Review Article

Hepatitis B and liver transplantation

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Abstract: Chronic Hepatitis B (CHB) infection remains a common cause for liver cirrhosis and hepatocellular carcinoma. Orthotopic liver transplantation (OLT) has been a treatment modality for CHB patients with decompensated cirrhosis and or hepatocellular carcinoma. Previously early outcomes of transplantation for CHB patients were associated with rapid recurrence of the virus and loss of the allograft. Development of hepatitis B immunoglobulin (HBIG) and its use in prophylaxis of CHB patients after liver transplantation resulted in significant improvement in patient and allograft survival. Continued use of HBIG mono-therapy however has been complicated by development of viral resistance. With the development of nucleos(t)ide (NA) inhibitors for treatment of CHB, liver transplant outcomes continued to improve. One of the most important risk factors for viral recurrence in post liver transplant setting is the HBV DNA level. Use of NAs prior to liver transplantation to reduce the viral load has been an important way to prevent recurrence of CHB in post liver transplant patients. Addition of NAs to HBIG was the standard of therapy for liver transplant patients for many years and reduced the development of viral resistance. Long-term use of HBIG however is expensive and inconvenient for patients. Development of more potent NAs, with low viral resistance, has allowed for reduction and in some cases elimination of use of HBIG in post liver transplant prophylaxis of patients with CHB.

Keywords: Chronic hepatitis B (CHB); orthotopic liver transplantation (OLT); nucleos(t)ide inhibitors; hepatitis B immunoglobulin (HBIG)

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Introduction

An estimated 250 million people worldwide live with chronic hepatitis B infection (CHB) (1). Despite increasing vaccination rates and advances in treatment, nearly 887,000 deaths each year are attributed to CHB, mostly from complications of liver cirrhosis and hepatocellular carcinoma (1). Since mid-1980's orthotopic liver transplant (OLT) has been an accepted treatment for CHB patients with decompensated cirrhosis and/or unresectable hepatocellular carcinoma (2). CHB accounts for 5–10% of OLT in North America and Europe and up to 50% in Asia where CHB is more prevalent.

Pre-prophylaxis era

Graft and patient survival rates after OLT have evolved dramatically in the past 2 decades. In the 1980's, graft reinfection rate by HBV was almost universal (3) resulting in allograft dysfunction characterized by reinfection, fibrosing cholestatic hepatitis, and graft loss (4). HBV DNA level at the time of transplantation remains the most important risk factor for reinfection. Other risk factors included reactive hepatitis B e antigen (HBeAg) and patients that have resistance to antiviral drugs (5,6). Patients with fulminant HBV or co-infection with delta hepatitis who generally have low HBV DNA levels were considered to be

Table 1 Post liver transplant HBV recurrence over the last three decades

Post Liver transplant HBV prophylaxis	HBV recurrence (%) (+ HBsAg and/or + HBV DNA)
No prophylaxis	80–100
HBIG only	30–40
HBIG + NA	<10
Oral NA combination with HBIG discontinuation post OLT	0–5
Oral NA monotherapy	0–8

HBIG, hepatitis B immunoglobulin; HBsAg, hepatitis B surface antigen; NA, nucleos(t)ide; OLT, orthotopic liver transplantation.

at a lower risk of reinfection (5,6).

In post OLT patients without prophylaxis, majority did well in the first 60 days (7). This was then followed by reappearance of hepatitis B surface antigen (HBsAg), HBV DNA, and reinfection progressed rapidly, sometimes leading to cirrhosis in less than 200 days (8). As many as 25% of patients developed fibrosing cholestatic hepatitis characterized by ballooning degeneration of hepatocytes, minimal inflammation, and variable degree of cholestasis that resulted in marked synthetic function abnormalities and rapid graft failure (4,8). Two-year graft survival was less than 50%. Due to these results there was a moratorium placed for CHB related liver transplantation in the U.S. especially for HBeAg patients (8). *Table 1* lists the evolution of hepatitis B prophylaxis in post liver transplant recipients over the last four decades.

HBIG monotherapy era

Hepatitis B immune globulin (HBIG) is a polyclonal antibody, which is derived from human plasma. It was used historically for passive immunoprophylaxis in cases of accidental exposure. Mechanism of action of HBIG is related to neutralization of circulating virions by binding to the surface antigen, and it has been demonstrated to then undergo endocytosis into the hepatocyte where it can decrease the release of HBsAg (9,10). In 1993, Samuel *et al.* first reported the benefit of using long-term high dose HBIG in drastically reducing the incidence of graft re-infection to 36% compared to 74% among patients who received short-term HBIG (5). In their multivariate analysis, the predictors of lower risk of HBV recurrence were the long-term administration of HBIG, hepatitis delta super infection, and acute liver failure due to HBV (5). HBIG was administered intravenously (IV) at high doses during the anhepatic phase, and daily in the first post-operation week followed by 10,000 IU/month thereafter.

