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MINIREVIEWS

# Management of chronic hepatitis B before and after liver transplantation

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## Abstract

Liver transplantation remains the only curative option for eligible patients with complications of chronic hepatitis B (CHB) infection, including severe acute hepatitis flares, decompensated cirrhosis, and hepatocellular carcinoma. In general, all patients with CHB awaiting liver transplantation should be treated with oral nucleos(t)ide analogs (NAs) with high barriers to resistance to prevent potential flares of hepatitis and reduce disease progression. After liver transplantation, lifelong antiviral therapy is also required to prevent graft hepatitis, which may lead to subsequent graft loss. Although combination therapy using NA and hepatitis B immune globulin (HBIG) has been the regimen most widely adopted for over a decade, recent studies have demonstrated that newer NAs with low rates of resistance are effective in preventing graft hepatitis even without the use of HBIG, achieving excellent long term outcome. For patients without pre-existing resistant mutations, monotherapy with a single NA has been shown to be effective. For those with resistant strains, a combination of nucleoside analog and nucleotide analog should be used. To date, clinical trials using therapeutic vaccination have shown suboptimal response, as CHB patients likely have an immune deficit against HBV epitopes. Future strategies include targeting different sites of the hepatitis B replication cycle and restoring the host immunity response to facilitate complete viral eradication.

**Key words:** Hepatitis B; Liver transplantation; Antiviral therapy; Prevention; Prophylaxis; Hepatitis B immune globulin



**Core tip:** In the era of highly potent nucleoside and nucleotide analogues for the treatment of hepatitis B, long term viral suppression can be achieved with minimal risk of drug resistance. The use of these agents without hepatitis B immune globulin has been shown to be highly effective in preventing hepatitis B-related graft hepatitis, with excellent long-term outcome. Complete eradication of hepatitis B from the host however is unlikely, and long-term therapy is therefore required. Future developments aiming at different target sites together with immune restoration of the host against hepatitis B may make this elusive goal possible.

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## INTRODUCTION

Chronic hepatitis B (CHB) remains a major health burden worldwide, with an estimated 400 million people affected. Of these, an estimated 15%-40% may develop complications of hepatitis B virus (HBV) infection, including cirrhosis, decompensation, and hepatocellular carcinoma (HCC)[1]. For those with life-threatening complications, liver transplantation (LT) remains the only curative option for those who are eligible and in regions where LT is available. The indications for LT for CHB-related complications fall into three major categories. Firstly, LT is indicated for those with cirrhosis with evidence of decompensation. The second indication for LT includes those patients with severe hepatitis flares with evidence of liver failure. Finally, for those patients with HBV-related HCC within transplantable criteria, and where resection is not feasible, LT is indicated.

The use of nucleos(t)ide analogs (NA) is currently the cornerstone of CHB management. The use of interferon-based regimen is largely contra-indicated in the setting of decompensated cirrhosis, and also not proven in the post transplant setting for CHB. There are currently 5 NAs approved for treating CHB, of which three are nucleoside analogs (lamivudine, telbivudine, and entecavir) and two are nucleotide analogs (adefovir and tenofovir). The major difference between the various NAs is the susceptibility to the development of drug resistant mutations. Lamivudine, the first NA to be approved, is associated with the highest resistance rate, with approximately 70% developing drug resistance after 5 years of therapy. In contrast, newer NAs including entecavir and tenofovir are associated with extremely low risk of resistance, and should be considered for first line therapy if available[2].

## TREATMENT OF CHB BEFORE LT

There are major regional guidelines with treatment recommendations regarding criteria for therapy, duration of therapy, and treatment endpoints[3-5]. Although the indications for LT may be different, the principles of CHB treatment for those waitlisted for transplantation remain identical. As all patients will have advance liver disease with liver failure, established cirrhosis, or both, the goal of antiviral therapy is to prevent further damage from ongoing hepatitis or from acute flares. Therefore, all CHB patients who are waitlisted or being worked up for LT should be treated with antiviral therapy. The major limitation of NAs is the development of drug resistant mutation, with subsequent virological rebound leading to hepatitis flares. Patient who require LT are unlikely to tolerate further insult to their compromised liver. Therefore, these patients should be treated with NAs such as entecavir or tenofovir with high barriers to resistance. For those with pre-existing drug-resistant mutations, a combination of a nucleoside and nucleotide analog is preferred. NAs are generally well tolerated with minimal adverse effects. As they undergo renal excretion predominantly, it is important to adjust the doses accordingly for those patients with impaired renal function. For patients with decompensated liver disease, an association with the development of severe lactic acidosis has been reported with the use of entecavir, especially for those with underlying renal impairment[6]. Nucleotide analogues can also directly be nephrotoxic causing proximal tubule dysfunction[7].

