Research Article

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Role of lower dose hepatitis B immune globulin prophylaxis in liver transplantation: A single center perspective

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Abstract

Background and Aim: Prevention of hepatitis B virus (HBV) reinfection is important for long-term outcomes following liver transplantation (LT). Hepatitis B immunoglobulin (HBIG) is used among recipients who have (i) native HBV disease, (ii) hepatitis B core antibody positivity (HBcAb positivity), or (iii) received HBcAb positive organs. Nucleos(t)ide analogue (NA) monotherapy is emerging for treating patients in this setting. There is no generalized consensus on the ideal dosage of HBIG. The aim of this study was to evaluate the efficacy of low-dose HBIG (1560 international unit [IU]) for post-LT HBV prevention.

Materials and Methods: HBcAb positive patients who received either HBcAb positive or hepatitis B core antibody negative (HBcAb negative) organs and HBcAb negative patients who received HBcAb positive organs between January 2016 and December 2020 were reviewed. Pre-LT HBV serologies were collected. HBV-prophylaxis strategy included NA with/without HBIG. HBV recurrence was defined as HBV deoxyribonucleic acid (DNA) positivity during the 1-year, post-LT follow-up. No HBV surface antibody titers were followed.

Results: A total of 103 patients with a median age of 60 years participated in the study. Hepatitis C virus was the most common etiology. Thirty-seven HBcAb negative recipients and 11 HBcAb positive recipients with undetectable HBV DNA received HBcAb positive organs and underwent prophylaxis with 4 doses of low-dose HBIG and NA. None of the recipients in our cohort had a recurrence of HBV at 1 year.

Conclusion: Low-dose HBIG (1560 IU) × 4 days and NA, for HBcAb positive recipients and HBcAb positive donors, appear to be effective in preventing HBV reinfection during the post-LT period. Further trials are needed to confirm this observation.

Keywords: HBV; HBIG; liver transplantation.

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Introduction

Chronic hepatitis B virus (HBV) infection affects 240 million people worldwide with variable prevalence in different parts of the world. Asia-Pacific, Eastern Europe, Africa, and the Middle East account for the majority of chronic HBV infections globally. Managing serious sequelae of HBV infection such as end-stage liver disease (ESLD), hepatic decompensation, and hepatocellular carcinoma (HCC) remains challenging and represents a significant public health burden.[1] Furthermore, large regional variations, changing socioeconomic landscapes, and population immigration have led to a rapidly changing epidemiology, suggesting the need for evolving guidelines in HBV management.[2]

HBV ESLD accounts for a large proportion of liver transplantation (LT). Prevention of HBV reinfection is an important long-term outcome in LT recipients who are chronically immunosuppressed. Altered host innate and adaptive immune microenvironment can lead to unopposed viral replication.[3] HBV recurrence after LT is characterized by hepatitis B surface antigen (HBsAg) positivity and/or detectable levels of HBV deoxyribonucleic acid (DNA), occasionally resulting in HBV flares.[4] Before the development of antivirals and hepatitis B immunoglobulin (HBIG), HBV was a relative contraindication for LT due to high rates of graft loss and poor survival rate of less than 40% at 5 years.[5,6] Those who received allografts from hepatitis B core antibody positive (HBcAb positive) donors had reinfection rates approaching 75%.[7] However, the use of HBIG has revolutionized HBV LT by decreasing HBV recurrence by 70%.[8,9] HBIG works by binding to the circulating virions and reducing HBsAg secretion during the anhepatic phase and the first postoperative week to prevent graft infection. Historically, high dose HBIG (i.e., 10 000 international unit [IU]/day) was thought to be associated with lower HBV recurrence.[7] However, HBIG is expensive ($30 000–$50 000 per year for the first week and monthly after), requires parenteral administration, is in limited supply, and requires frequent monitoring and long-term treatment, given the potential of HBsAg escape mutants.[10,11] HBIG infusion is also associated with several intolerable side effects such as headache, flushing, myalgias, lactic acidosis, and even anaphylaxis. Currently, there is no consensus on the duration, dosage, and route of HBIG use, which varies greatly according to local clinical practice.

