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REVIEW

Current therapeutic strategies for recurrent hepatitis B virus infection after liver transplantation

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Abstract

Hepatitis B virus (HBV)-related liver disease is the leading indication for liver transplantation (LT) in Asia, especially in China. With the introduction of hepatitis B immunoglobulin (HBIG) and oral antiviral drugs, the recurrent HBV infection rate after LT has been evidently reduced. However, complete eradication of recurrent HBV infection after LT is almost impossible. Recurrent graft infection may lead to rapid disease progression and is a frequent cause of death within the first year after LT. At present, the availability of new oral medications, especially nucleoside or nucleotide analogues such as adefovir dipivoxil, entecavir and tenofovir disoproxil fumarate, further strengthens our ability to treat recurrent HBV infection after LT. Moreover, since combined treatment with HBIG and antiviral agents after liver re-transplantation may play an important role in improving the prognosis of recurrent HBV infection, irreversible graft dysfunction secondary to recurrent HBV infection in spite of oral medications should no longer be considered an absolute contraindication for liver re-transplantation. Published reviews focusing on the therapeutic strategies for recurrent HBV infection after LT are very limited. In this article, the current therapeutic strategies for recurrent HBV infection after LT and evolving new trends are reviewed to guide clinical doctors to choose an optimal treatment plan in different clinical settings.

Key words: Therapy; Hepatitis B virus; Recurrent hepatitis B virus infection; Antiviral drugs; Liver transplantation

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INTRODUCTION

Hepatitis B virus (HBV)-related liver disease accounts for approximately 5%-10% of all liver diseases after liver transplantations (LT) performed each year in the United States and is the leading indication for LT in Asia[1,2]. It was reported that the recurrent HBV infection rate after LT is as high as 80%-100% without any prophylaxis[3,4]. The recurrent HBV infection rate has been decreased from 90% to approximately 30%-40% since the introduction of hepatitis B immunoglobulin (HBIG)[5,6]. With the advances in oral antiviral drugs, combined treatment with HBIG and lamivudine (LAM), recommended by many centers, has achieved encouraging outcomes, with the recurrent HBV infection rate reduced to less than 10% during a follow-up period of 1-2 years[7-11].

However, combined treatment with HBIG and LAM cannot control recurrent HBV infection. Recurrent graft infection may lead to rapid disease progression and is a frequent cause of death within the first year after LT[12].

Furthermore, the incidence of acquiring *de novo* HBV infection after LT in patients who are negative for hepatitis B surface antigen (HBsAg) is 1.7%-3.5%, and patients with *de novo* HBV infection are also at a risk for severe progressive liver injury[13-15]. The aggressive clinical course is probably due to stimulation of viral replication and direct cytotoxicity of HBV under immunosuppressive therapy. Therefore, suppression of HBV replication is paramount to prevent disease progression in the transplanted liver.

Unfortunately, almost all published reviews focusing on the prophylactic strategies against recurrent HBV infection after LT, have drawn less prominence to the treatment of recurrent HBV infection in recipients after LT. Published reviews, focusing on the therapeutic strategies against recurrent HBV infection after LT, are very limited, and almost all of them are already nearly obsolete. In the following, the current therapeutic strategies for recurrent HBV infection after LT and evolving new trends are reviewed.

INTERFERON

In the pre-LAM era, interferon α is a common therapeutic option for patients with recurrent HBV infection after LT. However, with the advent of LAM, it has not been used as a first-line treatment drug. Patients using interferon α have a lower efficacy and a higher risk of precipitating allograft rejection than those using LAM[16,17]. Furthermore, treatment of recurrent HBV infection after LT with interferon α can lead to side effects such as neutropenia.

