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An Overview of the Current Hepatitis B Treatment Strategies after Liver Transplantation

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ABSTRACT

Currently, liver transplantation (LT) is considered as the only option for the treatment of patients with various causes of liver failure, including patients with chronic hepatitis B virus (HBV) infections. Overall, patients with HBV who undergo LT are at increased risk of hepatitis B infection recurrence. Although the current knowledge regarding the pathophysiology of this infection has been dramatically increased over the past few decades, it is still considered a complex disease process with varying degrees of clinical characteristics and changing patterns over time. There are various treatment strategies for preventing HBV recurrence in the LT setting. Generally, these regimens include oral nucleoside/nucleotide analogues (NAs), hepatitis B immune globulin (HBIG), and vaccines or the combination of these drugs. The treatment strategy of choice should be based on cost-effectiveness, along with other patients underlying conditions. In this case, studies indicate that potent NAs are more cost-effective than HBIG in most case scenarios. In this article, we aimed to review the general medications used in the prophylaxis of the recurrence of HBV infection after LT.

KEYWORDS:
Liver transplantation, Hepatitis B, Treatment

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INTRODUCTION

Liver transplantation (LT) has been established as the only viable treatment option for patients with advanced liver cirrhosis.[1,2] Hepatitis B virus (HBV) infection is one of the most common etiologies of liver diseases worldwide, which is associated with a wide range of complications.[3] It has been estimated that about 240 million people are affected by this infection globally, and more than 780,000 cases will eventually die every year because of its debilitating complications.[4,5] Although the current knowledge regarding the pathophysiology of this infection has been dramatically increased over the past few decades, it is still considered a complex disease process with varying degrees of clinical characteristics and changing patterns during the time.[6] Currently, the recurrence of hepatitis B following LT is still common and contributes to the major cause of death within 4-12 months after surgery.[7] Recurrence of HBV after LT can be confirmed by positive HBsAg, detection of HBV-DNA in serum, detection of covalently closed circular DNA (cccDNA)

in the liver tissue, increased alanine aminotransferase, and/or present liver damage in a liver biops.[8] Since the introduction of intravenous hepatitis B immunoglobulin (HBIG), a dramatic breakthrough has been noticed in preventing post-LT recurrence of hepatitis B. Moreover, additional therapeutic regimens such as antivirals nucleoside analogues (NAs) and vaccines have been used for controlling the recurrence of HBV infections.[9] Despite recent advances in treatment protocols and clinical guidelines of management of hepatitis B, it is still considered as a potentially life-threatening viral infection after performing LT.[10-13] In this review, the current HBV prophylactic strategies after LT is discussed.

Mechanisms for reactivation of HBV infection after LT

The reasons behind HBV reactivation are still unclear, however, studies showed a unique replication strategy for HBV by forming a cccDNA in the hepatocyte nucleus, which is immune to antiviral therapies and detection by the human immune system.[14,15] Another possible mechanism for the recurrence of hepatitis B is the presence of HBV in extrahepatic tissues such as peripheral blood mononuclear cells (PBMCs), which can act as potential sources of reinfection.[16]

Risk factors for recurrent HBV infection after LT

Reactivation of HBV after LT is associated with various factors such as the viral load at the time of LT, defined as HBV-DNA levels higher than 105 copies/mL or 20,000 IU/mL,[17,18] HBeAg positivity,[18] Hepatocellular carcinoma (HCC),[19] and LT from donors with HBV infections that may significantly decrease by prophylactic therapy.[20,21] Consequently, the risk of HBV recurrence must be evaluated before selecting the prophylactic strategy. High viral load at the time of LT, history of antiviral drug resistance, HBeAg positivity, HCC at LT, HCC recurrence, and having chemotherapy treatments for HCC are high-risk patient indicators. In contrast, low viral load, HBeAg negativity, acute liver failure, and hepatitis delta virus (HDV) co-infection are indicators of low-risk patients for recurrent HBV after LT. It is suggested that most high-risk patients use a combination of HBIG and NAs while low dose HBIG or even HBIG-free regimens containing potent NAs can be used in low-risk patients.[22, 23]

