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Recent advances in prevention of hepatitis B recurrence after liver transplantation

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Abstract

Liver transplantation is the only effective treatment for hepatitis B virus (HBV)-related end-stage liver disease. However, without antiviral prophylaxis, the recurrence rate of hepatitis B is as high as 80%-100%, which leads to a 50% mortality rate in the first 2 years after liver transplantation. Combination therapy of hepatitis B immunoglobulin (HBIG) and lamivudine demonstrated a higher efficacy of prophylaxis and further reduced the rate of recurrence to < 10%. The strategy of HBIG combined with lamivudine has been the standard treatment in many centers. However, the high rate of lamivudine resistance and the many disadvantages of HBIG have compelled surgeons to reconsider the long-term efficacy of this strategy for the prevention of HBV reinfection. Recently, new nucleos(t)ide analogues, such as entecavir and tenofovir, have been approved as first-line monotherapies for the treatment of chronic hepatitis B infection. These antiviral medicines have replaced lamivudine as the first choice in the prevention of HBV recurrence after liver transplantation. Various therapies that are composed of entecavir, tenofovir, and lamivudine plus adefovir, with or without HBIG have been adopted in several liver transplant centers. This article reviews the recent advances in prophylaxis for the recurrence of hepatitis B after liver transplantation.

Key words: Liver transplantation; Hepatitis B recurrence; Hepatitis B immunoglobulin; Lamivudine; Entecavir; Tenofovir

Core tip: The strategy of hepatitis B immunoglobulin (HBIG) combined with lamivudine has been the standard treatment for the prophylaxis of hepatitis B virus recurrence after liver transplantation. However, the high rate of lamivudine resistance and the many disadvantages of HBIG have compelled surgeons to reconsider the long-term efficacy of this strategy for the prevention of hepatitis B virus reinfection. This review discusses new strategies for prophylaxis of the recurrence of hepatitis B after liver transplantation.

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INTRODUCTION

Hepatitis B infection is a major global health problem. More than 240 million people have been chronically infected, and more than 780000 people die every year due to the acute or chronic effects of hepatitis B[1]. Liver transplantation is the only effective treatment for hepatitis B virus (HBV)-related end-stage liver disease[2]. However, without antiviral prophylaxis, the recurrence rate of hepatitis B is as high as 80%-100%, which leads to a 50% mortality rate within the first 2 years after liver transplantation[3-5]. The introduction of hepatitis B immunoglobulin (HBIG) in the early 1990s has dramatically reduced the incidence of hepatitis B recurrence and has raised the survival rate after transplantation[6-8]. Subsequently, oral nucleos(t)ide analogues, such as lamivudine (LAM), were used in perioperative transplant patients. The combination of HBIG and LAM demonstrated a higher efficacy of prophylaxis and further reduced the recurrence rate to < 10%[9-12]. Until recently, the strategy of LAM combined with HBIG has been the standard of care of prophylaxis for the recurrence of HBV after orthotropic liver transplantation (OLT) in many liver transplant centers. However, the long-term use of HBIG has many disadvantages, including high cost, the need for lifelong monthly parenteral injections, headache, flushing, and chest pain[13,14] . In addition, the long-term use of both LAM and HBIG induces viral resistance, which leads to a high rate of recurrence after liver transplantation[15]. On the contrary, more potent nucleos(t)ide analogues with a higher genetic barrier, such as entecavir and tenofovir, have been used in liver transplant patients. Therefore, developing more effective therapies of prophylaxis for the recurrence of hepatitis B after liver transplantation is urgently needed.