In recent years, studies have combined nucleos(t)ide analogues (NAs) such as lamivudine and adefovir dipivoxil with HBIG to prevent post-LT HBV recurrence.[12–15] Lamivudine and adefovir dipivoxil are not used in more recent protocols due to their weak potencies with a high rate of viral resistance.[13,14] More potent NAs such as entecavir and tenofovir disoproxil fumarate in combination with high-dose HBIG have been shown to be superior to HBIG monotherapy in preventing post-LT HBV recurrence.[14]

Newer studies have suggested that monotherapy with NA might be just as effective as combination therapy of HBIG and NA. A study on HBcAb positive donors found only a marginal net benefit in the group that received lamivudine than the HBIG plus lamivudine group in terms of HBV reactivation, liver-associated deaths, and cancer-associated deaths.[16] Additionally, with newer and more potent NA such as entecavir, a study of 80 patients who received a LT with chronic HBV infection found 91% of patients lost HBsAg and 98.8% achieved undetectable levels of HBV DNA.[17] More recent studies have also found that treatment with two different NAs may be as effective as HBIG initiation followed by long-term NA use.[18]

Given the many challenges involved in HBIG administration and recent insights into the possibility of dose reduction or even HBIG-free regimen, we sought to examine the efficacy of combination low-dose HBIG and NA among recipients (i) with chronic HBV or (ii) received HBcAb positive organs regardless of recipient status, and (iii) monotherapy NA in recipients with HBcAb positivity who received HBcAb negative organs, in preventing HBV recurrence posttransplantation.

Materials and Methods

Institutional Review Board (IRB) approval was obtained (IRB00290064). Electronic medical records of adults (>18 years old) who underwent cadaveric LT at Johns Hopkins Hospital (Baltimore, MD, USA) between January 2016 and December 2020 were retrospectively reviewed. Clinical and demographic data, including HBV serologies at the time of LT, were collected. HBV prophylaxis regimen was stratified depending on donor and recipient serologies. Recipients who had chronic HBV or matched to HBcAb positive organs regardless of recipient status received combination therapy consisting of 4 doses of HBIG 1560 IU intravenously daily (with the first dose given intraoperatively during the anhepatic phase) plus NA (entecavir or tenofovir), which was started postoperatively and continued indefinitely. Recipients who were HBcAb positive and received HBcAb negative organs received monotherapy with NA (entecavir or tenofovir) indefinitely. No hepatitis B surface antibody titers were followed. HBV recurrence was monitored at 1 year by measuring HBV DNA viral load levels.

Results

Our cohort included 103 patients who received LT during the study period with a follow-up period of at least 1 year (Table 1). The median age at LT was 60 years (interquartile range, 9.25 years), and 77 recipients (75%) were males. The most common etiology for transplant was hepatitis C virus infection (50%), followed by alcohol (16%), hepatitis B (11%), and nonalcoholic steatohepatitis (10%). Forty patients of the study group had concomitant HCC, and 14 recipients underwent simultaneous liver kidney (SLK) transplants (Table 1).

Of the patients, 48 received HBcAb positive organs and received combination therapy of HBIG and NA (37 HBcAb negative recipients and 11 HBcAb positive recipients with undetectable HBV DNA levels) (Table 2). There were 2 HBcAb positive recipients with low-level HBV viremia who received HBcAb negative organs and received HBIG plus NA. None of these recipients had HBV reoccurrence at 1-year posttransplantation. Additionally, 53 HBcAb positive recipients who received HBcAb negative organs received monotherapy with NA and had no reoccurrence of HBV at 1-year posttransplantation (Table 2).

Table 1. Baseline characteristics of the cohort

Cohort characteristics	Cohort (n=103)	
	n	%
Gender		
Male	77	75
Female	26	25
Race		
Caucasian	65	63
African American	21	20
Asian	4	4
Hispanic	5	5
American Indian	1	1
Declined	2	2
Unknown	5	5
Additional characteristics		
Age, median (IQR)	60 (9.25)	
Presence of HCC	40	39
Simultaneous liver kidney recipient	14	14
Liver transplant indications		
Hepatitis C	52	50
Alcohol related	16	16
Hepatitis B	11	11
Nonalcoholic steatohepatitis	10	10
Autoimmune hepatitis	4	4
Primary biliary cholangitis	2	2
Polycystic kidney disease	2	2
Acute liver failure	2	2
Other causes*	4	4

IQR: InterQuartile range; *: Other causes include hepatitis C/alcohol related (1), nonalcoholic steatohepatitis/alcohol related (1), primary biliary cholangitis (1), cystic fibrosis (1), and alpha 1 antitrypsin 1 (1).

