Hepatitis B and Liver Transplantation

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Liver transplantation is the treatment of choice for patients with liver failure secondary to chronic hepatitis B. However, liver transplantation is complicated by the risk of recurrent hepatitis B virus infection, which significantly impairs graft and patient survival. The main risk factor for the development of recurrent hepatitis B virus infection is the virus load at the time of transplantation. The development of antiviral medications, such as lamivudine and adefovir, and the implementation of effective prophylactic regimens using hepatitis B immune globulin have significantly improved the outcomes of hepatitis B after liver transplantation. However, current approaches continue to be hampered by the extremely high cost of treatment and the emergence of drug-resistant viral mutations. Ongoing studies are necessary to establish the most cost-effective approaches to prevent recurrent hepatitis B virus infection after liver transplantation.

Chronic hepatitis B virus (HBV) infection remains a major global health issue, affecting up to 350 million people worldwide. Patients with chronic HBV infection are at significantly increased risk for the development of cirrhosis, hepatic failure, and hepatocellular carcinoma. Orthotopic liver transplantation (OLT) is now a well-established treatment for liver failure and hepatocellular carcinoma. However, the presence of HBV infection poses many unique issues in patients undergoing OLT. In the absence of prophylaxis or treatment, HBV reinfection occurs in 75%–80% of persons who undergo OLT [1]. Recurrent HBV infection after OLT often follows an aggressive clinical course and is associated with a significant decrease in graft and patient survival rates. More recently, newer antiviral therapies (such as lamivudine and adefovir treatment) and prophylactic strategies utilizing hepatitis B immune globulin (HBIG) have been developed to reduce the risk of recurrent HBV infection after OLT. These newer approaches have led to significant improvements in graft and patient outcomes after OLT for HBV infection (figure 1) [2]. In this article, we discuss risk factors and mechanisms for the development of recurrent HBV infection, prophylactic strategies for the prevention of recurrence of HBV infection, and treatment of HBV-infected patients before and after OLT, and we address controversies in the treatment of these challenging patient populations.

RISK FACTORS FOR RECURRENT HBV INFECTION AFTER LIVER TRANSPLANTATION

The most important factor that determines the risk of recurrent HBV infection after OLT is the HBV level at the time of transplantation. Early experience in Europe demonstrated that the risk of recurrence of HBV infection was greatest in patients with high virus levels before transplantation and that it approached 85% in patients who were found to be positive for HBV DNA with use of a hybridization assay (approximate lower limit of detection, 1 × 10^6 copies/mL) [1]. The risk of a recurrence of HBV infection was significantly lower in hepatitis B e antigen (HBeAg)–negative patients, those with fulminant hepatitis B, and patients with hepatitis D virus coinfection; these represent subgroups in which serum HBV DNA levels are typically lower. Therefore, one of the primary goals in the treatment of HBV-infected OLT recipients is to minimize the serum hepatitis B virus level at the time of transplantation.

TREATMENT OF HBV INFECTION BEFORE LIVER TRANSPLANTATION

There are several goals of antiviral therapy in patients with cirrhosis secondary to chronic HBV infection. In patients with compensated cirrhosis, antiviral therapy may prevent progression to decompensated cirrhosis and potentially eliminate the need for OLT. Antiviral therapy could also potentially reduce the risk of progression to hepatocellular carcinoma. In patients
with decompensated cirrhosis, antiviral therapy may stabilize or even improve liver function, potentially delaying the need for transplantation. In patients whose conditions progress to the point at which transplantation is required, the goal of antiviral therapy is to minimize the HBV titer at the time of transplantation, thereby reducing the risk of recurrent HBV infection after OLT.