## TREATMENT OF CHB AFTER LT

In CHB infection, complete eradication of HBV from the host is exceedingly rare. Even after hepatitis B surface antigen (HBsAg) seroclearance, it is likely that HBV still persists within the host[8,9]. This is the reason why lifelong antiviral therapy is required. Despite the removal of the liver, HBV may still persist in extrahepatic sites such as the lymph nodes, spleen, peripheral blood mononuclear cells, and other organs[10-13]. HBV may also persist in the circulation at the time of transplantation. These sites serve as reservoirs for re-infection of the new graft. Furthermore, reactivation of latent HBV occurs with the use of immunosuppressive therapy after transplantation[14]. Therefore, in the absence of effective antiviral therapy, severe hepatitis leading to graft failure from recurrent HBV infection is almost universal[15-17]. In fact, prior to the advent of effective HBV therapy, liver transplantation was considered a contraindication because of untreatable HBV recurrence.

### *Hepatitis B immune globulin*

Hepatitis B immune globulin (HBIG) is pooled human immune globulins from donors with high antibody titers, and is administered as a form of passive immuno-prophylaxis. The exact mechanism as to how HBIG reduces recurrence rate after liver transplantation is unclear. Several proposed mechanisms include the blockage of putative receptors involved in the exportation of virions from extrahepatic sites, and in the formation of immune complexes with subsequent neutralization of viral particles[18]. In a landmark study published in 1993 of 372 consecutive HBsAg-positive patients undergoing liver transplantation across 17 European centers, the recurrence rate was significantly less for patients treated with HBIG for 6 mo or longer compared with those receiving no treatment (36% *vs* 75% respectively, $P < 0.001$)[16].

Several strategies have been adopted to maintain a protective level of antibody titer in the circulation. These include injecting at a regular interval (usually monthly) or administering when the antibody level falls below an arbitrary cut-off level that is considered protective. Higher doses have been shown to be more protective, but at a much higher cost[19-21]. The major disadvantage of using HBIG is the need for regular parental injections, its high costs, and the risk for developing escape mutations. The G145A mutation at the antigenic loop of the "a" determinant is the most common mutation

associated with immune escape, and may diminish the efficacy of HBIG[22-24].

### NA

Although the rate of HBV recurrence was reduced with the use of HBIG, a significant proportion still developed recurrence of hepatitis. The most widely adopted use of HBIG as post transplant prophylaxis has been as part of a combination regimen with oral NA. Lamivudine was the first oral antiviral agent approved for CHB treatment. By itself, it reduced the recurrence of HBV to 3.8%-40.4%[25-28]. The combination of HBIG and lamivudine was synergistic as either agent was suboptimal when administered alone in preventing HBV recurrence. The recurrence rate was further reduced to less than 5% with combination therapy. Subsequently, a lower dose of HBIG given intramuscularly in combination with lamivudine was shown to be effective[29,30]. Although the addition of NAs to HBIG significantly reduces the rate of recurrence after transplantation, the reverse may no longer be true with the newer and more potent NAs. An earlier study of 33 CHB patients receiving combination therapy with lamivudine + HBIG for at least 12 mo after liver transplantation without evidence of HBV recurrence, patients were randomized to either continue HBIG or replace HBIG with adefovir[31]. At the end of follow up, only 1 patient developed HBsAg positivity without evidence of detectable HBV DNA in the adefovir arm. In another study of 37 CHB patients treated with tenofovir + emtricitabine + HBIG for at least 12 wk after liver transplantation, participants were randomized to either continue or stop HBIG[32]. At 96 wk, there was no HBV recurrence reported in both arms. These studies demonstrated that HBIG withdrawal was safe and effective for those receiving combination NA therapy.

The effectiveness of NAs alone without HBIG can be primarily attributed to newer NAs having significantly lower rates of resistance. The major disadvantage in using lamivudine is due to its high resistance rate, with up to 70% after 5 years of therapy in non-transplant patients[33]. In contrast, both entecavir and tenofovir have been associated with resistance rates of < 2% after 5 years in patients without pre-existing resistant mutations[34,35]. Therefore these newer agents would appear to be ideal agents to prevent HBV recurrence after transplantation. In this instance, the role of HBIG in the era of these new NAs become less obvious, as resistance and virological breakthrough rates are extremely low. In a study of 80 CHB patients undergoing liver transplantation, entecavir was used as monotherapy in a completely HBIG-free regimen with a median follow up of 26 mo[36]. There was a high HBsAg seroclearance rate of 86% and 91% after 1 and 2 years respectively despite the absence of HBIG administration. Although a small proportion (13.7%) had HBsAg positivity either from re-appearance of HBsAg after initial seroclearance, or from persistence of HBsAg status after transplantation, none of the patients had evidence of virological rebound or resistance. Importantly, there was no incidence of HBV related hepatitis, graft loss, or mortality. Furthermore, quantitative HBsAg measurements in those with positive HBsAg revealed a persistently low level in the absence of HBV DNA. A larger study of 362 patients using a completely HBIG free regimen also demonstrated excellent long-term survival of 83% at 8 years[37]. In this particular study, there was no difference in the rate of HBsAg seroclearance and HBV DNA suppression between those on lamivudie, combination NA, or entecavir. The key difference was the significantly lower rate of virological rebound observed at 3 years after liver transplantation with entecavir when compared to those treated with combination NA therapy and lamivudine (0%, 7% and 17% respectively, $P < 0.001$).