Discussion

Chronic HBV infection remains one the leading causes of ESLD and HCC, for which LT is considered the treatment. LT recipients with chronic HBV infection or prior exposure are at increased of reinfection, graft failure, and subsequent reduced survival rate. There is no generalized consensus on the ideal perioperative prophylactic regimen. Most transplant centers endorse the use of HBIG and NA combination therapy as the standard protocol. Our findings suggested low dose HBIG (1560 IU) for 4 days and NA for HBcAb positive recipients with HBcAb positive donors appear to be effective in preventing HBV re-infection. Furthermore, NA monotherapy in patients without chronic HBV receiving HBcAb positive donors compared with combination therapy involving both high-dose and low-dose HBIG has been shown to be similarly effective,[19,20] which our current study also shows. The primary outcome of the current study is HBV recurrence as measured by HBV DNA whereas that of previous studies was survival rate.

HBV recurrence after LT is characterized by the presence of circulating HBsAg with or without detectable HBV DNA, and persistent elevation of viral load can put patients at higher risk for clinical disease and graft loss. HBV recurrence is due to the fact that most of the patients with

Table 2. HBV reinfection prophylaxis strategy

Recipient HBcAb status	Recipient HBV DNA level	Donor HBcAb status	Prophylaxis treatment	Patients (n)	HBV recurrence (n)
HBcAb negative	–	HBcAb positive	HBIG 1560 IU × 4 doses plus NA	37	0
HBcAb positive	Undetectable	HBcAb positive	HBIG 1560 IU × 4 doses plus NA	11	0
HBcAb positive	Low level*	HBcAb negative	HBIG 1560 IU × 4 doses plus NA	2	0
HBcAb positive	Undetectable	HBcAb negative	NA alone	53	0

*: Low level defined as serum HBV DNA <1000 IU/mL.

isolated HBcAb positivity have HBV cccDNA and a minuscule HBV DNA in the hepatocyte nucleus. Factors such as HCC or chemotherapy can increase the risk of HBV recurrence due to immunosuppressed status. HBV virions can originate from the graft or extrahepatic sources such as peripheral blood mononuclear cells or both.[21]

A systematic review of 46 studies demonstrated that second-generation NAs were more efficacious when combined with HBIG compared with first-generation NA, which has led to changing practices around the world, including our own institution, to include more potent NA class.[12] Furthermore, there was no significant difference in HBV DNA detectability in HBIG-free prophylaxis with more potent NAs compared with that of the combination HBIG and lamivudine; however, more patients on NA monotherapy had HBsAg positivity.[14] Regarding the effect of HBsAg seropositivity on graft and patient survival, recent studies by Fung et al.[22] revealed that HBsAg seropositivity did not result in HBV-related graft hepatitis and that long-term outcomes of HBIG-free NA monoprophylaxis resulted in durable HBsAg seroclearance rate with undetectable HBV DNA. There were no cases of graft loss or death caused by HBV recurrence.[23] Therefore, it has also been postulated that NA monotherapy or two different NA combination therapy are as efficacious as those including HBIG.[17]