Another risk factor for the recurrence of hepatitis B infection is the limitations in the administration of more effective drugs. These limitations can be due to previously existing drug resistance, drug intolerance, contraindications, or their cost.[18,24-26]

Current drug treatment protocols

Lamivudine

Lamivudine, a dideoxynucleoside analogue, is an antiviral drug generally used in the treatment of hepatitis B as well as human immunodeficiency virus (HIV) infections.[27-29] Lamivudine is classified as nucleoside analogue reverse transcriptase inhibitors (NRTIs), and its antiviral activity is due to inhibition of reverse transcriptase enzyme in the form of lamivudine triphosphate.[27,29,30] Phosphorylation of lamivudine is critical for antiviral activity. In contrast, the reverse transcriptase enzymes of HIV and polymerase of HBV exhibit pyrophosphorolysis activity, which results in resistance to lamivudine and dideoxynucleoside analogs.[30,31] The recommended dose for lamivudine in patients with normal creatinine clearance is 100 mg orally once-daily [32] and has been shown to be safe in adults,[33] children,[34] and even during pregnancy.[35] Also, studies strongly recommend the use of lamivudine in the prevention of HBV of mother-to-child transmission, which is one of the most common transmission modes of HBV.[36] On the other hand, several meta-analyses showed a less favorable outcome of using lamivudine in the treatment and prevention of reactivation compared with entecavir or tenofovir .[37-39] It is worth mentioning that sorbitol, as a common liquid excipient, has an impact on decreasing the absorption of lamivudine.[40] Therefore, co-administration of sorbitol-containing medicines should be generally avoided.

Adefovir dipivoxil

Adefovir is another oral nucleoside/nucleotide analogue (NA) with a similar mechanism to lamivudine.[41] It is also approved in the treatment of chronic hepatitis

B (CHB) with an oral dose of 10 mg once daily.[41,42] One of the advantages of adefovir over lamivudine is the less chance of developing resistance. Also, studies showed that a combination of lamivudine plus adefovir is effective in lamivudine-resistant patients with CHB.[42-44]

Entecavir

Similar to adefovir and lamivudine, entecavir is an oral NA, and it is approved for CHB infection .[41,42] In patients with no renal dysfunction, entecavir is suggested 0.5 mg daily for adults, and 1 mg in lamivudine experienced patients and patients with decompensated cirrhosis.[45] Entecavir is also preferred to lamivudine and adefovir in recent Hepatitis B Guidance.[45]

Tenofovir dipovoxil fumarate

Tenofovir dipovoxil fumarate is the prodrug of tenofovir, which is also used in the treatment of chronic HBV. It is an NA in the mediational class of NRTIs.[46,47] Tenofovir exhibits a longer half-life in both serum and intracellular media compared with other NAs.[48] Tenofovir dipovoxil fumarate is recommended as 300 mg daily for adults and children aged ≥ 12 years with normal renal function.[45]

Immunization therapies

HBIG is a human immune globulin against hepatitis B surface antigen (HBsAg).[49] HBIG is known to be used for the prevention of HBV reactivation and in situations of acute exposure to HBV.[49, 50] Studies showed that a combination of HBIG and NAs is significantly effective in the prevention of HBV reactivation.[51-53] In contrast with HBIG, the vaccine causes active immunity by exposure of a subunit (an antigen) to the immune system.[54] A study by Bienzle and colleagues showed the possibility of successful vaccination after LT.[55]

Management strategies of HBV in patients on the waiting list

There are several studies on the prevention of HBV reactivation after LT. Antiviral drugs may differ in safety, efficacy, rate of resistance, and long-term clinical outcome, alone and/or in combination with other antiviral drugs.[52,56,57]A summary of the studies is represented in Table 1. Extending waiting time for patients in the waiting-list of LT due to CHB by effective suppression of infection can be lifesaving .[58] In a study by Gane and co-workers, administration of lamivudine plus adefovir, which is initiated at the time of being on the waiting list, was safe and effective against reactivation of HBV.[59]