LAM

LAM can potentially inhibit HBV replication by competitively suppressing the reverse transcriptase and termination of proviral DNA chain extension, and has been used in treatment of recurrent HBV infection, with an excellent safety profile in both compensated and decompensated cirrhotic patients. The use of LAM in treatment of recurrent HBV infection after LT has shown promising results as is shown in a multicenter North American study on 52 patients with chronic hepatitis B after LT, demonstrating that use of LAM for 52 wk can result in loss of serum HBV DNA in 60%, undetectable hepatitis B e antigen (HBeAg) in 31%, undetectable HBsAg in 6%, normalization of serum alanine transaminase (ALT) levels in 71% of patients, respectively[18]. The results from other studies[19-27] are summarized in Table 1, showing that LAM can suppress HBV DNA to undetectable levels in 32.5%-100%, anti-HBeAg seroconversion in 4.2%-100%, and anti-HBsAg seroconversion in 0%-83.3% of patients, respectively, after 4.6-36 mo of treatment. Notably, use of LAM in treatment of *de novo* HBV infection or acute recurrent HBV infection of the graft after LT tends to effectively suppress HBV DNA, and converse serum anti-HBeAg and anti-HBsAg.

However, the major factor limiting the use of LAM in treatment of graft HBV infection after LT is the development of mutations in thyrosine-methionine-aspartate-aspartate (YMDD) motif of the HBV DNA polymerase gene, which confers resistance to LAM. In non-immunosuppressed patients, the LAM resistance rate is 15%-20%[28]. LAM resistance can be detected in 45% of immunosuppressed patients within the first year of treatment[29,30]. It has been reported that YMDD mutation occurs in 26.9%, 27.3%, 29.4% and 62.5% of patients with recurrent HBV infection[18,20,22,24] after 12, 15, 21 and 36 mo of treatment with LAM, respectively. It has also been reported that YMDD mutation occurs in patients with *de novo* HBV infection after LT, in 0%, 0% and 14.3% of patients with recurrent HBV infection[19,21,27] after 4.6, 11 and 24.5 mo of treatment with LAM, respectively. One possible explanation for it is the short-term use of LAM in patients with *de novo* HBV infection and low HBV-DNA levels at the acute phase of *de novo* HBV reactivation.

Available data from the literature regarding the outcomes secondary to YMDD mutation are controversial. Perrillo *et al*[18] reported that the YMDD mutant virus is not consistently associated with hepatic disease progression, whereas elevated serum ALT can be frequently observed at the time when serum HBV DNA becomes detectable again, and the mean ALT values after breakthrough often remain below the pretreatment values. However, McCaughan *et al*[31] reported that patients infected with procure mutant strains of HBV develop drug resistance or liver failure after 11 mo of rescue therapy with LAM. Mutimer *et al*[32] also demonstrated that LAM-resistant phenotype can cause severe graft damage. Hence, long-term, randomized, blinded, and controlled clinical trials are needed to further observe the clinical outcomes following LAM resistance.

In summary, LAM therapy results in not only a loss of viral replication markers in serum and an improved hepatic biochemical profile, but also improvement or stabilization in liver histology. However, LAM resistance and its possible accompanying clinical deterioration have limited its long-term use in treatment of recurrent HBV infection after LT.

Adefovir dipivoxil

Adefovir dipivoxil (ADV), a nucleotide analog that selectively inhibits viral polymerases and reverse transcriptase, is effective against both negative and positive HBeAg[33-36]. Furthermore, it has been shown that ADV has an excellent activity against wild-type as well as LAM-resistant HBV strains[37-41], suggesting that ADV contributes to the development of LAM-resistant mutants and *de novo* LAM-resistant HBV infection after LT. Schiff *et al*[42] in a landmark multicenter study showed that PCR DNA levels are decreased with a 1-year survival rate of 93%, undetectable serum HBV DNA, normal serum ALT, albumin, bilirubin and prothrombin time in 34%, 49%, 76%, 75% and 20% of patients, respectively, after 24 and 48 wk of treatment with ADV. Four years later, Schiff *et al*[43] further showed that the serum HBV DNA

