

## Review

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**Management of HBV Infection in Liver Transplantation Patients****John M. Vierling**

David Geffen School of Medicine at University of California, Los Angeles, CA, USA

**Abstract**

In the absence of preventative therapy, reinfection of allografts with hepatitis B virus (HBV) after orthotopic liver transplantation (OLT) resulted in dismal allograft and patient survival. Major advances in the management of HBV-infected recipients of OLT during the past 15 years have steadily reduced the rate of reinfection, resulting in improved outcomes. Initially, long-term use of hepatitis B immune globulin (HBIG) as a source of anti-HBs antibodies was effective in preventing or delaying reinfection. Lamivudine monotherapy made it possible to suppress HBV replication prior to OLT, markedly decreasing the risk of reinfection. Although lamivudine monotherapy used before and after OLT could prevent reinfection, its effectiveness was limited by progressive development of lamivudine-resistant mutant infections. Combination therapy with HBIG and lamivudine after OLT reduced both HBV recurrence and the risk of lamivudine resistance even in patients with active HBV replication. Introduction of adefovir provided a safe, alternative oral antiviral able to treat effectively lamivudine-resistant mutants HBV. Available strategies to prevent reinfection have resulted in OLT outcomes for HBV-infected patients comparable to those for patients transplanted for non-HBV indications. In the future, combination therapies of HBIG and both nucleoside and/or nucleotide agents will undoubtedly be optimized. Development of new drugs to treat HBV will increase opportunities to combine agents to enhance safety, efficacy and prevent emergence of HBV escape mutants. New vaccines and adjuvants may make it possible to generate anti-HBs in immunosuppressed patients, eliminating the need for HBIG.

**Key words**

HBV Infection, Liver Transplantation, Patient Management

**Author biography**

**John M. Vierling** is Professor of Medicine at the David Geffen School of Medicine at UCLA. He is the former Director of Hepatology and Medical Director of Multi-Organ Transplantation at Cedars-Sinai Medical Center. His basic and translational research interests involve the immunological and inflammatory mechanisms of pathogenesis in alloimmune and autoimmune liver diseases and viral hepatitis. He received his undergraduate degree in Biology at Stanford University with great distinction and his M.D. degree from Stanford University School of Medicine. He has served the American Association for the Study of Liver Diseases as past Chairman of both the Training and Education and the Publications Committees. He is also a past councilor of the International Liver Transplantation Society, and selection by his peers as one of the Best Physicians in America. He has served on the Editorial Boards of Gastroenterology, Hepatology and Liver Transplantation. Prof. Vierling is a member of the Board of Directors of Ribapharm, Inc. and the Scientific Advisory Boards of Immusol, Inc. and ICN Pharmaceuticals. He has been active for many years in the American Liver Foundation and is the immediate past Chairman of the National Board of Directors.

**Corresponding address**John M. Vierling, M.D., F.A.C.P. [hepatol@aol.com](mailto:hepatol@aol.com)

## 1. Introduction

Innovations in the management of HBV infection before and after orthotopic liver transplantation (OLT) have revolutionized outcomes for hepatitis B virus (HBV)-infected recipients. In the absence of preventative therapies, OLT for patients with acute or chronic replicating HBV infections resulted in universal reinfection of the allograft, progressive graft failure and excessive mortality, even with retransplantation [1-3]. Thus, HBV-related liver disease was initially regarded as a contraindication to OLT [4] and was excluded as an indication by Medicare in the U.S.A. [5]. Over the past 15 years, sequential application of therapeutic strategies to prevent recurrent HBV infection after OLT and to inhibit HBV replication before and after OLT has steadily improved outcomes [6-8]. Indefinite administration of passive immunoprophylaxis with hepatitis B immune globulin (HBIG, a source of high titer, polyvalent anti-HBs antibodies) resulted in a significant reduction in recurrent hepatitis B, especially among recipients without active HBV replication at the time of OLT [9-12]. Pre-OLT inhibition of HBV replication using lamivudine (LAM) rendered patients with active replication eligible for transplantation, prevented recurrence post-OLT (unless LAM-resistant escape mutations developed) and improved the outcome of patients who became reinfected [13-17]. The combination of HBIG and lamivudine enhanced prevention of HBV reinfection [14,18], and the advent of adefovir dipoxil (ADV) provided an safe and efficacious therapeutic option for patients with LAM-resistant infection [19]. As a result of this progress in prevention and treatment of HBV reinfection, acute or chronic hepatitis B is now universally accepted as an excellent indication for OLT [8].