**IFN-α.** The risks and benefits of IFN-α therapy must be carefully weighed in patients with cirrhosis due to chronic HBV infection. IFN-α therapy is associated with a flare in serum aminotransferases in 30%–50% of treated patients. In patients with advanced liver disease, IFN-α therapy may precipitate further hepatic decompensation and should be avoided. In addition, IFN-α therapy may exacerbate cytopenia and further increase the risk of serious bacterial infections. IFN-α therapy can be given safely with close monitoring in patients with well-compensated cirrhosis. Perrillo et al. [3] demonstrated that 31% of cirrhotic HBV patients treated with IFN-α-2b had seroconversion to antibody to hepatitis B e antigen and lost detectable HBV DNA, with response rates comparable to those from noncirrhotic patients. Long-term studies have shown that cirrhotic patients who lose HBeAg have a superior 10-year survival rate, compared with patients who do not respond to IFN-α therapy [4]. In addition, some studies have suggested that the incidence of hepatocellular carcinoma may be lower in patients treated with IFN-α, particularly in the subgroup of patients who clear HBV DNA from the serum [5, 6]. Overall, the risks associated with IFN-α therapy and the emergence of safe and well-tolerated oral antiviral therapies have decreased the utility of IFN-α therapy in patients with cirrhosis. Pegylated IFN-α-2a was recently approved by the US Food and Drug Administration for the treatment of chronic hepatitis B. However, few data are currently available on the use of pegylated IFN-α in cirrhotic patients with hepatitis B.

**Lamivudine.** Lamivudine is a nucleoside analogue and a potent inhibitor of HBV replication. It was the first orally administered medication approved for the treatment of chronic HBV infection, and it has demonstrated an excellent safety profile in both compensated and decompensated cirrhotic patients. In patients with decompensated cirrhosis due to HBV, lamivudine has been shown to be a safe and effective agent. Early uncontrolled studies demonstrated conflicting results as to whether lamivudine therapy delays progression to death or liver transplantation [7, 8]. Recently, Liaw et al. [9] reported the results of a large, prospective, multicenter randomized trial in which 651 patients with chronic hepatitis B and bridging fibrosis or cirrhosis were randomized to receive either lamivudine or placebo. The primary end point of the study was time to disease progression, defined as hepatic decompensation, hepatocellular carcinoma, spontaneous bacterial peritonitis, variceal bleeding, or death related to liver disease. After a median treatment duration of 32.4 months (range, 0–42 months), a significantly greater percentage of patients in the placebo group than in the lamivudine group had developed disease progression (17.7% vs. 7.8%; P = .001), and the study was terminated early. Furthermore, hepatocellular carcinoma occurred in a lower percentage of patients in the lamivudine treatment group than in the placebo group (3.9% vs. 7.4%; P = .047). These findings demonstrate that lamivudine treatment reduces the incidence of hepatic decompensation and hepatocellular carcinoma in patients with chronic HBV infection and advanced fibrosis or cirrhosis.

The major factor limiting the use of lamivudine is the development of mutations in the YMDD motif of the HBV DNA polymerase gene, which confers resistance to lamivudine. YMDD mutations develop at a rate of ~20% for each year of lamivudine therapy and are associated with return of active viral replication [10]. The clinical consequences of lamivudine resistance vary according to the severity of underlying liver damage. The earliest sign of resistance is usually a rebound in the HBV DNA level, without other abnormal biochemical or clinical findings. However, progressive liver failure has been described in association with the emergence of YMDD mutations. Therefore, cirrhotic patients require close monitoring while receiving extended lamivudine therapy. The nucleotide analogue adefovir dipivoxil has been shown to have activity against lamivudine-resistant strains carrying YMDD mutations and is the agent of choice when lamivudine resistance develops.

**Adefovir dipivoxil.** Adefovir dipivoxil is an oral prodrug
of adefovir, a nucleotide analogue of adenosine monophosphate that inhibits HBV DNA polymerase. Previous studies have demonstrated that adefovir has excellent activity against wild-type as well as lamivudine-resistant HBV strains. Schiff et al. [11] evaluated the safety and efficacy of adefovir dipivoxil (10 mg daily) in 128 patients with lamivudine-resistant hepatitis B who were awaiting liver transplantation. Treatment for 48 weeks led to a median reduction in HBV DNA titer of 4.1 log_{10} copies/mL, nondetectable HBV DNA (by PCR; lower limit of detection, <400 copies/mL) in 81%, and stable or improved Child-Pugh score in 92%. Adefovir dipivoxil therapy was generally very well tolerated, with an increase in the serum creatinine level of >0.5 mg/dL from baseline in 12% of patients, but no patients needed to stop adefovir dipivoxil therapy as a result of nephrotoxicity. The 48-week survival rate was 84% in this study—significantly better than the rate for historical control subjects. No adefovir dipivoxil–resistant mutations were described in this study, although the N236T and A181V mutations in HBV polymerase have recently been shown to confer resistance to adefovir dipivoxil. Reassuringly, the development of adefovir dipivoxil resistance remains relatively rare (3% after 2 years of therapy and 18% after 4 years [12]). In addition, both the N236T and the A181V mutations remain susceptible to lamivudine.