### Vaccination

The use of vaccination after liver transplantation is currently not standard practice, and can only be recommended within the clinical trials setting. Results so far have been unconvincing. Although initial studies have been encouraging, subsequent studies have demonstrated low response rates of 7.7%-17.6% only[38-44]. Perhaps this is not surprising given that CHB patients have been exposed to high levels of HBsAg epitopes for most of their lives with the inability to mount an effective immune response. Therefore, further exposure to HBV antigens *via* vaccination is unlikely to trigger a novel and effective response, especially in an immunosuppressed host. However, studies using higher doses of pre-S vaccines have shown that a proportion of patients may develop an immune response[44]. Whether the anti-HBs titers induced by vaccination strategies can be maintained and confer protection also remains to be determined. The use of vaccination may also be associated with the potential risk of developing escape mutations, rendering the antibody production ineffective.

### Adoptive transfer of immunity

In addition to vaccination, adoptive transfer of immunity against HBV represents another strategy to restore the immune deficit against HBV. This phenomenon was initially described in recipients of bone marrow transplants from donors immune to HBV[45]. In liver transplant recipients, the anti-HBs have been frequently detectable after transplantation even without the administration of HBIG[36,37]. Furthermore, donor-derived HBV-specific lymphocytes were found to be present in the liver graft[46]. However, the antibody titers that is observed appears to be transient in the majority of liver recipients, suggesting that in a proportion of these patients, passive transfer of antibody and donor lymphocytes at the time of transplant may occur.

## FUTURE STRATEGIES

New approaches for CHB therapy continue to build on

the current strategies of either targeting factors involved in viral replication or at the host immune response[47]. Potential target sites for the former includes methods to prevent viral entry, lower covalently closed circular DNA levels, disrupt viral transcription, assembly, and exportation of virions. To restore or enhance the immune response against HBV, other strategies apart from therapeutic vaccination have been explored. These include targeting T-cell inhibitor receptors and blocking suppressive cytokines and regulatory T-cells in the liver.

## DISCUSSION

In the last 15 years, NAs have revolutionized the treatment paradigm of CHB infection. The major limitation with early NAs was the associated high resistance rate associated with increase risk of virological breakthrough and hepatitic flare. This risk has largely been diminished by the approval of highly potent NAs with high barriers to resistance. For patients awaiting liver transplantation with CHB infection, it is recommended that all should be on NAs irrespective of the viral load. As most of the patients will already have established cirrhosis, hepatitic flares may result in further decompensation. This is also the main reason why NAs with high barriers should be used to lower the risk of virological breakthrough and subsequent flare.

After liver transplantation, the choice of NAs will be dependent on the NA used prior to surgery, and also whether drug-resistant mutations are present. The role of HBIG has become diminished with newer NAs, and studies have already demonstrated the efficacy of an HBIG-free regimen as antiviral therapy after transplantation. Although several meta-analyses have demonstrated that combination therapy with HBIG appears to be more efficacious than NA alone, it has to be said that the overwhelming majority of the studies included in these meta-analyses were patients using the early NAs such as lamivudine[48-51]. Therefore it is not surprising that the additional of HBIG would be beneficial.

As complete eradication of HBV from the host is still not attainable with current antiviral regimens, life long treatment is required. Intrahepatic HBV remains detectable even if there is no serological evidence of HBV infection[52,53]. In this respect, antiviral therapy after liver transplantation does not prevent recurrent infection. The recipient is unlikely to have complete clearance of HBV even with removal of the infected liver, as HBV may be present in the circulation and extra-hepatic sites. Therefore, antiviral therapy serves to prevent recurrent hepatitic flares, rather than recurrent infection, given the patient is already chronically infected. The significance of HBsAg positivity remains unclear, especially when it remains at very low levels in the absence of virological rebound or detectable HBV DNA. The administration of HBIG will bind on to HBsAg, leading to its undetectability, and a higher rate of HBsAg negativity compared to HBIG-free regimens. The level of hepatitis B core related antigen however remains unchanged by the administration of HBIG, and has been shown to persist despite maintaining an anti-HBs titer of > 100 U/L[54].

In summary, all patients wait-listed for liver transplantation with CHB infection should receive antiviral therapy with high barriers to resistance. After transplantation, life-long prophylaxis to prevent recurrent hepatitis flares is required. A shifting paradigm of using high dose HBIG, low dose HBIG, limited-duration HBIG, to no HBIG using combination of NAs or monotherapy with NA with high barrier to resistance has been observed, with the latter showing excellent clinical outcomes. In the future, other novel methods targeting different sites of viral replication cycle together with restoration of the host immune response may allow complete eradication or long-term immune control of HBV, thereby obviating the need for long-term therapy.

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