Transplantation of livers from donors with isolated anti-HBc-positivity (i.e. negative for HBsAg and anti-HBs) has resulted in additional challenges, since isolated anti-HBc-positive livers are capable of transferring HBV infection to 50-78% of HBV-naïve recipients in the absence of preventative therapy [20,21]. In addition, HBV-naïve recipients who have not been vaccinated to prevent hepatitis B prior to OLT have an ongoing risk of acquiring parenterally transmitted HBV infections that require prompt diagnosis and treatment [22-24]. Mandatory hepatitis B vaccination for all HBV-naïve patients with diseases that could require OLT could significantly reduce this risk.

## 2. Impact of Strategies to Prevent and Treat HBV Infections in Transplant Recipients

A report of OLT outcomes for HBV-infected patients in the U.S.A. from 1987 to 2002 underscores the positive, cumulative impact of advances to prevent and treat HBV reinfection [8]. This retrospective study analyzed cohorts of patients transplanted during three eras: Era 1 (1987-91, n= 6,708), Era 2 (1992-96, n= 13,995) and Era 3 (1997-2002, n= 20,730). Survival of patients was statistically significantly better for Era 2 compared with Era 1 ( $p<0.01$ ) and Era 3 compared with Era 2 ( $p<0.01$ ). No difference in survival was noted for Era 3 patients and patients transplanted for all non-HBV indications. Importantly, multivariate analysis showed that the effect of eras persisted even after consideration of confounding variables, such as donor and recipient age, ischemia time, severity of pre-OLT disease and presence of hepatocellular carcinoma. In contrast to earlier reports, Asian race [25-27] did not adversely affect survival and transplantation of patients with fulminant hepatitis B [9] did not enhance survival. The results of this study and those reported from Europe [13,28], indicate that application of innovative strategies to prevent and treat HBV infections before and after OLT are responsible for improved outcomes.

## 3. HBV Reinfection of Allografts

Two mechanisms have been implicated in allograft reinfection: 1) rapid reinfection by HBV in the circulation of the recipient and/or 2) reinfection from HBV replicating in extrahepatic sites [29]. Since the former mechanism predominates in recipients with high HBV viral loads at the time of OLT, patients with active replication detected by insensitive molecular hybridization assays were considered as inferior candidates [9].

Among patients receiving immunoprophylactic HBIG, late reinfections were attributed to either insufficient serum levels of anti-HBs to prevent infection from extrahepatic HBV [11,30] or emergence of anti-HBs escape mutations in the HBV S ORF [31,32]. Subsequent experience using LAM [33,34] and ADV [35] as prophylactic therapies has also demonstrated reinfections due to specific escape mutants. Thus, HBV-infected and HBV-naïve recipients of livers from donors positive for isolated anti-HBc remain at risk for reinfection unless adequate preventative therapy is maintained.

The impact of HBV genotype and precore mutants on reinfection has only recently been assessed. In London, genotypes A, D and A/D accounted for 89% of the European population undergoing OLT. Reinfection occurred in 40% a median of 10 months post-OLT, and 22% died [36]. The rate of reinfection was not significantly greater for genotype D than A, and the reinfection rate in patients with genotype A/D was similar to genotype D patients. Among a heterogeneous population of recipients from the Middle East, Eastern and Western Europe, the U.S.A. and Asia, genotype D was present in 96% and A in 4% [37]. Reinfection occurred in 22%, and no differences were noted among genotypes with respect to risk or prevalence of reinfection, development of LAM resistance or prevalence of precore mutations.

## 4. Management of Patients Prior to Transplantation

Studies of HBIG monotherapy established active HBV replication before OLT as a dominant risk factor for reinfection [9,30]. Thus, therapies to reduce or eliminate HBV replication prior to OLT should result in a lower incidence of reinfection. The characteristics of ideal antiviral agent(s) would include low toxicity in the setting of decompensated cirrhosis and the rapid ability to eliminate HBV replication in patients with either acute or chronic infections. Despite clear progress in our ability to eliminate HBV replication, additional advances in drug development and application of antiviral strategies is required to achieve this goal.