Other oral agents. Entecavir is a new guanosine nucleoside analogue that was recently approved by the US Food and Drug Administration for the treatment of chronic hepatitis B. Although not yet published, a large phase III study demonstrated that HBeAg-positive patients treated with entecavir (0.5 mg daily for 48 weeks) developed a mean change in HBV DNA titer of −6.98 log_{10} copies/mL, which was significantly better than that seen with lamivudine [13]. Entecavir has also demonstrated activity against lamivudine- and adefovir dipivoxil–resistant HBV strains. The mean change in the HBV DNA titer in patients infected with lamivudine-resistant HBV who were treated with entecavir (1.0 mg daily for 48 weeks) was −5.11 log_{10} copies/mL. To date, there are no specific data available on the use of entecavir in patients with decompensated cirrhosis or in association with liver transplantation.

Studies of patients coinfected with HIV and HBV have demonstrated that reverse-transcriptase inhibitors used for treatment of HIV infection may also be highly active against HBV. Both tenofovir disoproxil fumarate and emtricitabine are approved for use against HIV infection and have demonstrated excellent antiviral activity against HBV in preliminary studies. In addition, tenofovir has demonstrated efficacy against lamivudine-resistant strains of HBV, without significant renal toxicity [14]. The precise role of these agents in the treatment of hepatitis B, and the potential efficacy of nucleoside/nucleotide combination therapy have yet to be fully elucidated.

MECHANISMS FOR RECURRENT HBV INFECTION AFTER LIVER TRANSPLANTATION

The source of HBV reinfection after OLT may be from either the presence of circulating viremia at the time of transplantation, or reservoirs of hepatitis B virions in extrahepatic sites such as PBMCs [15]. The mechanisms by which passive immunoprophylaxis with HBIG prevents reinfection are not completely understood. It is felt that antibodies to hepatitis B surface antigen (anti-HBs) bind to circulating virions to prevent allograft reinfection, which is supported by the dose-dependent response to HBIG therapy. In addition, it has been postulated that HBIG may block a putative HBV receptor on the surface of hepatocytes. Recent in vitro studies have demonstrated that anti-HBs may bind to hepatocytes, undergo endocytosis, and colocalize in intracellular compartments with HBsAg, thereby preventing HBsAg secretion [16].

Although the incidence of recurrent HBV infection after OLT is significantly reduced with HBIG therapy, reinfection of the allograft may still occur. Recurrence of HBV infection despite HBIG prophylaxis typically follows 1 of 2 scenarios. HBV recurrence in the early posttransplantation period is believed to be due to insufficient titers of anti-HBs antibodies (i.e., inadequate dosing of HBIG). This is also consistent with the observation that patients with higher HBV loads at the time of transplantation are more likely to develop recurrent HBV infection, despite receiving HBIG prophylaxis. The second scenario is late recurrence of HBV infection, developing after 6 months of HBIG therapy, despite adequate anti-HBs antibody titers. It has been shown that selection pressure from the use of HBIG may induce the development of mutations in the pre S/S region of the HBV genome. These HBIG escape mutants lead to alterations in the “a” determinant of the surface antigen protein, reducing the binding affinity of HBIG for surface protein [17]. The emergence of escape mutations in the “a” determinant has been associated with HBV reinfection and poor outcome after liver transplantation. The notion that such escape mutants develop in response to selection pressure from HBIG is supported by the observation that withdrawal of HBIG therapy leads to reversion to wild-type virus [18].