Table 1 Use of LAM in treatment of recurrent HBV graft infection after LT

Author (Ref.)	*n*	Pre-treatment		Treatment duration (mo), mean (range)	LAM dosage (mg/d)	Post-treatment			
		HBV DNA+ (%)	HBeAg+ (%)			HBV DNA negative following treatment (%)	HBeAg seroconversion (%)	HBsAg seroconversion (%)	Development of LAM resistant mutants (%)
Ben-Ari *et al*[20]	8	100	62.5	36 (24-50)	100	32.5	20	0	62.5
Umeda *et al*[19]	6[1]	100	NA	4.6 (0.7-11)	100	NA	NA	83.3	0
Castells *et al*[21]	7[1]	100	85.7	24.5 (12-49)	100	71.4	50	14.3	14.3
Fontana *et al*[22]	33	94	75	21 (4-36)	NA	72	4.2	0	29.4
Andreone *et al*[23]	11[2]	100	18.2	17 (8-27)	100	100	100	9.1	27.3
Perrillo *et al*[18]	52	90.4	86.5	12	100	68.1	11.1	3.8	26.9
Nery *et al*[24]	11	90.9	NA	15 (13-21)	NA	90	NA	NA	27.3
Fischer *et al*[25]	12	100	NA	10.5 (5-43)	100-150	83.3	NA	NA	NA
Rayes *et al*[26]	41	100	NA	12-36	150	75.6	NA	NA	24.4
Malkan *et al*[27]	4[1]	100	75	11 (4-28)	100-150	100	NA	25	0

[1]All patients had *de novo* HBV infection after LT; [2]This study reported treatment of acute recurrent graft HBV infection. NA: Not available; HBV: Hepatitis B virus; LT: Liver transplantation; HBeAg: Hepatitis B e antigen; HBsAg: Hepatitis B surface antigen; LAM: Lamivudine.

Table 2 Use of ADV in treatment of recurrent graft infection after LT

Author (Ref.)	*n*	Pre-treatment		Treatment duration (mo), mean (range)	ADV dosage (mg/d)	Concurrent LAM use	Post-treatment			
		HBV DNA+ (%)	HBeAg+ (%)				HBV DNA negative following treatment (%)	HBsAg seroconversion (%)	ALT normalization (%)	Development of ADV mutants
Akyildiz *et al*[44]	11	81.8	9.1	18 (6-48)	10	Yes	77.8	11.1	81.8	None
Limquiaco *et al*[45]	7	100	71.4	35 (22-48)	10	Yes	28.6	20	86	None
Bárcena *et al*[46]	42	100	71.4	21.5 (12-31)	10	No	64	20	70.5	None
Herreros de Tejada Echanojáuregui *et al*[47]	7	100	71.4	11	10	Yes[1]	42.9	20	NA	None
Neff *et al*[48]	9	100	77.8	30 (6-48)	10	No	0	57.1	NA	None

[1]LAM was changed to ADV in 5 patients and ADV was added to LAM in the other 2 patients. ADV: Adefovir dipivoxil.

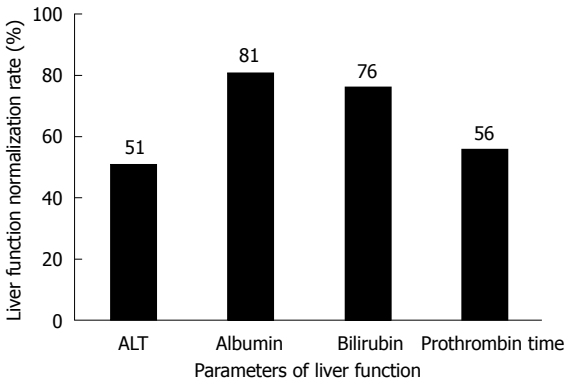

Figure 1 Alanine transaminase (ALT), albumin and bilirubin levels and prothrombin time 48 wk after adefovir dipivoxil treatment[43].

levels are undetectable in 40%, 65% and 78% of patients with recurrent HBV infection and LAM resistance 48, 96 and 114 wk after ADV treatment (10 mg, once a day), respectively, as well as loss or seroconversion of HBeAg in 31% and 11% of patients by week 48, and in 58% and 34% of patients by week 96. Liver function and other parameters after treatment with ADV are shown in Figure 1. Other studies[44-48] are summarized in Table 2. Toniutto *et al*[38] reported that ADV plus LAM can achieve favorable outcomes of HBsAg seroconversion and undetectable HBV DNA in patients with *de novo* graft HBV infection and LAM resistance.