NEW NUCLEOS(T)IDE ANALOGUES COMBINED WITH LONG-TERM HBIG TREATMENT

Entecavir

Entecavir, a guanosine nucleoside analogue with activity against HBV polymerase, is effective in both hepatitis B e antigen (HBeAg)-positive and -negative hepatitis B infected-patients[16]. In two phase Ⅲ trials, nucleoside-naïve HBeAg-positive or -negative patients with chronic hepatitis B (CHB) who received 0.5 mg of entecavir per day for 48 wk achieved a superior virological, histologic, and biochemical efficacy than the patients who received 100 mg per day of LAM[17,18]. Entecavir is an antiviral medicine with a high genetic barrier. The resistance is associated with the LAM-resistance substitutions M204 V/ I and L180 M in combination with an additional substitution at residue T184, S202 or M250 in the reverse-transcriptase region of the HBV polymerase[19-21]. In nucleoside-naïve patients, the probability of the development of resistance to entecavir remains consistently low (< 1.2%) even after 96 wk of treatment[20]. A recent article reported that the strategy that included entecavir yielded the most quality-adjusted life years (QALYs) for both HBeAg-positive and -negative patients compared with the strategies that encompassed "no treatment," or treatment with LAM, adefovir, or telbivudine[22]. Therefore, entecavir is not only effective but also cost-effective as an antiviral treatment. Recently, entecavir and tenofovir have been approved as first-line monotherapies for the treatment of CHB according to the practice guidelines of the EASL (European Association for the Study of the Liver) for the management of chronic hepatitis B[23]. The guidelines also proposed that a potent nucleos(t)ide analogue with a high barrier to resistance is recommended for all HBsAg-positive patients undergoing liver transplantation for HBV-related end-stage liver disease or HCC, to achieve the lowest possible level of HBV DNA before transplantation. With regards to the use of entecavir in the prevention of HBV reinfection after liver transplantation, one abstract in 2008 showed that entecavir, in addition to HBIG, was effective and tolerable in patients with HBV-related post-transplantation hepatic decompensation. However, only 9 patients were included in this study[24]. A study by Xi *et al*[25] compared the efficiency of entecavir with LAM in patients who received a liver transplant. Thirty patients with end-stage hepatitis B-related liver disease received entecavir, and 90 patients received LAM after liver transplantation. HBV reinfection was not detected in any patient at the time of the latest follow-up in the entecavir group. However, 10 patients were diagnosed with HBV reinfection in the LAM group (0% *vs* 11%, $P = 0.049$). It was concluded that entecavir was superior to LAM in the prevention of hepatitis B recurrence after liver transplantation. In recent years, many other articles that concern the efficacy of entecavir have been published. Different rates of recurrence of hepatitis B were reported in those articles. Kim *et al*[26] retrospectively assessed the clinical outcomes in 154 patients who received entecavir and HBIG after liver transplantation. A total of 5 patients (3.2%) were diagnosed with HBV reinfection without entecavir resistance. In 4 of those 5 patients, recurrence of HCC was detected prior to the recurrence of HBV. Recurrent HCC was an independent risk factor for the recurrence of HBV ($P = 0.06$). In a trial by Cai *et al*[27], no recurrence of HBV occurred in patients who received entecavir after liver transplantation during the median 41.2-mo follow-up period. However, 18 patients in the LAM group developed HBV reinfection during the median 38.5-mo follow-up period (0/63 *vs* 18/189, $P < 0.01$). Similar results were shown in a study by a Japanese group. Ueda *et al*[28] evaluated the efficacy and safety of prophylaxis with entecavir and HBIG in the prevention of hepatitis B recurrence after living-donor liver transplantation.

Twenty-six patients who received entecavir plus HBIG after liver transplantation were compared with 63 patients who received LAM and HBIG. No HBV recurrence was detected during the median follow-up period of 25.1 mo in the entecavir group, whereas the HBV recurrence rate was 4% at 3 years and 6% at 5 years in the LAM group. Hu *et al*[29] showed a lower hepatitis B recurrence rate in patients who received entecavir rather than LAM. A total of 145 patients were administered entecavir plus low-dose on-demand HBIG, and 171 patients in the control group received LAM plus HBIG. Two of the 145 patients in the entecavir group developed HBV reinfection with no evidence of viral resistance in the median 36-mo follow-up period. A total of 11 of 171 patients in the LAM group developed HBV reinfection, 3 of whom demonstrated HBV resistance in the median 77-mo follow-up period. Further analysis showed that HCC at the time of liver transplantation and low anti-HBs titer post-liver transplantation were independent risk factors for the recurrence of HBV infection. Perrillo *et al*[30] assessed the efficacy of entcavir together with various HBIG regimens after liver transplantation. Sixty-one patients with HBV-related liver disease took 1.0 mg of entecavir combined with various HBIG regimens. In the median 72-wk follow-up time, only 2 patients demonstrated positivity for HBsAg while HBV DNA remained undetected. Na *et al*[31] reported that 4 of 262 recipients who received entecavir combined with HBIG experienced a recurrence of HBV infection after liver transplantation during the median 49-mo follow-up period. Among the 4 patients with recurrence, three had received LAM followed by entecavir. They also showed that the incidence of pre-transplant HCC was significantly associated with the recurrence of hepatitis B. Currently, most liver transplant centers have converted to the combination of entecavir and low-dose HBIG as the standard treatment for the prevention of hepatitis B recurrence after liver transplantation.