PROPHYLACTIC STRATEGIES AGAINST RECURRENT HBV INFECTION AFTER OLT

HBIG monotherapy. The efficacy of HBIG in prevention of recurrent HBV infection after OLT was first demonstrated in a large, retrospective, European multicenter trial [1]. Among 359 patients who underwent liver transplantation for HBV infection, the risk of recurrent HBV infection ≤5 years after OLT was 75% among patients who received no or short-term (i.e., <6 months) HBIG therapy, compared with 33% among
those who received HBIG for \( \geq 6 \) months after transplantation (figure 2).

Most prophylactic regimens use high doses of HBIG (10,000 IU) during the anhepatic phase and daily for the first week after transplantation, followed by decreasing frequency of dosing. In general, titers of anti-HBs of \( >500 \) IU/L during the first week after transplantation, \( >250 \) IU/L during the first 3 months, and \( >100 \) IU/L thereafter are believed to be protective against HBV reinfection. There is considerable variability between liver transplantation centers with regard to HBIG dosing regimens. Some centers advocate fixed dosing of HBIG at regular intervals, such as 10,000 IU given intravenously monthly. Other centers prefer HBIG dosing at variable intervals to maintain a titer of anti-HBs greater than \( 100-150 \) IU/L after the third month after OLT. The route of administration of HBIG may also vary. To help reduce costs, some centers have advocated an intramuscular route of HBIG administration, although experience with this approach is limited. Despite long-term HBIG monotherapy, recurrent HBV infection occurs in \( >30\% \) of patients 5 years after OLT (figure 2). As discussed previously, many of such patients develop escape mutants in the “a” determinant of the surface antigen protein.

**Lamivudine monotherapy.** Several studies have examined the benefit of lamivudine monotherapy for the prevention of recurrence of HBV infection after OLT. Initial reports from the United Kingdom demonstrated only a \( 10\% \) rate of recurrence after 1 year of therapy [20]. In a multicenter North American study involving 47 patients with chronic HBV infection who underwent OLT and who received lamivudine monotherapy prophylaxis, recurrence of HBV infection developed in \( 32\% \) of the patients at 1 year and \( 41\% \) at 3 years after OLT [21], and recurrence was usually associated with the emergence of YMDD mutations. In the North American study of lamivudine prophylaxis, recurrent HBV infection developed within 3 years in \( 60\% \) of patients who were found to be positive for HBV DNA by solution hybridization assay, compared with a \( 0\% \) rate of recurrence among patients who were HBV DNA negative at the time of transplantation.

Overall, the results for lamivudine monotherapy are similar to—but no better than—those for HBIG monotherapy for prophylaxis against recurrent HBV infection (figure 2). As in the pre-OLT period, it is clear that the major limitation of lamivudine monotherapy is the development of resistant YMDD mutants. The rate at which these mutations emerge is higher after OLT than it is among patients who have not undergone transplantation. For this reason, the efficacy of lamivudine monotherapy in long-term prophylaxis after OLT is limited, and most transplantation centers currently advocate a combination of lamivudine with HBIG.

**HBIG and lamivudine combination therapy.** Although monotherapy with either HBIG or lamivudine lowers the risk of HBV reinfection after OLT, recurrence may nevertheless occur, primarily as a result of emergence of drug-resistance mutations, as described above (figure 2). For these reasons, the combination of HBIG and lamivudine has been widely adopted for prophylaxis against recurrence of HBV infection after OLT. It is clear that the combination of HBIG and lamivudine is more effective at preventing recurrent HBV infection than is monotherapy with either agent alone. Although protocols have varied considerably among centers, the risk of recurrent HBV is generally \( <10\% \) in patients treated with a combination of HBIG and lamivudine after OLT (figure 2) [22]. Interestingly, even in patients without overt recurrence of HBV infection, HBV DNA may be detectable by PCR in serum, PBMCs, or liver tissue in \( 45\% \) of patients 10 years after OLT [19].

Although a regimen combining HBIG and lamivudine is very effective in preventing recurrent HBV infection, the major limitation of such a regimen is cost, which averages more than \$50,000\ annually. The addition of lamivudine does allow reduced dosing of HBIG, compared with monotherapy, although the most cost-effective regimen has not been established. With use of an intramuscular route, doses of HBIG may be reduced by \( \geq 50\% \) to achieve similar titers of anti-HBs [23].