Management strategies of prevention of HBV reactivation in patients after LT

HBIG monotherapy

Induction of passive immunity by administering HBIG with or without antivirals has been the gold standard for the prevention of HBV reactivation, and many studies support the effectiveness of using HBIG.[60-62] However, controversies on the dose, duration, and route of (administration Intravenous(IV), Intramuscular (IM), or Subcutaneous (SC)) still exist.[63] In a study done by Avolio and colleagues,[64] 16 patients with the mean Model For End-Stage Liver Disease score) MELD Score (of 19 ± 9, were assessed for HBV reactivation. Ten patients were found to be at risk for recurrence, and 10,000 IU of HBIG were administered at the end of the anhepatic phase, followed by 5,000 IU for the next 7 days. Subsequently, the doses of HBIG were adjusted to maintain anti-HBs > 400 U/L in the first three months and > 200 U/L afterward. The recurrence rate was 30% in this group. In contrast, in a study by Terrault and others,[61] 10,000 IU of HBIG were administered daily during the anhepatic phase for the next 7 days and continued monthly afterward. The recurrence rate was 19% in patients who received HBIG, while it was 76% in patients who did not receive the prophylaxis regimen. The adverse effects of HBIG are rare, but there is the possibility of anaphylaxis/hypersensitivity reactions and thrombotic events, which should be considered.[65,66]

NA monotherapy

Monotherapies of NA in the prophylaxis of HBV recurrence were studied due to the high cost and

Table 1: Clinical studies on the management of patients with HBV after liver transplantation

Patients' information	study approach	Time of study	result	Description	Ref.
17 HBsAg positive patients	13 patients received a high dose of HBIG (A), 4 patients did not receive HBIG (B)		A: 10 of 13 patients did not experience recurrence. B: all patients reoccurred within 3 months.		62
52 HBsAg-positive patients	24 patients received a high dose of HBIG (A),28 patients did not receive therapy (B)	2 years	A: 19% of patients did not experience recurrence. B: 76% of patients reoccurred within 3 months		61
52 patients with CHB	All patients received 100 mg of lamivudine daily	52 weeks	60% of patients had undetectable HBV DNA after treatment	Also, serum alanine transaminase levels normalized in 71%	67
24 HBsAg-positive patients who had received HBIG for at least 6 months	A: treated with lamivudine (n =12), B: treated with HBIG (n=12)	52 weeks	A: 10 of 12 without recurrence B: 11 of 12 without recurrence	This study recommends a cost-effectiveness study due to the similar efficacy of both HBIG and lamivudine.	94
47 HBsAg positive LT candidates	All patients treated with 100 mg lamivudine daily without HBIG	38 months	60% of patients were HBsAg negative 12 weeks after LT		68
80 patients who had post-transplant prophylaxis of lamivudine and HBIG	Lamivudine (300 mg/day) plus HBIG (200-400 IU/2-4 weeks)	21 months	Recurrence occurred in 4% of patients.		52
42 post-LT patients with lamivudine-resistant HBV infection	Adefovir (10 mg/day)	12 to 31 months	In 64% of patients, serum HBV-DNA was undetectable	ALT levels decreased significantly in 62.9% of cases.	69
30 HBsAg positive patients	5% HBIG plus lamivudine	36 months	Recurrence occurred in only one patient.	The study showed the safety and efficacy of high dose HBIG in combination with lamivudine.	76
14 HBsAg positive patients	Lamivudine plus adefovir (n=13)and lamivudine plus tenofovir (n=1)	32 months	Only one patient who had very high HBV-DNA remained HBsAg positive.	This study suggested not using HBIG in maintenance therapy, which is cost-effective.	77
20 HBsAg positive patients	Lamivudine (100 mg daily) plus adefovir (10 mg daily)	36 months	none of the patients had a recurrence of hepatitis B.		59
Eight patients	Entecavir and/or tenofovir after LT for treatment or prevention of HBV infection	12 months	No significant side effects were observed during the follow-up period.		56
14 patients	A: Eight patients received lamivudine before LT which one of them converted to entecavir after LT, B: Two patients received lamivudine plus adefovir, C: four patients did not receive NAs which one of them received entecavir, one of them received lamivudine plus adefovir, and two of them received lamivudine after LT. All patients received 20,000 U of HBIG at day 0 after LT, 10,000 U at day 1 after LT, 10,000 at day 2 after LT, a monthly maintenance dose (2,000-3,000 U) to keep IG level at 100-150 U/L for one year.	42 months	Only two patients had a recurrence of hepatitis B.		95
23 patients	Patients switched from monthly IV to weekly SC use of a novel HBIG: BT088 (Zutectra)	18 weeks	None of the patients had a recurrence of hepatitis B.	BT088 is effective, safe, and presents an easy-to-apply treatment option.	96
17 patients with hepatitis-related diseases	Patients received both lamivudine and HBIG for less than 18 months and discontinued HBIG.	42–86 months	Two patients had HBV recurrence.	Two patients were excluded from the study	79