### Alpha Interferon and Famciclovir

The need for an extended period of interferon (IFN) therapy prior to OLT limited its potential for patients with fulminant or acute HBV infections, and its adverse effects, especially neutropenia and thrombocytopenia, resulted in poor tolerability in decompensated cirrhotics [38]. In a controlled trial of pre-OLT IFN therapy followed by HBIG immunoprophylaxis, the rate of reinfection was unchanged [39], while another study showed a reduced rate after IFN treatment [40]. In the same era, results of treatment with famciclovir were disappointing [41]. Neither IFN nor famciclovir are currently indicated treatments.

## Lamivudine Monotherapy

LAM has been extensively studied in OLT candidates (Table 1), is well tolerated in decompensated cirrhosis and results in undetectable HBV DNA using molecular hybridization in 63-100% of patients within 2-3 months [15, 42-52]. LAM is effective for both wild type (WT) and precore mutant (HBeAg-negative) strains [51]. Uninterrupted therapy is required prior to OLT, since premature cessation results in recurrent HBV replication [53]. Unfortunately, prolonged therapy, which is necessary for clinical benefit, increases the risk of developing LAM-resistant mutations as a result of amino acid substitutions in the YMDD motif encoded by the HBV RNA-dependent DNA polymerase gene [54]. The incidence of such mutations was 15-20% per year in the studies summarized in Table 1, and development of mutations can worsen liver failure [52]. Results of OLT in patients with YMDD mutations before transplantation have been reported for only a few patients and were conflicting [48,49,55,56]. Combination HBIG and LAM prevented recurrence in some [55,56], but not all recipients [48,49]. Since ADV and tenofovir have excellent efficacy against LAM-resistant HBV mutants [57,58], they should be used to treat patients with LAM resistance prior to OLT.

**Table 1.** Results of Lamivudine Monotherapy Prior to OLT (\*Mean or Median. NR; not reported.)

Authors	N=	Duration of Therapy* (months)	Negative HBV DNA (%)	Resistant Mutants (%)	Reference
Grellier, et al.	17	> 1	100	NR	42
Markowitz, et al.	10	2.7	100	NR	43
Villeneuve, et al.	35	19	100	25	44
Lo, et al.	31	3.2	63	NR	45
Perrillo, et al.	30	29	74	22	46
Yao, et al.	23	13	100	10	47
Seehofer, et al.	17	7.2	88	18	48
Rosenau, et al.	19	12	NR	10.5	49
Marzano, et al.	33	16	73	3	15
Fontana, et al.	162	16	67	11	50
Andreone, et al.	25	4.5	92	8	51
Fontana, et al.	154	5.7	>80	27	52

patients with milder disease [50]. The Child-Turcotte-Pugh (CTP) score was the only variable significantly associated with pre-OLT death and prediction of OLT-free survival. In a prospective study of indefinite LAM pre-OLT therapy, 32 of 154 patients (21%) died and 25 of the 32 deaths occurred within 6 months of initiating therapy [52]. Bilirubin, creatinine and detectable serum HBV DNA were independent predictors of death within the 6 month period. In contrast, the estimated actuarial 3 yr survival for patients that survived  $\geq 6$  mo on therapy was 88%. Since rates of virological response to LAM were similar for patients who died or survived, both the initial and persistent severity of liver disease remain the best predictors of pre-OLT survival. Since liver allocation priority increases with liver disease severity in the U.S.A., LAM therapy does not jeopardize access to a donated organ.

## Adefovir Monotherapy

ADV is active against WT HBV, precore mutants and LAM-resistant strains [61]. In a study of 128 patients with decompensated cirrhosis who had failed LAM therapy while awaiting OLT, ADV treatment for a median of 18 weeks reduced the HBV DNA level by 2.2 log<sub>10</sub> by 4 week, by 4.1 log<sub>10</sub> after 24 weeks and improved the CTP score [62]. Patients with renal dysfunction required ADV dose reductions. Although no patient developed ADV resistance in the study, ADV resistant mutants [63] have been recently described in the post-OLT setting [35]. Neither the clinical nor virological impacts of ADV mutations have been defined. As noted earlier, ADV is an excellent therapy for pre-OLT patients with LAM-resistant infections [19,62].