Tenofovir

Tenofovir disoproxil fumarate, a nucleotide analogue, inhibits viral polymerases by directly binding to the DNA or by the termination of the DNA chain due to the absence of a requisite 3' hydroxyl on the tenofovir molecule[32,33]. It has been found to be efficient in the treatment of HBV infection in patients who have not received a liver transplant[34-37]. It was further shown that resistance to tenofovir did not emerge in patients in six years of follow-up time after transplant[38]. Together with entecavir, tenofovir has been recommended as the first-line therapy for patients with hepatitis B infection[23]. Studies regarding the efficacy of tenofovir in the prevention of hepatitis B recurrence after liver transplantation are limited. A small trial[39] reported that four patients received tenofovir plus HBIG with or without entecavir for the prevention of hepatitis B recurrence. After 12 mo, no hepatitis B recurrence was observed in these four patients. In a study by Teperman *et al*[40], 19 patients were administered emtricitabine/tenofovir combined with HBIG post-liver transplantation. No patient experienced a recurrence of HBV infection at 96 wk, and no tenofovir-related renal failure was observed in the study.

DISCONTINUATION OF HBIG FOLLOWED BY NUCLEOS(T)IDE ANALOGUE

HBIG plus a nucleos(t)ide analogue was the standard treatment for the prevention of hepatitis B recurrence. However, the long-term use of HBIG has many disadvantages, including high cost, the need for lifelong monthly parenteral injections, headache, flushing, and chest pain. Recently, more potent antiviral agents, such as tenofovir and entecavir, have been introduced which challenge the necessity of the long-term use of HBIG in combination therapy[41]. Many centers have adopted the strategy of treatment with HBIG for a finite period of time but in conjunction with one or two nucleos(t)ide analogues.

LAM alone

Although several studies have been performed to determine the efficacy of the withdrawal of HBIG with concurrent LAM treatment[42-45], the long-term effects of LAM treatment after HBIG withdrawal should be established due to the increasing resistance rate associated with the long-term use of this drug[15]. In a retrospective study by Tanaka *et al*[46], 132 patients who presented with positive HBsAg at the time of post-liver transplantation and received a nucleos(t)ide analogue with one year of HBIG post-transplant were included. A total of 97 patients received LAM + HBIG (LAM group) while 35 received a non-LAM nucleos(i)de analogue + HBIG. Recurrent hepatitis B was observed only in the LAM group during the follow-up period of 1752 d. In another randomized study by Buti *et al*[45], 29 patients with undetectable HBV DNA at the time of post-liver transplantation were randomized to receive HBIG with LAM for 1 mo followed by LAM (n = 14) or both drugs (n = 15) for 17 mo. After 18 mo of follow-up, all patients survived without recurrence of HBV. However, in the subsequent follow-up trial[46], 15% of these patients developed a recurrence of HBV infection after a mean follow-up period of 91 mo. Therefore, additional studies regarding HBIG withdrawal followed by treatment with a new nucleos(t)ide analogue other than LAM were conducted.

LAM and adefovir

In a trial conducted by Neff *et al*[47], the treatment strategy of HBIG and LAM was replaced with adefovir and LAM at 6 mo post-transplantation in 10 patients. After 31 mo of follow-up, no patients experienced a recurrence of hepatitis B. The cost of adefovir and LAM vastly outweighed that of HBIG and LAM ($7235 *vs* $110700 per year for adefovir/LAM and HBIG/LAM, respectively). An abstract published in 2007[48] showed that no recurrence of hepatitis B was observed during an 11.7-mo follow-