Patients' information	study approach	Time of study	result	Description	Ref.
29 patients	Patients received 0.5 mg of entecavir for more than 2 years and HBIG only in the first year after LT.	31 months	None of the patients had a recurrence of hepatitis B.	one of the patients had HCC recurrence	78
24 adults with HBV-related liver disease	Tenofovir disoproxil fumarate (with or without lamivudine) and HBIG (only in the first year after LT) were used to prevent recurrence of HBV infection.	29.1 months	None of the patients had a recurrence of hepatitis B.	Patient survival in 1 year: 100% Patient survival in 5 years: 84.1%	80
71 HBsAg negative patients who received anti-HBc positive grafts	Patients received HBV vaccinations. 24 patients with high anti-HBs titer before LT did not receive prophylaxis(A). 30 patients responded to vaccination and received lamivudine (B). 17 patients did not respond to vaccination and received lamivudine (C).	24 months	Only patients of group C developed De novo hepatitis B infection.		89

incompliances of HBIG administration and described in Table 1.[67-71] Lamivudine with a daily dose of 100 mg is the most studied prophylaxis for HBV reactivation.[67,68] However, due to its renal elimination, doses may be adjusted related to creatinine clearance (CrCl).[72] However, until CrCl is < 30 mL/min, dosage adjustment can be avoided. Also, a study showed no side effect in using 300 mg daily for patients with CrCl higher than 30 mL/min, 150 mg daily for patients with CrCl between 15 and 29 mL/min, and 100-150 mg daily for patients with CrCl less than 15 mL/min or patients on hemodialysis. In this study, the maximum serum concentration of these three groups were approximately 3.30, 3.48, and 3.21, respectively.[24] On the other hand, adefovir monotherapy showed similar efficacy to lamivudine,[69] and it needs dose adjustment in renal dysfunctions. Dosage intervals should be adjusted in patients with CrCl less than 50 mL/min.[73] For tenofovir disoproxil fumarate, dose adjustments must be applied for patients with CrCL < 50 ml/min. Patients with CrCl between 30 and 49 mL/min should receive double the interval administered by patients with CrCl ≥ 50 mL/min. Patients with CrCL between 10 and 29 mL/min should use tenofovir disoproxil fumarate once or twice weekly. For hemodialysis patients, tenofovir disoproxil can be used after each hemodialysis or every 7 days.[74] Tenofovir is also safe and tolerable for both mother and infant in pregnancy, according to a meta-analysis done by Wenhui and colleagues.[75]