## Tenofovir Monotherapy

Tenofovir disoproxil fumarate (TDF) is a nucleotide analogue that is FDA-approved for the treatment of HIV [64,65]. TDF also potently inhibits replication of WT and LAM-resistant HBV in infected patients but is not FDA-approved for this indication [58,66,67]. Since the antiviral effect of TDF is more rapid than that of ADV [68], it may be advantageous in patients with rapidly progressive disease or in those predicted to have a very short waiting period prior to OLT. Controlled trials of the safety and efficacy of TDF in pretransplant patients with WT and LAM-resistant infections should be performed.

## Entecavir Monotherapy

Entecavir (ETV), a deoxyguanine nucleoside analogue, is a potent antiviral agent for both WT and LAM-resistant forms of HBV [69] that reduces HBV DNA levels to a greater degree than LAM [70]. ETV is currently in phase III clinical trials in non-transplant patients, and ETV-resistant mutations have been reported in 2 patients to date [71]. Its future role in the treatment of pretransplant patients to eliminate HBV replication should be determined in future controlled trials.

## 5. Monotherapy to Prevent HBV Reinfection After Transplantation

### Hepatitis B Immune Globulin Monotherapy

Long-term use of HBIG in the late 1980s in Europe and in the early 1990s in the U.S.A. significantly reduced the rate of reinfection and improved both graft and patient survival [9-12]. Although mechanism(s) of action of passive immunoprophylaxis with polyvalent anti-HBs antibodies remain unclear, the primary hypothesis is that anti-HBs bound to the surface of infectious HBV prevents HBV-receptor-mediated uptake by hepatocytes. Thus, HBIG is administered first during the anhepatic phase of OLT and subsequent dose regimens are designed to maintain an effective concentration of opsonizing anti-HBs. Immediately post-OLT, when the amount of circulating HBV remains high, a target trough level of anti-HBs of 500 IU/L has been recommended [72]. Later, when

The impact of lamivudine therapy for 3 to 6 months prior to OLT on hepatic function and transplant-free survival have been analyzed in several studies [46,47,50,52,59,60]. In one study, long-term treatment of decompensated cirrhotics on the OLT waiting list improved both hepatic function and survival compared to untreated, historical controls [47]. However, a retrospective analysis of LAM treatment of 309 patients listed for OLT showed no overall benefit in mortality before OLT or duration of transplant-free survival, except for

extrahepatic sites of replication become the source of HBV, a lower trough level of 100-150 IU/L has been considered protective if maintained indefinitely [7,72]. In the initial multicenter, European report, the rate of recurrent infection in patients receiving HBIG was directly correlated with the amount of HBV replication prior to and after OLT, being least in patients transplanted with fulminant hepatitis B (17%) and greatest in cirrhotics (67%) [9]. The rate of reinfection in patients receiving HBIG who were transplanted with fulminant hepatitis delta virus (HDV) infection and HDV cirrhosis was 40% and 32%, respectively [9]. In patients with active HBV replication pre-OLT, reinfection could be prevented by using higher doses of HBIG to maintain anti-HBs levels > 500 IU/L [10,11]. Overall, HBIG immunoprophylaxis reduced reinfection rates for cirrhotic patients to 16-35% in the presence of replicating HBV pre-OLT and to 0-15% in the absence of replication [9,11,12,28]. In Europe, an intravenous formulation of HBIG made infusion the preferred route [9]. Intramuscular formulations available in the U.S.A. [73] were most often infused, but intramuscular injections were also effective [74,75]. The need to monitor trough anti-HBs levels can be overcome by using a fixed dose of 10,000 IU once monthly [10]. However, monitoring of serum anti-HBs trough levels to define variability in immunoglobulin catabolism permits individualized dosing and significant cost savings.

HBIG therapy is safe and most adverse events have primarily been ascribed to the intravenous administration of intramuscular preparations [10,72]. A report of mercury toxicity in one patient has not been verified by others [76]. Unfortunately, the indefinite administration of HBIG remains expensive, and repeated measurements of trough anti-HBs levels add to the costs.

Despite HBIG immunoprophylaxis, late reinfection occurs, especially in patients with active pre-OLT replication of HBV. Late reinfections can be caused by failing to maintain adequate anti-HBs levels or by emergence of escape mutations, resulting selective pressure of anti-HBs. The primary escape mutation is G145R in the small surface protein "a" determinant that conformationally prevents anti-HBs binding [31,32,77]. Once HBIG is discontinued, WT HBV reemerges [31].

