 - 54)	40 months (17 - 54)	111* months	59* months
Outcome				
Alive	2	7	1	1
DRM / TRM	1 / 0	0 / 1	2 / 0	3 / 4
Other death causes	0	0	0	3
Donor HBV serology				
HBsAg +	0	0	0	0
Anti-HBc +	3	0	3	0
Anti-HBs +	2	1	3	0
HBV-DNA (IU/mL) +	0	0	0	0
Donor HBV prophylaxis	No	No	No	No

Anti-HBc indicates anti-hepatitis B core antibodies; MM, multiple myeloma; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; NHL, non Hodgkin lymphoma; GVHD, graft-versus-host disease; CsA, cyclosporine; MMF, mycophenolate mophetil; MTX, methotrexate; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; Anti-HBs, anti-hepatitis B surface antigen antibodies; NA, not available; DRM, disease related mortality; TRM, treatment related mortality.
§Developed after early lamivudine discontinuation.
*Only one patient evaluable.

Raimondo et al. [30] described occult HBV infections in anti-HBc positive patients and, though infrequent, in HBV serum marker-negative individuals in the Italian general population. In hematologic patients, it is unknown whether the complete absence of HBV serum markers in recipients could be ascribed to a gradual and progressive disappearance of antibodies, because of the disease-related immunosuppression, to a real naïve condition for all viral markers susceptible of a new infection posttransplant or to an occult HBV infection [32].

In the setting of liver transplantation, a posttransplant risk of hepatitis B has been shown in naïve recipients with anti-HBc positive donors, whereas reports in allogeneic SCT are scarce [7]. In our experience, naïve patients did not receive prophylactic lamivudine and did not develop hepatitis B during follow-up, indicating no risk of clinical reactivation. Moreover, no hepatitis B was observed in the 5 naïve recipients with anti-HBc positive donors. However, we observed that 1 HBV serum marker-negative patient with an anti-HBc positive donor developed anti-HBc antibodies after transplant without evidence of HBV reactivation. The appearance of HBV markers in originally naïve patients has already been described after solid organ transplantation, sometimes with a short detectable HBV viremia without clinical evidence of hepatitis [33,34]. Thus, in our patient, it is not possible to determine if the appearance of anti-HBc antibodies followed a pretransplant occult infection [13] or this immunity was transferred from the donor.

In a multicenter study on 2586 transplant patients not given prophylactic lamivudine, only 24 (0.9%) donors were HBsAg positive; however, 22% of the originally pretransplant HBsAg negative recipients with HBV carrier donors seroconverted after transplant [2]. In our experience, lamivudine was administered to 3 recipients who received the graft from HBsAg positive donors and to 2 donors with detectable HBV-DNA. The lack of viral reactivation suggests the efficacy of lamivudine in abating donor pretransplant viral load and in preventing posttransplant HBV reactivation in the recipients. Similarly, Hui et al. [35] retrospectively compared 29 recipients treated with booster doses of HBV vaccine and lamivudine to 25 historic controls who received no prophylaxis. The study demonstrated

the efficacy of anti-HBV prophylaxis, however, without being able to differentiate the role of HBV vaccination from that of lamivudine.

The efficacy of lamivudine in HBsAg positive recipients undergoing an allograft has been supported in 3 recent meta-analyses [5,6,36], which showed a statistically significant difference in the incidence of HBV reactivation and mortality between patients treated with lamivudine and the control group. In our study, lamivudine was given to 2 patients with detectable HBsAg. Interestingly, both patients received the graft from anti-HBs positive donors and became HBsAg negative with no signs of HBV reactivation.

In occult HBV carriers with isolated anti-HBc antibodies, viral replication has been shown to persist in the liver and in peripheral blood mononuclear cells [37,38]. In the setting of allografting, immunosuppression and loss of the patient B and T cell repertoires may lead to viral reactivation, with the reappearance of HBsAg after gradual loss of anti-HBs, defined as reverse seroconversion. Its incidence has been described to be up to 50% [1,39,40]. More recently, HBV reactivation in occult carriers has been reported also in a patient receiving an autograft followed by bortezomib, and in 5 of 17 allotransplant patients positive for anti-HBc, but not in 38 negative prior to transplant [31]. Furthermore, the availability of new, potent immunosuppressive drugs like the anti-CD20 and the anti-CD52 monoclonal antibodies, recently introduced in treatment plans, has further increased the risk of HBV reactivation in patients with hematologic malignancies [8,24,25,37,41]. Nevertheless, there are still some controversies about the use of prophylaxis in this setting. In our report, among 25 patients with anti-HBc antibodies, reverse seroconversion and hepatitis B were not observed in patients treated with lamivudine, whereas hepatitis B developed in 3 of the untreated patients (including 1 patient who prematurely discontinued the drug because of intolerance). These results are suggestive of a protective role of lamivudine in this setting. Indeed, our findings should be confirmed on a larger series of patients. Interestingly, all reverse seroconversions and hepatitis B occurred in patients prepared for transplant with an RIC or an NMA conditioning. This observation indicates that a less myelosuppressive conditioning regimen does not confer protection against HBV reactivation. This may be explained by a number of reasons such as patient older age and heavy pretreatments, the use of highly immunosuppressive agents (ie, fludarabine) in the conditioning regimen and the prolonged posttransplant immunosuppression. In a similar setting, the efficacy of HBV vaccine 1 year after the discontinuation of the posttransplant immunosuppression has also been reported. However, about half of the patients evaluated were not eligible for vaccination, and the incidence of reverse seroconversion in vaccinated patients was similar to that of the historic control [42].

Given that among the 16 patients receiving lamivudine prophylaxis for a median of 19 months none developed reverse seroconversion or hepatitis, we assume that the efficacy of lamivudine was maintained during the entire follow-up. When lamivudine prophylaxis was started, HBV-DNA was undetectable in all but 1 patient. Interestingly, Hsiao and colleagues [43] evaluated the impact of lamivudine resistance in 16 patients with detectable HBV-DNA at the time of autologous or allogeneic transplantation. Despite the extensive use of lamivudine and the emergence of mutations in 63% of the patients, no deaths were related to HBV reactivation or severe HBV hepatitis. With the new potent antiviral drugs [44], lamivudine may be preferable for prophylaxis, where resistance may be a rare event, rather than for treatment of HBV hepatitis.

Optimal duration of lamivudine prophylaxis remains to be determined. In our setting, we considered lamivudine discontinuation only in patients at least 12-18 months after all immunosuppression was stopped and with no signs of HBV reactivation. The need of prolonged treatment even in patients off immunosuppressive drugs may have been confirmed by our observation of an HBV reactivation 18 months after the discontinuation of immunosuppression. Overall, in 5 patients who had discontinued prophylaxis at the time of our analysis, hepatitis had occurred only in the 1 who had developed intolerance to lamivudine and prematurely interrupted prophylaxis.

Finally, we did not observe a correlation between previous exposure to HBV and development of liver GVHD.

In conclusion, viral reactivation or hepatitis B after allogeneic SCT were not observed in HBV naïve recipients, transplanted from HBsAg negative/anti-HBc positive or negative donors. Lamivudine was effective in controlling reactivation in: HBsAg positive recipients, in patients transplanted from HBsAg positive donors and in HBsAg negative/antiHBc positive recipients. Furthermore, our findings indicate a significant risk in HBsAg negative/anti-HBc positive recipients in the absence of prolonged prophylaxis.

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