**Other prophylactic strategies.** Other strategies to lower the overall cost of prophylactic therapy are aimed at discontinuing HBIG therapy in subsets of patients who are at lowest risk of recurrence of HBV infection. A few small studies have suggested that, in patients with no detectable viremia at the time of transplantation, transitioning from HBIG prophylaxis to lamivudine monotherapy is associated with a low risk of recurrence of HBV infection [24, 25]. However, these studies have relatively short follow-up periods, and low-level viremia may be detectable by
PCR in these patients [19, 24]. Given the risk of developing lamivudine resistance during long-term therapy regimens, longer clinical follow-up periods are required to fully evaluate this approach. Another interesting approach to reduce long-term costs is the strategy of replacing HBIG prophylaxis with HBV vaccination after OLT in patients with no detectable HBV DNA at the time of transplantation. Studies that have examined this approach have yielded variable results [26–28]. Although some patients may respond appropriately, inadequate anti-HBs titers develop in others and may decrease over time. Thus, it appears that discontinuation of HBIG prophylaxis and HBV vaccination may be a viable approach in selected patients after OLT for HBV infection. Certain subsets of patients may develop protective anti-HBs titers to vaccination after transplantation, although the optimal approach has not been determined and requires further study.

**TREATMENT OF RECURRENT HBV INFECTION AFTER OLT**

Recurrence of HBV infection after OLT is associated with a more aggressive course than is HBV infection in immunocompetent hosts. It is well known that the HBV genome contains a glucocorticoid-responsive element. For this reason, most transplantation centers have opted to treat HBV-infected patients with immunosuppressive regimens that avoid or minimize exposure to corticosteroids. In 10%–30% of cases of recurrent HBV infection, an extremely aggressive variant may develop, called fibrosing cholestatic hepatitis. Patients with fibrosing cholestatic hepatitis present with an acute cholestatic picture, and the condition may progress very quickly to graft failure and death.

In the largest published study of lamivudine therapy for recurrent HBV infection following OLT, 60% of subjects were found to be HBV DNA negative by solution hybridization assay, 31% had lost HBsAg, and 6% had lost hepatitis B surface antigen after 52 weeks of lamivudine therapy [29]. However, 27% of patients developed YMDD mutations. Other studies have confirmed that lamivudine is effective in patients with recurrent HBV infection, but that long-term therapy is limited by the emergence of drug-resistance mutations.

Adefovir dipivoxil is effective against wild-type and YMDD-mutant lamivudine-resistant strains of HBV. The efficacy of adefovir dipivoxil in lamivudine-resistant strains has also been demonstrated in the post-OLT situation, during which a mean reduction in the HBV level of 4.3 log_10 copies/mL and patient survival rates of 93% were seen after 48 weeks of therapy [11]. Mild elevations in serum creatinine level may occur with adefovir dipivoxil therapy, especially with concomitant calcineurin inhibitor use, but only a small number of patients who have undergone OLT require discontinuation of therapy. Nevertheless, renal function should be monitored periodically, with dose adjustments based on renal function, as necessary. Adefovir dipivoxil may also be beneficial for patients who develop fibrosing cholestatic hepatitis after OLT.

**SUMMARY**

Liver transplantation for hepatitis B is complicated by the risk of recurrent HBV infection, which significantly reduces the rates of graft and patient survival. The primary risk factor for the development of recurrent HBV infection is the virus load at the time of transplantation. Effective therapy for the OLT recipient with chronic HBV infection involves administration of antiviral therapy before OLT to minimize the hepatitis B viral titer at the time of transplantation, and prophylactic therapy after OLT with HBIG in combination with lamivudine or adefovir. With this approach, the risk of recurrent HBV infection is <10% after 3 years, and overall patient survival has improved. However, the high cost of prophylactic therapy and the development of drug-resistance mutations continue to complicate the post-OLT care of patients with hepatitis B. Additional study is necessary to determine the most cost-effective approach to prevent recurrent HBV infection after OLT.

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