up period after the conversion from HBIG with LAM to adefovir with LAM one week after liver transplantation. The subsequent outcome of the study was reported in 2013. Gane *et al*[49] showed that all patients who received LAM and adefovir remained alive and healthy with no recurrence of HBV infection (defined as both detectable HBsAg and HBV DNA in the serum) after a median follow-up of 22 mo after transplantation. One patient who experienced a recurrence of HCC developed HBsAg positivity 41 mo after transplantation. Serological tests for HBV DNA in this patient remained negative throughout the follow-up period. Serum levels of HBsAg became undetectable again 1 mo after the excision of this metastasis. In another randomized study by Angus *et al*[50], 34 patients who received LAM together with low-dose HBIG who did not experience a recurrence of hepatitis B at least one year post-transplantation were enrolled. Patients were randomized to receive both adefovir and LAM (n = 16) or to receive the current standard of HBIG and LAM (n = 18). One patient in the adefovir/LAM group presented with a detectable level of HBsAg (titer 0.05 IU/mL) at 5 mo; however, HBV DNA was undetectable until the last follow-up time point. The total cost per year for the treatment of patients in the adefovir/LAM group was less than that for patients in the HBIG/LAM group ($8290 *vs* $13718). Cholongitas *et al*[51] evaluated the risk of recurrence of HBV infection after the withdrawal of HBIG in patients who had received HBIG and nucleos(t)ide analogues after liver transplantation. A total of 47 patients who had received a combination of HBIG and LAM for at least one year after liver transplantation discontinued treatment with HBIG and received treatment with new nucleos(t)ide analogues *(i.e.*, adefovir, entecavir or tenofovir). The median follow-up time after HBIG withdrawal was 24 mo. In all, 28 patients continued treatment with LAM in combination with adefovir (n = 23) or tenofovir (n = 5); 10 and 9 of the 47 patients continued on tenofovir and entecavir monoprophylaxis, respectively. Three patients developed transiently detectable levels of HBsAg. Nath *et al*[52] reported that high-dose HBIG (10000 IU) was administered only 7 d after liver transplantation, which was followed by treatment with adefovir combined with LAM. With a mean duration of follow-up of 14.1 mo, one patient remained HBsAg-positive but had normal lab values.

Entecavir or tenofovir

Entecavir and tenofovir are potent antiviral agents with a high genetic barrier that are both recommended as the first-line nucleos(t)ide analogues for the treatment of patients with CHB. In a study in 2014 by Cholongitas *et al*[53], 28 patients who received entecavir (n = 11) or tenofovir (n = 17) combined with HBIG discontinued use of HBIG but continued treatment with nucleostide analogue monotherapy 6 mo after liver transplantation. No hepatitis B recurrence occurred during the follow-up period of 21 mo. Three patients who received tenofovir (17%) and 2 (18%) who received entecavir required a reduction in dosage frequency (alternate day) at some points during the follow-up period because the estimated glomerular filtration rate of these patients was less than 50 mL/min. Yi *et al*[54] reported the efficacy of entecavir monotherapy following HBIG withdrawal one year after liver transplantation. In that study, 29 patients with undetectable levels of HBV DNA who were negative for HBeAg at the time of transplantation were enrolled. After the first 12 mo of primary combination therapy of HBIG and entecavir, HBIG was discontinued. During the follow-up period of 31 mo, only one patient experienced a recurrence of HBV infection after the recurrence of HCC. Tanaka *et al*[55] showed that none of the 29 patients who received tenofovir in combination with one year of low-dose HBIG developed a recurrence of hepatitis B. In a randomized trial by Teperman *et al*[40], patients who were administered emtricitabine/tenofovir and HBIG for at least 24 wk were randomized to receive emtricitabine/tenofovir plus HBIG (n = 19) or emtricitabine/tenofovir alone (n = 18) for an additional 72 wk. No patient experienced a recurrence of HBV infection throughout the 72 wk. Both the combination of emtricitabine/tenofovir and HBIG and the treatment with emtricitabine/tenofovir alone were effective in the prevention of HBV reinfection. Another study in 2013 by Wesdorp *et al*[56] reported the safety and efficacy of tenofovir and emtricitabine after the cessation of HBIG after OLT in patients with chronic HBV infection. A total of 17 consecutive patients who were administered HBIG for at least 6 mo before the discontinuation of HBIG converted from their current HBV prophylaxis regimen (LAM + adefovir) to tenofovir/emtricitabine. HBsAg positivity without detectable levels of HBV DNA was demonstrated in one patient during the 26-mo follow-up period. Renal function remained stable during follow-up for most patients. The authors also showed that the use of tenofovir/emtricitabine saved €16262/year over the standard of care (HBIG + LAM). Stravitz *et al*[57] assigned 21 patients without recurrence of HBV infection who were treated with HBIG ± a nucleos(t)ide analogue for at least 6 mo to receive treatment with tenofovir/emtricitabine for the prophylaxis against HBV reinfection. HBIG was discontinued when they began to receive the tenofovir/emtricitabine therapy. Three patients tested positive for HBsAg after 31 mo. Three patients developed acute renal failure during the study, one of whom demonstrated a tenofovir-related acute tubular necrosis. Tenofovir/emtricitabine treatment was discontinued in two patients due to a suspicion of drug toxicity. All 3 recovered normal renal function and were withdrawn from hemodialysis during the treatment. Although only one patient in this study demonstrated convincing evidence of tenofovir-related nephrotoxicity, renal function should be closely monitored when tenofovir/emtricitabine is given.