### Lamivudine Monotherapy

The goal of LAM monotherapy after OLT is to prevent reinfection of the allograft by inhibiting HBV replication in extrahepatic sites. Unfortunately, post-OLT monotherapy has been associated with reinfection with LAM-resistant YMDD mutants in 23-50% of patients, with increased mortality in some [42,45,46,78,79]. Thus, LAM monotherapy for post-OLT prophylaxis has been abandoned in favor of combination therapies.

## 6. Combination Therapies to Prevent HBV Reinfection After Transplantation

### Hepatitis B Immune Globulin and Lamivudine

The combination of LAM therapy pre- and post-OLT with HBIG post-OLT has become the standard of care for most liver transplant programs (Table 2). Multiple studies showed that the mean reinfection rate was only 5.2% (range 0-18%) after 1 to 2 years, [14,15,18,28,43,48,49,75,80,81]. Importantly, using highly sensitive PCR, circulating HBV DNA was undetectable in most patients after OLT [7,28,82]. The mechanism(s) contributing to the efficacy of combination LAM and HBIG remain poorly defined. Postulated mechanisms include the synergy of: 1) LAM reducing HBV replication and altering synthesis of HBsAg necessary for generation of HBIG escape mutations and 2) HBIG preventing the receptor-mediated entry of HBV into hepatocytes and extrahepatic cells required for production of escape mutations in the YMDD motif. In addition to efficacy, combination therapy is more cost effective because the dosage of expensive HBIG can be reduced [14,49]. Combination therapy also permitted effective conversion of a high dose intravenous HBIG regimen to a lower dose intramuscular regimen in 98% of patients [74]. A recent study demonstrated efficacy and further cost reductions as a result of injecting HBIG only when anti-HBs levels fell below 70 IU/L [83]. Given differences in HBIG preparations and variations in their use, it is important to note that the optimal protocol for safety, efficacy and cost of combination LAM and HBIG prophylaxis has not been defined.

**Table 2.** Effect of Combination Therapy with HBIG and Lamivudine to Prevent HBV Reinfection After OLT. (IV, intravenous; IM, intramuscular, NR, not reported.)

Authors	N=	Pre-OLT Duration* of LAM (mos)	HBV DNA Negative at OLT (%)	HBIG Route of Administration	HBV Reinfection (%)	Reference
Markowitz, et al.	14	3	93	IV	0	43
Yao, et al.	10	8.6	80	IV then IM	10	75
Yoshida, et al.	7	NR	100	IM	0	80
Angus, et al.	37	3.2	NR	IM	3	18
Marzano, et al.	33	4.6	100	IV	4	15
McCaughan, et al.	9	0	NR	IM	0	81
Rosenau, et al.	21	4.6	77	IV	10	49
Roche, et al.	15	4.6	73	IV	7	28
Han, et al.	59	NR	NR	IV	0	14
Seehofer, et al.	17	10.6	71	IV	18	48

Development of LAM-resistant mutants during LAM monotherapy pre-OLT (Table 1) complicates analysis of the benefits of combination LAM and HBIG therapy post-OLT, since most patients with LAM resistance pre-OLT have received LAM and HBIG combination therapy after OLT (Tables 1 and 2). One such patient had not developed reinfection 32 months after OLT [56], while two patients rapidly developed reinfection 13 and 75 days post operatively [84]. ADV treatment of 128 pre-OLT patients with LAM resistance showed undetectable HBV DNA (<400 copies/ml) in 81% of those treated for 48 weeks, and 50-83% showed concurrent improvement in liver tests [62]. These reports indicate that ADV should be used once LAM resistance is detected pre-OLT and that combination ADV and HBIG be used after transplantation.

## Hepatitis B Immune Globulin and Ganciclovir

Intravenous ganciclovir failed to provide additional prophylaxis against HBV reinfection in patients receiving HBIG [85] and should no longer be used.

## Hepatitis B Immune Globulin and Adefovir

Controlled trials of this combination therapy have not been reported, but the lower incidence of escape mutations to ADV [35] compared to LAM enhances the rationale for such studies.