Mildly elevated serum creatinine level may occur after treatment with ADV, especially with calcineurin inhibitors, but only a small number of patients require dose adjustment, and even discontinuance. However, renal function should be regularly monitored, with dose adjustments based on renal function, as necessary.

In short, ADV is a safe and effective treatment option for recurrent HBV infection, especially as a salvage treatment for recurrent HBV infection due to LAM resistance.

Entecavir

Entecavir (ETV), a very potent anti-HBV selective guanosine analogue, approved by the US FDA in 2005, can be used in treatment of chronic HBV infection. Unfortunately, few reports are available on ETV in treatment of recurrent HBV infection. Most data concerning its efficacy and safety are obtained from patients with no LT. It was reported that 0.5 mg of ETV or 100 mg of LAM, once daily for 48 wk, can improve the histology

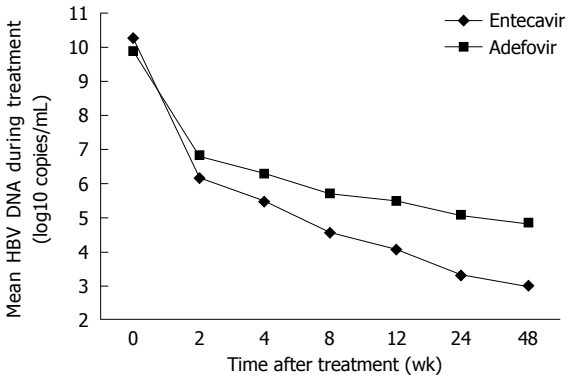

Figure 2 Mean serum hepatitis B virus (HBV) DNA level in patients after entecavir (ETV) and adefovir (ADV) treatment[53].

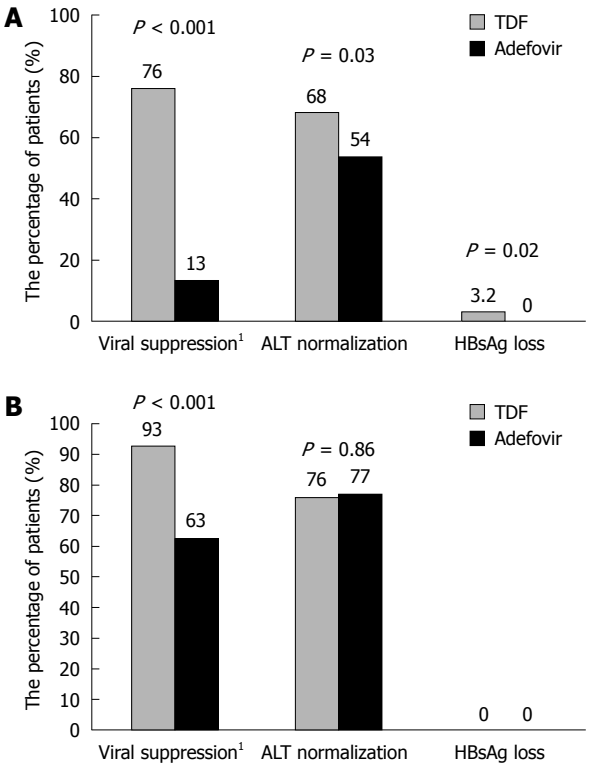

Figure 3 Viral suppression, ALT normalization and hepatitis B surface antigen (HBsAg) loss in hepatitis B e antigen (HBeAg)-positive (A) and HBeAg-negative (B) patients after tenofovir disoproxil fumarate (TDF) and adefovir treatment[61]. [1]HBV DNA level of less than 400 copies/mL.

in 72% and 62% of patients, respectively, with serum HBV DNA undetectable in 67% and 36% of patients, respectively, and normal ALT in 68% and 60% of patients, respectively, and no evidence of viral resistance to ETV[49]. It has been shown that 0.5 mg of ETV or 100 mg of LAM, once daily for 48 wk, can also achieve favorable outcomes in patients with nucleoside-naive HBeAg-negative chronic hepatitis B[50], suggesting that the histologic, virologic and biochemical improvement rates are significantly higher after ETV treatment than after LAM treatment, in patients with nucleoside-naive HBeAg-positive or -negative chronic hepatitis B, with no evidence of viral resistance to ETV, which is consistent with the findings in other studies[51-53]. The mean decrease in serum HBV DNA after 2, 4, 8, 12, 24 and 48 wk of ETV and ADV treatment in patients is shown in Figure 2. A recent study demonstrated that ETV therapy is safe and efficient for recipients with ADV-resistant HBV infection[54].