However, use of high dose IV HBIG administration was associated with high cost, the inconvenience of the IV route, and side effects including headache, flushing, and chest pain (11). Long-term use of HBIG has also been associated with development of HBV mutants, which may cause the virus to become resistant to neutralization. Most of the mutations involve substitution of one or more amino acids in the predominant epitope of the HBsAg that result in decreased binding to hepatitis B surface antibody (anti-HBs) and therefore may escape neutralization (12). The most common mutation reported in liver recipients who were administered HBIG is the substitution of glycine by arginine at codon 145 of the HBV surface protein (13). Cessation of HBIG therapy most of the time resulted in reversion of these mutations to the original genetic sequence (14). To minimize the risk of development of HBV mutants individualized HBIG dosing based on anti-HBs titers was adopted by many centers (15). While differences exist among centers anti-HBs titers greater than 500 IU/L for the first 3 months, 100–250 IU/L between 3 and 6 months, and 100 IU/L after 6 months are generally considered as safe targets (16) .

In order to minimize the cost and the side effects associated with IV route of HBIG, centers have also reported the efficacy of administering HBIG via the intramuscular (IM) route. The IM route has been shown to be as effective as the IV route to produce high anti-HBs titers (17). Other studies have also evaluated pharmacokinetics of subcutaneous administration of HBIG (18) showing similar efficacy between subcutaneous or intramuscular routes (19). In addition, subcutaneous injection has allowed self-administration at home with high compliance while maintaining protective anti-HBs titers (20). De Simone *et al.* reported a prospective, open label, single-arm, phase III, 6-month study in which 47 patients were switched from intravenous HBIG to weekly subcutaneous administration by week 3 after liver transplantation. Mean anti-HBs declined progressively to month 6 however it remained at a protective titer around 290 IU/L. HBV DNA was reported on 45 patients and remained negative (21). Currently, however, only the IV and IM routes of administration remain commercially available.

Early nucleos(t)ide era

Development of NA analogs drastically transformed the landscape for patients with CHB undergoing OLT, beginning with lamivudine (LAM) (22) followed by adefovir (ADV) (23) NA therapy in CHB patients with decompensated cirrhosis often led to improvement in clinical function and removal from the liver transplant waiting list (24). Indeed, the numbers of hepatitis B transplants have decreased since the availability of NAs although the number of hepatocellular carcinoma cases among CHB patients continues to rise (25).

LAM monotherapy is associated with development of drug resistance due to viral mutations (26). Tyrosine-methionine-aspartate-aspartate (YMDD) mutation in the HBV genome resulted in LAM resistance after 9–10 months of therapy with an incidence of 38% and 67% after 2 and 4 years of LAM therapy, respectively (27). Fontana *et al.* reported that YMDD mutations were also seen after 61 weeks of therapy in 39% of post OLT patients (28). However, used in combination with HBIG, in post OLT setting, HBV DNA recurrence rates associated with LAM or ADV decreased significantly to less than 10% (29,30). Combination of NA and HBIG became the mainstay of therapy for prevention of hepatitis B recurrence in post OLT setting for many years.

ETV and TDF era

Entecavir (ETV) and tenofovir (TDF) are potent NAs with low rates of resistance. Use of these NAs became first line therapy in pre and post OLT patients. In a network meta-analysis of 17 studies on 7,274 OLT recipients with HBV who were treated with combination therapy of HBIG and 6 different NAs, those patients who were treated with tenofovir or entecavir had the lowest risk of recurrence (31). Indeed, for OLT recipients with CHB, current AASLD and EASL guidelines recommend the use of high barrier to resistance NAs with low dose HBIG on demand or at fixed intervals. For patients with low risk of HBV recurrence post OLT (low or undetectable HBV DNA levels before transplantation) HBIG can be discontinued with continued antiviral therapy. AASLD guidelines suggest that if drugs with a low genetic barrier to resistance are used combination NA therapy is preferred to monotherapy (32,33). APASL guidelines recommend that if the HBV DNA levels at the time of OLT are undetectable then HBIG free regimens can be used. High potency NAs should be used for life. In higher risk recipients (detectable HBV DNA levels at the time of transplant, presence of drug-resistant HBV, HIV or HDV co-infection, HCC, or poor compliance to antiviral therapy) HBIG can be used for one year followed by continuation of high potency NAs (34).

With the development of high genetic barrier to resistance NAs and the cost and inconvenience of utilization of HBIG, post OLT HBV prophylaxis has evolved further and in the past decade there have been number of growing experiences with various regimens with discontinuation of HBIG and use of potent NAs.