## 7. Sequential and Modified Combination Therapies

To assess the reinfection rate among low risk patients receiving HBIG, patients were randomized to continue HBIG or to discontinue it and begin LAM [86]. Low risk was defined as an absence of detectable HBV DNA at the time of OLT and absence of reinfection for a minimum of 6 months post-OLT. After one year, reinfection occurred in 20% of patients in each group, but the finding of circulating HBV DNA by PCR in 2 of 11 receiving HBIG and 5 of 10 receiving LAM suggests that reinfection would be likely in additional patients with longer observation. Discontinuation of HBIG from a combination regimen of HBIG and LAM was also studied in 14 randomly selected patients from a group of 29 who were HBV DNA negative at the time of OLT (17 induced by LAM pre-OLT) and had received combination therapy for one month [87]. Although none of the patients developed clinical reinfection during 18 months of observation, HBV DNA and polymerase mutations were detected in both groups. In a non-randomized study, no reinfections were identified after 12 months in 16 patients who were treated with LAM monotherapy after having received HBIG for 24 months [88]. Despite the advantages of ease of patient care and cost reduction, discontinuation of HBIG remains risky because there are no definitive tests to identify patients have cleared HBV from liver and plasma, and once reinfection occurs, HBIG cannot be reinstated. Indeed, HBV DNA has been detected in the liver, serum or leukocytes in 50% of HBsAg-negative patients treated for 10 years with HBIG prophylaxis [28] and among patients treated with combination HBIG and LAM [15,86].

## 8. Manipulation of the Immune Response

**Adoptive Transfer of HBV Immunity from Donor Livers:** Effective adoptive transfer of humoral immunity to hepatitis B was first demonstrated in recipients of bone marrow transplants from immune donors [89,90]. Transplantation of livers from HBV vaccinated woodchucks into HBV-infected recipients also has been shown to reduce or delay severity of reinfection, presumably due to the effects of HBV-specific memory cells among passenger leukocytes [91]. An initially low recurrence rate in a Chinese cohort receiving LAM monotherapy was hypothesized to be due to transplantation of passenger leukocytes in HBV-immune donors that produced anti-HBs in the recipients [45]. A recent report ascribed the successful elimination of a de novo HBV infection post-OLT with development of anti-HBs to the fact that the liver donor had been immunized against hepatitis B [92].

**Vaccination After Transplantation:** The prospect of generating active immunity against HBsAg epitopes remains an intriguing strategy that could obviate the need for passive immunoprophylaxis. Following replacement of HBIG with HBV vaccination, 14 of 17 responders (anti-HBs levels of 10-100 IU/L) did not develop reinfection after a median observation period of 14 months (range 3-50 months) [93]. In contrast, discontinuation of HBIG with triple course of vaccine produced detectable anti-HBs levels in only 18% of recipients in another study [94]. HBV vaccination of pediatric patients post-OLT resulted in detectable anti-HBs in 17 or 19 (89%) [95]. Among 9 patients who received livers from anti-HBc-positive donors, anti-HBs developed in 7 and only 1 of the non-responders developed de novo HBV infection. New strategies to enhance immunogenicity of hepatitis B vaccines in immunosuppressed patients post-OLT also have been reported. Repeated immunization of patients receiving HBIG who were HBV DNA negative prior to OLT with multiple doses of recombinant HBV vaccine emulsified in novel adjuvants resulted in substantial anti-HBs levels (range 721-83,121 IU/L) in 80% and permitted discontinuation of HBIG [96]. Although preliminary, these results provide proof of principle that HBV vaccination can generate protective levels of anti-HBs in immunosuppressed patients.

**Immunosuppressive Regimen:** The majority of studies of the prevention of HBV reinfection have been from centers using a combination of steroids and either cyclosporine or tacrolimus as immunosuppression. Early steroid withdrawal has been considered desirable because it limits the duration of stimulation of the glucocorticoid response element in the HBV genome [97]. Although rapid withdrawal of steroids can be achieved [98], its impact on the incidence and timing of HBV reinfection has not been systematically studied. The increasing use of nucleoside and nucleotide therapies to eliminate HBV replication prior to OLT and the effectiveness of post-OLT preventative strategies despite immunosuppression argue against an urgent need for such studies.

## 9. Prevention of Transmission from Isolated Anti-HBc Positive Donor Livers

Because of the shortage of deceased donor organs, livers from isolated anti-HBc-positive donors (negative for HBsAg and anti-HBs) are being routinely transplanted into HBV-naïve recipients [99]. In the absence of preventative measures, HBV infection occurred in 50% to 78% of such recipients in Spain [20] and the U.S.A. [21], respectively. However, livers from anti-HBc-positive donors can be successfully used without reinfection if recipients receive prophylactic therapy with a combination of HBIG and LAM [100,101] or LAM monotherapy [102]. Recent reports also indicate that anti-HBc positivity in the donor is not a contraindication for live donor liver transplantation when effective prophylaxis is given [103,104].