ETV resistance is associated with the LAM-resistance substitutions M204V/I and L180M in combination with an additional substitution at residues T184, S202 or M250 in the reverse-transcriptase region of HBV polymerase[55]. In other words, ETV is associated with a high genetic barrier to resistance requiring multiple mutations for resistance development. In nucleoside-naïve patients, the probability of developing resistance to ETV remains consistently low (< 1.2%) even after 96 wk of treatment[56]. By contrast, ETV gives rise to ETV-resistant mutants in patients with LAM resistance. The rate of ETV resistance in LAM-resistant patients 4 years after treatment of may reach 35%[57], which is due to a particular selection mode of ETV strains that follows a 2-step process, with the selection of primary resistance mutations at position M204V/I (which are also resistant to LAM) followed by the addition of secondary resistance mutations on the same viral genomes[58]. Once these secondary substitutions occur, high-level resistance to ETV occurs. Therefore, the high probability of resistance to long-term ETV in LAM resistant patients with no LT suggests that ETV is not a good choice for LAM-resistant patients after LT, although ETV has been tried in some LAM resistant patients after LT[54]. However, ETV can be used in non-LAM resistant patients, due to its great potency, high genetic barrier and absence of nephrotoxicity. More data are urgently needed to confirm the safety and efficacy of ETV after LT.

Tenofovir disoproxil fumarate

Tenofovir disoproxil fumarate (TDF), a nucleotide analogue, inhibits viral polymerases by direct binding to DNA or by terminating the DNA chain due to the absence of a requisite 3' hydroxyl on the tenofovir molecule[59]. In 2001, TDF was licensed for HIV therapy as a potent inhibitor of HIV replication. Subsequently, it has been proved to be a potent and selective anti-HBV agent *in vitro*[60]. Several clinical studies have currently confirmed the efficacy of TDF in suppressing HBV replication. Marcellin *et al*[61] showed that the antiviral efficacy of TDF is higher than that of ADV with no resistance mutation in patients with HBeAg-negative or HBeAg-positive chronic HBV infection. Detail data regarding viral suppression, liver function improvement, and serologic response are shown in Figure 3. It has been shown that TDF has an excellent antiviral activity against both wild-type and LAM-resistant HBV both *in vitro* and *in vivo*[62,63]. Furthermore, TDF shows a stronger antiviral effect than ADV on LAM-resistant HBV[64,65]. Hann *et al*[66] reported that the mean level of HBV DNA is 1.5 ± 1.0 log10 copies/mL and 4.3 ± 2.2 log10 copies/mL, respectively, in patients with LAM

resistance after treatment with TDF and ADV. A recent study demonstrated that TDF plus LAM can safely and markedly suppress HBV replication in patients with or without resistance to ADV[67].

The daily TDF dose (300 mg) has been approved as a standard dose for controlling HBV infection. To reduce the cost of therapy, a low TDF dose (75 mg) can be used to control HBV viremia in patients with chronic HBeAg-negative hepatitis B, which can more effectively inhibit HBV replication than ADV at the standard dose[68]. However, further studies are needed to determine its efficacy and safety in a larger number of HBeAg-positive subjects.