Shortening duration of HBIG treatment by replacing HBIG with second NA at various time points post OLT

Four case series reported the discontinuation of HBIG with the addition of a second NA at various time intervals post OLT (35-38). Post-OLT HBsAg recurrence rates ranged between 6% and 12% in patients treated with the combination of adefovir and lamivudine. Other NA combinations including tenofovir and emtricitabine have also been used with similar outcomes (39-43). In our institution we reported 26 patients that were followed for 31.9 months after being switched to combination TDF/ETV. All patients had undetectable HBV DNA, and 24 patients remained HBsAg negative (44). In order to avoid cross-resistance most studies used a combination of nucleoside and nucleotide as prophylaxis. In majority of these studies there was considerable variability in the duration of use of HBIG anywhere from 7 days to 26 months post OLT.

More recently Radhakrishnan *et al.* reported a retrospective study of 42 patients who received a very short course of HBIG (5 days) while in the hospital after liver transplantation. NA monotherapy was initiated prior to transplant and maintained indefinitely with tenofovir, entecavir, or tenofovir/emtricitabine. Major inclusion criteria included HBV DNA viral load less than 100 IU/mL within 3 months before transplantation, absence of resistance, hepatitis D infection, or HIV infection. One and 3 years cumulative incidence of recurrence, based on reappearance of HBsAg, was only 2.9% (45).

HBIG-free prophylaxis

There have been several studies that have reported on use of no HBIG at all peri- and post liver transplant (46-50) (*Table 2*). Various NA use were reported with these studies with

Table 2 Clinical trials utilizing no HBIG post liver transplantation

Author	Year	N	HBV status at time of OLT	NAs	Median follow-up	Outcome
Genzini	2010	19	28.5% HBV DNA (–)	LAM, LAM + ADV, ETV	19.5 mos	No recurrence
Ahn	2011	1	Unknown	TDF	Unknown	No recurrence
Perillo	2013	1	HBV DNA (–)	ETV	2 yrs	No recurrence
Gane	2013	18	All HBV DNA (–)	LAM + DV	22 mos	No recurrence
Wadhawan	2013	75	All HBV DNA (–)	LAM + ADV, ETV + TDF, TDF, ETV	21 mos	8% HBV DNA (+) 8% HBsAg (+)
Fung	2011	80	26% HBV DNA (–)	ETV	26 mos	22.5% HBsAg (+), all HBV DNA (–)
	2017	265	39% HBV DNA (–)	ETV	59 mos	8% HBsAg (+), all HBV DNA (–)

LAM, lamivudine; ADV, adefovir; ETV, entecavir; TDF, tenofovir; HBIG, hepatitis B immunoglobulin; HBsAg, hepatitis B surface antigen; NA, nucleos(t)ide; OLT, orthotopic liver transplantation; N, number; mos, months; yrs, years.

follow-up up to 2 years. Some studies using HBsAg and others HBV DNA as marker of HBV recurrence reported recurrence rates ranging from 0% to 8%. The largest HBIG-free experience has been reported from the group from Hong Kong University. In 2011, Fung and colleagues first reported 80 patients who underwent OLT and received ETV monotherapy as prophylaxis without the use of HBIG. Twenty-six percent of patients had complete viral suppression at the time of transplant, 91% lost HBsAg, with 98.8% achieving undetectable levels of HBV DNA (51). In a follow-up study, they reported use of ETV monotherapy in 265 post OLT patients with up to 8 years of follow-up. The rates of HBsAg seroclearance were 90% and 95% at 1 and 5 years respectively. In addition 92% of the patients remained HBsAg negative and 100% remained HBV DNA negative at the 8-year follow-up. Overall 9-year survival was reported at 85% and none of the deaths were attributed to hepatitis B recurrence (52). Even though 8% of patients had HBsAg recurrence, all patients remained HBV DNA negative indicating that this is treatable and did not impact graft or patient survival.

While the inconvenience of use of HBIG needs to be considered, some studies have also suggested that HBIG may also be protective against acute cellular rejection of the transplanted liver (53,54). These studies however are older and with the current use of immunosuppression this may not be as significant. Further studies would certainly be needed. In addition, it would be important to understand if HBIG plays any role in preventing development of HCC post liver transplant which has been reported (55).

Conclusions

Post transplant HBV prophylaxis has evolved dramatically over the previous two to three decades. Pre-transplant and post-transplant NA therapy has made a great impact on the outcomes of patients requiring liver transplant due to HBV. While use of HBIG had significant impact on improvement of graft and patient survival, recent studies have demonstrated that minimization or even discontinuation of use of HBIG is feasible with the use of potent and high genetic barrier to resistant NAs. Role of HBIG in HBV patients undergoing liver transplantation may be limited to higher risk patients with high levels of HBV DNA level at the time of transplant but this requires further study. With potent NAs HBV can be managed in patients being transplanted for CHB.

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