More specifically, at Johns Hopkins Hospital, the recent guidelines adapted to prevent HBV reactivation call for HBIG 1560 IU IV administration intraoperatively during the anhepatic phase plus 3 more daily doses (total of 4 doses) and antiviral continued indefinitely starting day 0, for HBcAb positive recipients with a history of HBV DNA positivity or HBsAg positivity (at any time). Among HBcAb positive and HBV DNA negative patients who are receiving HBcAb negative donor grafts, no prophylaxis is necessary as the source of HBV was removed with the explanted liver and the risk of reactivation is negligible. HBsAg negative recipients of HBcAb positive donor organs will need an oral antiviral started on postoperative day 0 and continued indefinitely. Preferred antivirals include entecavir and tenofovir disoproxil fumarate/tenofovir alafenamide, with adjustments required for impaired renal function. Following the transplant, routine monitoring of hepatitis B serologies is recommended within the first week to 10 days posttransplant. This is consistent with current guidelines by the American Association for the Study of Liver Diseases 2018 Hepatitis B Guidance, which states that NA monotherapy with or without 5–7-day HBIG course is reasonable in low-risk patients and combination therapy is recommended for those at high risk,[24] perhaps due to demographic similarities and access to healthcare, the Northern American guidelines and similar to those of the European Association for the Study of the Liver. HBIG and potent NA combination is recommended, and patients with a low risk of recurrence can discontinue HBIG but need continued monoprophylaxis with a potent NA. HBsAg negative patients receiving HBcAb positive livers are at risk of HBV recurrence and should receive antiviral prophylaxis with a NA.[25] The Spanish Society of Liver Transplantation recommends a low-dose HBIG prophylactic regimen in the anhepatic phase (1000–5000 IU/IV) and first week (1000–2000 IU/IV or IM/day) post-LT, followed by weekly or on-demand HBIG dosing schedule to maintain HBsAb titers of >200 IU for the first month and >100 IU thereafter.[26] The European Liver and Intestine Transplantation Association further discusses the possibility of third-generation NA monotherapy or short-term (4 weeks) HBIG and third-generation NA combination therapy in low-risk patients and that HBIG can be discontinued in high-risk patients once HBV DNA becomes undetectable.[9] Recent Australian guidelines suggested there was no role for HBIG and recommended lifelong use of high potency NAs among recipients of an HBcAb positive graft.[16]

Per recent protocols suggested by Sarin et al.,[27] for the Asia Pacific region particularly, NA should be used before transplantation to achieve undetectable HBV DNA levels to reduce the risk of HBV recurrence. Lifelong prophylactic monotherapy therapy with high potency NAs should be used for low-risk patients (i.e., with undetectable HBV DNA levels at the time of transplant), while high-risk patients (detectable HBV DNA levels at LT, presence of drug-resistant HBV, Human immunodeficiency virus, or hepatitis D virus coinfection, and HCC at LT or poor compliance to antiviral therapy) should receive high dose IV HBIG during the anhepatic phase, followed by a 1-year HBIG taper course along with lifelong high potency NAs.[27] However, the current recommendations by the Turkish Association for the Study of the Liver, Acute Liver Failure and Liver Transplantation Special Interest Group suggest 5000 IU of HBIG should be administered intravenously to low-risk patients and 10 000 IU should be administered to high-risk patients while NA monoprophylaxis without HBIG administration is not recommended in the early periods following LT.[6]

Among HBIG-free protocol, lamivudine monotherapy is associated with the emergence of escape mutation, while lamivudine/adefovir combination had no HBV recurrence at 22-month follow-up.[28] With the advent of more potent antivirals with lower resistance, more patients have undetectable HBV DNA prior to LT, thereby decreasing posttransplant reinfection rates. Similar arguments can be made to explain the variability in prophylactic recommendations in different parts of the world. In North America, Europe, and Australia, there may be a larger percentage of patients with undetected HBV DNA before transplant, whereas in Eastern Europe and Asia, chronic HBV-infected patients might present with ESLD without a history of treatment, and therefore high-dose HBIG and/or HBIG combination therapy is recommended.

This study has several limitations, given the fact that we present preliminary descriptive data. We will further share our experience after a longer follow-up has been established. First, our study is limited to transplant data from a single center with limited data, as well as other comorbidities. Second, we included a short follow-up period status

posttransplantation. Third, we did not explore the efficacy of the intervention on graft survival or overall mortality. Nevertheless, the study suggests a promising role of antiviral monotherapy with low-dose HBIG to prevent HBV recurrence for LT.

Conclusion

Our HBV prophylaxis strategy with low dose HBIG (1560 units) 4 days plus NA for (i) HBcAb positive patients (with or without detectable HBV DNA) receiving HBcAb positive grafts and (ii) HBcAb negative patients receiving HBcAb positive grafts appear to be effective in preventing HBV reinfection. This lower HBIG dose can potentially control the cost of LT. Further multicenter studies using lower-dose HBIG and NA monotherapy should be considered.

Ethics Committee Approval: The Johns Hopkins University Clinical Research Ethics Committee granted approval for this study (date: 06.07.2021, number: IRB00290064).

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