NUCLEOS(T)IDE ANALOGUE MONOTHERAPY

In recent years, new nucleos(t)ide analogues have been approved for the treatment of hepatitis B. Higher efficacy and lower rates of resistance have transformed these new oral medicines such as entecavir and tenofovir into first-line treatments for chronic hepatitis B patients. Entecavir was also recommended as the first choice treatment for the prevention of HBV reinfection after liver transplantation. A strategy with new nucleos(t)ide analogue monotherapies for the prevention of HBV reinfection may avoid the disadvantages associated with HBIG and may achieve effective outcomes. However, studies that have focused on an HBIG-free prophylactic approach are limited. Fung *et al*[58] reported that 80 patients received entecavir without HBIG as a primary prophylaxis for the prevention of HBV recurrence. Throughout the median follow-up period of 26 mo, 10 patients tested positive for HBsAg, and 8 patients remained HBsAg-positive without seroclearance after liver transplantation. No entecavir-related viral resistance was detected in these 18 patients. In a prospective trial by Wadhawan *et al*[59], 75 patients tested negative for HBV DNA or who had levels < 2000 IU/mL at the time of transplantation were not given HBIG. Nineteen patients received a combination of LAM and adefovir, 42 received entecavir, 12 received tenofovir, and 2 received a combination of entecavir and tenofovir. At the last follow-up (median 21 mo, range: 1-83 mo), all patients were HBV DNA-negative. HBV DNA reappeared in 6 patients during the median 21-mo follow-up. Five of the 6 patients had stopped treatment with oral antiviral medication on their own. All of these patients with recurrence were HBV DNA-negative at the last follow-up after they changed their antiviral therapy. Nine patients never experienced HBsAg clearance but were negative for HBV DNA at the last follow-up. Additional studies that focus on the long-term efficacy and safety of nucleos(t)ide analogue monotherapy for the prevention of hepatitis B infection should be performed.

CONCLUSION

Patients with high levels of HBV DNA in serum at the time of liver transplantation were considered to be at a higher risk for the recurrence of HBV infection after transplantation[60,61]. The choice of an antiviral medicine with a high genetic barrier in order to achieve the lowest level of HBV DNA in serum before transplantation was crucial for the prevention of hepatitis B recurrence after liver transplantation. From our experience in the prevention of hepatitis B recurrence post-transplantation, entecavir seems to be more cost-effective than tenofovir because of the high cost of tenofovir in China.

A recent trend in liver transplantation is the increased use of new strategies for prophylaxis of hepatitis B recurrence after transplantation. Highly potent antiviral medicines with minimal or risk-free viral resistance have replaced LAM as the first-line therapy in patients who undergo a liver transplant. As a high rate of resistance occurred with LAM treatment, the discontinuation of HBIG was not recommended for patients who were treated with LAM and HBIG[62]. HBIG withdrawal followed by treatment with new nucleos(t)ide analogues, such as entecavir and tenofovir, is a promising alternative strategy for the prevention of hepatitis B recurrence. The timing of HBIG withdrawal is still controversial; however, one year post-transplantation seems to be safe and feasible[50,51]. New oral antiviral monotherapies without HBIG may be effective in patients at low risk of HBV recurrence at the time of transplantation. However, the long-term efficacy and safety of these therapies need to be determined with more adequately powered studies in the future.

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