Combination therapy

The most successful prophylaxis of HBV reinfection can be achieved by combination therapies.[52,59,76-78] Monotherapy with HBIG or NAs results in similar effectiveness [78], while co-administration of both HBIG and NAs shows a better outcome in the prophylaxis of HBV reinfection.[52, 59,76-78] Most studies that used a combination of HBIG and NAs for prophylaxis used HBIG only after LT or for a short period after LT.[78-80] Nassiri-Toosi and co-workers demonstrated that low-dose intramuscular HBIG injection with oral agents of tenofovir or lamivudine and discontinuation of HBIG after one year post-liver transplantation can provide safe protection and plays a preventive role against hepatitis B reinfection after transplantation. Additionally, another study done by Nassiri-Toosi and colleagues showed that this combination was also cost-effective in preventing the recurrence of hepatitis B.[81-83] On the other hand, a combination of 100 mg lamivudine daily and 10 mg adefovir daily showed no recurrence of hepatitis B in a follow up of 36 months.[59]

Vaccination

Inducing active immunity for the prevention of HBV reactivation can be another prophylaxis strategy, but despite the potential efficacy of vaccines, studies have failed to confirm an acceptable outcome of using vaccines.[71] This might be due to the immune system's inability to develop an effective response to the continuous exposure of patients with chronic hepatitis B to HBV antigens before LT.[84,85] A study on

52 patients who were on lamivudine prophylaxis and received two courses of double-dose recombinant HBV vaccine showed a limited efficacy for the recombinant HBV vaccine.[85] Nevertheless, vaccines targeting the preS1 domain, which can potentially overcome immune tolerance in HBV, are showing promising efficacy in developing immune response in clinical studies.[86-88] On the other hand, HBV vaccines might be more effective in the prophylaxis of de novo hepatitis B infection in HBsAg negative patients who receive grafts from anti-HBc positive donors. In a study on 71 HBsAg negative patients who received anti-HBc positive grafts, 54 who received HBV vaccine did not develop de novo hepatitis B infection.[89]

Discontinuation of all prophylaxis

A study by Lenci and colleagues shows a low rate of HBV recurrence in patients with no detectable HBV cccDNA and a total HBV in intrahepatic and blood in 2 years after the discontinuation of prophylaxis.[90] However, it is not suggested due to the lack of sufficient and long-term studies.[90, 91] A systematic review by Cholongitas E. et al. suggested prophylaxis with lamivudine HBsAg-negative patients and no prophylaxis for both anti-HBc and anti-HBs positive patients.[92]

Monitoring for HBV recurrence

The best monitoring protocol cannot be determined due to the lack of comparative studies.[93] However, it is suggested to monitor HBsAg and HBV DNA every 3 months in the first year after LT and in HBsAg positive recipients or patients who receive a graft from an HBcAb positive donor, it should be continued every 6 months after the first year regardless of prophylaxis or treatment regimen.[93] Also, in self-reported or suspected non-adherence cases monitoring intervals should be shortened.[93]

CONCLUSION

Although most studies show satisfying outcomes in the prevention of hepatitis B recurrence using HBIG with or without NAs, there is no clear strategy of prophylaxis yet. Two parameters should be considered in making the decision to choose the medication regimen: first, the effectiveness of the regimen in the prevention of HBV reinfection and second, its cost. Thus, the cost-effectiveness studies are crucial for each health care systems. Also, several recent studies showed similar efficacy in both combination therapies involving with or without HBIG usage, which suggests the fact that HBIG can be replaced with low-cost potent NAs. Furthermore, other factors, including drug interactions, HBV co-infection (such as HDV and HIV), renal dysfunctions, and resistance or intolerances to regimen must be considered in prescribing prophylaxis before and/or after LT. On the other hand, NAs and HBIG provide the state of control by suppressing the viral reactivation and does not affect stealth HBV (e.g., cccDNA in hepatocytes and extrahepatic HBV). Induction of active immunity via vaccinations and administration of cccDNA inhibitors might be a future solution for the prevention of HBV reactivation after LT.

ETHICAL APPROVAL

There is nothing to be declared.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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