Only 2 reports are available on TDF-related mutations conferring resistance to TDF[69,70]. Transfection experiments showed that rtA194T mutation alone can result in a 7.6-fold decrease in susceptibility to TDF, but rtA194T mutation in combination with ADV-resistant mutations can lead to a more than 10-fold decrease in susceptibility to TDF[70]. However, TDF susceptibility to rtA194T mutation is not consistent with its clinical significance. Since 2005, ADV-resistance mutations (rtN236T, rtA194T, rtA181V) have not caused a significant change in TDF susceptibility[71,72]. Only one study is available on the application of TDF in treatment of recurrent HBV infection after LT[73]. Although TDF can significantly decrease LAM-resistant HBV variant replication after LT, further studies are needed to determine its efficacy and safety profile with a long follow-up time and a large cohort of patients.

RETRANSPLANTATION

With the advent of new antiviral drugs such as ADV, ETV and TDF, satisfactory outcomes can be achieved in patients with recurrent HBV infection by suppressing viral replication. However, some patients with irreversible graft dysfunction secondary to recurrent HBV infection still need a second LT to replace the primary graft[74,75]. To date, second LT accounts for 5%-22% of all LTs in adults[76]. Samuel *et al*[77] reported that recurrent graft HBV infection is the direct cause of death in patients with hepatitis B after a second LT. Crippin *et al*[78] showed that the mortality rate of patients with recurrent HBV infection is 95% after a second LT, which is consistent with the findings in other studies[12,79-81].

Ishitani *et al*[82] showed that long-term HBIG therapy can continuously maintain a serum anti-HBs level > 500 IU/L and prevent recurrent HBV infection in 86% of patients after a second LT. Roche *et al*[80] reported that prophylactic intravenous ganciclovir can maintain an anti-HBs titre greater than 500 IU/L, with a satisfactory prognosis of all patients after a second LT. Lo *et al*[83] demonstrated that combined injection of ADV, LAM and HBIG can maintain an anti-HBs titre greater than 100 IU/L in patients with LAM-resistant HBV mutants after a second LT.

In summary, recurrent HBV infection after a primary LT should no longer be considered an absolute contraindication for a second LT. Combined HBIG and antiviral agents may play an important role in improving the prognosis of patients with recurrent HBV infection after a second LT. Further randomized study is needed to definitely confirm it.

Table 3 Summary of recommended therapeutic strategies for recurrent HBV infection after LT

Clinical setting	Recommended first line therapies	Recommended second line therapies
De novo HBV infection, wild-type HBV infection	LAM for short-term therapy; ADV for long-term therapy	ETV, TDF
LAM resistance	ADV, ADV + LAM	TDF
ADV resistance	ETV	TDF + LAM
Irreversible graft dysfunction	SLT	

ETV: Entecavir; TDF: Tenofovir disoproxil fumarate; SLT: Second liver transplantation.

CONCLUSION

The emergence of new oral medications, especially nucleoside or nucleotide analogues such as ADV, ETV and TDF, further increases our ability to treat recurrent HBV infection after LT. By recognizing the efficacies and features of such drugs, various therapeutic strategies, according to different clinical settings, have been recommended to control the recurrent graft infection after LT (Table 3). For the *de novo* or wild-type HBV infection after LT, long-term use of LAM is limited by the high risk of developing mutations in YMDD motif. Hence, ADV is the first choice in this setting, if needing long-term administration. For the LAM-resistant HBV infection after LT, ADV, administered in combination with LAM or as a monotherapy, appears to be safe and effective in this setting. Theoretically, "add therapy" may minimize the risk of resistance, but needs long-term, randomized, blinded, controlled clinical trials to further confirm it. In addition, ETV is not a good choice for LAM-resistant patients after LT because of its high probability of resistance in patients with LAM resistance without LT. ETV therapy for ADV-resistant HBV infection after LT is safe and efficient in this setting. Additionally, combined TDF and LAM therapy may be an alternative approach based on its favorable therapeutic effects in patients without LT. However, no or few data are available on the efficacy of ETV and TDF in patients after LT. Further clinical trials are needed to evaluate their efficacy and safety in this special setting. Second LT is the only rescue procedure for patients with irreversible graft dysfunction secondary to recurrent HBV infection. Since combined HBIG and antiviral agents may play an important role in improving the prognosis of patients with recurrent HBV infection after LT, recurrent HBV infection after a primary LT should no longer be considered an absolute contraindication for a second LT.

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