## 10. Therapy for Established Reinfection After Transplantation

**Lamivudine and Adefovir:** As discussed above, the majority of hepatitis B OLT recipients are currently treated with LAM preoperatively (Table 1) and a combination of HBIG and LAM postoperatively (Table 2). Prolonged therapy with LAM pre-OLT results in a progressive risk of developing resistant YMDD mutants post-OLT [42,45,46,78,79]. The effectiveness of ADV treatment of LAM-resistant mutations has been reported in patients with significant reinfections with YMDD mutants post-OLT [62,105]. Thus, ADV treatment should be started as soon as YMDD mutations are identified pre- or post-OLT. Since ADV resistance also has been identified in an OLT recipient [35], serum HBV DNA should be serially monitored in patients treated long-term with ADV.

**Tenofovir:** TDF is a potent inhibitor of both WT and LAM-resistant HBV replication but is not FDA-approved for this indication [58,66-68]. The accelerated onset of antiviral activity of TDF against HBV compared to ADV [66] suggests that it should be considered for patients with rapidly progressive reinfections. Controlled trials of safety and efficacy in patients with reinfections should be performed.

**Entecavir:** ETV is also a potent inhibitor of both WT and LAM-resistant forms of HBV [106,107]. ETV was superior to LAM in reducing HBV DNA in patients with chronic hepatitis B, suggesting a potential role in the treatment of severe reinfections [70]. However, the role of ETV in the treatment of HBV post-OLT has not been determined in controlled trials.

**Alpha Interferon:** Although IFN therapy is difficult to tolerate and manage post-OLT, it has been successfully used to treat HBV reinfections [108-110]. Using standard TIW dosing for a median of 23.5 weeks, 4 of 14 (29%) reinfected patients had a sustained virological response with undetectable HBV DNA and 2 (14%) had seroconversion of HBeAg [110]. IFN treatment of LAM-resistant reinfections in 4 patients resulted in reduction of HBV DNA levels in all, loss of detectable HBV DNA in 3 and sustained virological responses in 2 [108]. Overall these favorable results do not outweigh the liabilities of IFN treatment of reinfections compared to the safety and tolerability of nucleoside and nucleotide agents.

**Ganciclovir:** Intravenous ganciclovir persistently inhibited HBV replication in reinfected patients post-OLT [111], but its overall efficacy was poor [85,111,112]. It is now only of historical interest.

## 11. Treatment of De Novo HBV Infections

Unvaccinated, HBV-naïve patients are at risk of acquiring hepatitis B post-OLT. In addition, transplantation of livers harboring occult HBV and those from donors with isolated anti-HBc-positivity represent additional risks of infection in naïve transplant recipients. Although famciclovir therapy has been reported to be beneficial [113], de novo HBV infections after OLT [24,114] should be treated with FDA-approved agents specific for HBV. Both LAM [115] and ADV [92] have been effective.

## 12. Future Directions

Development of new antiviral agents to treat HBV infection promises to provide a greater choice of effective medications and new opportunities to study combination therapies to eliminate HBV replication prior to after OLT. The goals of such combination therapies would include not only safety and antiviral efficacy, but elimination of the risk of viable escape mutations. Since patients without HBV replication prior to OLT have the lowest risk of reinfection, the dominant strategy will be the use of antiviral agents alone or in combination to terminate HBV replication. The effectiveness of LAM monotherapy pre- and post-OLT represents proof of principle that combination antiviral therapies post-OLT should be capable of preventing reinfection from extrahepatic reservoirs of HBV if escape mutants do not emerge. If effective oral therapies are developed, passive immunoprophylaxis with HBIG will likely be reserved for patients with residual circulating HBV DNA at the time of OLT. Increased sophistication in detecting occult HBV in liver biopsies, circulating leukocytes and extrahepatic sites may ultimately be exploited to identify patients who no longer require post-OLT therapy. Further development of HBV vaccines, especially those containing the product of the PreS1 ORF, and more potent adjuvants may permit effective therapeutic immunization of post-OLT patients, despite immunosuppression. However, the greatest achievement would be the resolve to provide worldwide immunization with HBV vaccine early in life to eradicate HBV infection and the need for transplantation for this indication.

## Conflict of interest

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