World Journal of Hepatology

Online Submissions: http://www.wjgnet.com/1948-5182office
wjh@wjgnet.com
doi:10.4254/wjh.v2.i12.447

World J Hepatol 2010 December 27; 2(12): 447-450
ISSN 1948-5182 (online)

CASE REPORT

Simple nucleos(t)ides as HBV prophylaxis regime of post-liver transplantation: Six-year followed up

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Received: March 11, 2010 Revised: November 9, 2010
Accepted: November 16, 2010
Published online: December 27, 2010

Abstract

A combination of nucleos(t)ides and hepatitis B immunoglobulin (HBIg) has been found to be effective for the prevention of hepatitis B viral (HBV) reinfection after liver transplantation (LT), but its administration is costly, and not always available. We report the case of a male, 33-year-old cirrhotic patient who has tested positive for serum HBsAg, and HBeAg, with 9.04×10^7 copies/mL of HBV DNA. He suffered from acute liver failure and was near death before undergoing emergency LT. No HBIg was available at the time, so only lamivudine was used. He routinely received immunosuppression medication. Serum HBV DNA and HBsAg still showed positive post-LT, and the graft re-infected. Hepatitis B flared three months later. Adefovir dipivoxil was added to the treatment, but in the 24th mo of treatment, the patient developed lamivudine resistance and a worsening of the hepatitis occurred shortly thereafter. The treatment combination was then changed to a double dosage of entecavir and the disease was gradually resolved. After 60-mo of post-LT nucleos(t)ide analogue therapy, anti-HBs seroconverted, and the antiviral was stopped. By the end of a 12-mo follow-up, the patient had achieved sustained recovery. In conclusion, the case seems to point to evidence that more potent and less resistant analogues like entecavir might fully replace HBIg as an HBV prophylaxis and treatment regimen.

Key words: Chronic hepatitis B; Hepatitis B immunoglobulin; Liver transplantation; Nucleos(t)ides

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Luo KX, Zhou FY, Liu DL, Feng XR. Simple nucleos(t)ides as HBV prophylaxis regime of post-liver transplantation: Six-year followed up. *World J Hepatol* 2010; 2(12): 447-450 Available from: URL: http://www.wjgnet.com/1948-5182/full/v2/i12/447.htm DOI: http://dx.doi.org/10.4254/wjh.v2.i12.447

INTRODUCTION

Because of immunosuppression usage, liver transplantation (LT) due to hepatitis B virus (HBV)-related diseases is often followed by HBV re-infection of the allograft which is associated with severe liver damage, and often progresses to graft loss[1]. However, prophylaxis strategies have greatly advanced in the past few years. Initially, long-term intravenous (IV) high-dose hepatitis B immunoglobulin (HBIg) was used, but it was very expensive, and the recurrence rate still remained high[2]. Since lamivudine (LMV) has been introduced in treatment of chronic hepatitis B, it has also been used in HBV prophylaxis post-LT. The LMV and HBIg combination reduces HBV recurrence rates to less than 5% in 5 years[3], and thus a new era of LT for HBV-related disease had begun. Recently,

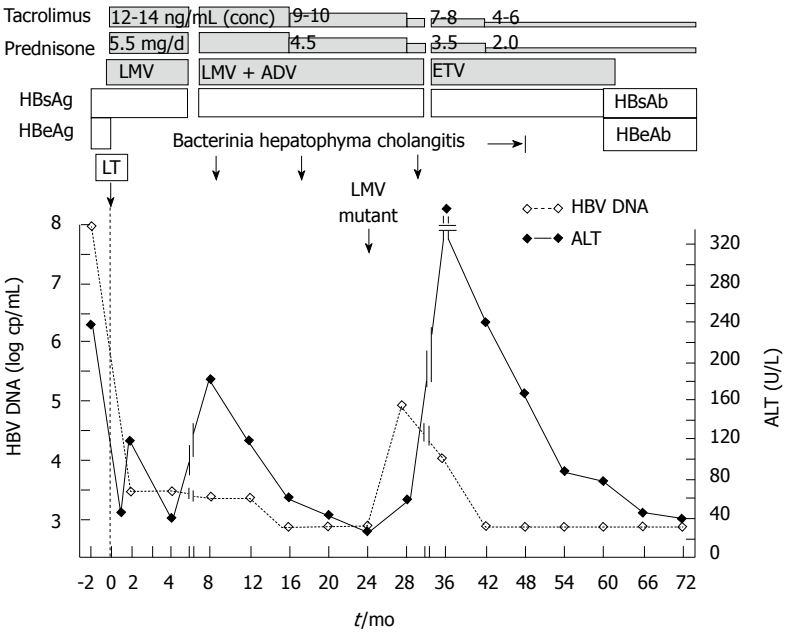

Figure 1 Clinical course and virological features of the patient. Conc: concentration; LMV: lamivudine; ADV: adefovir dipivoxil; ETV: entecavir; LT: liver transplantation.

high-dose IV HBIg in combination has been replaced by low-dose intramuscular (IM) HBIg, which has achieved similar results[4,5]; hence the latter regimen has been widely adopted in most hepatology departments. However, a low-dose HBIg regimen is still costly and not always available, and strategies using HBIg-free nucleos(t)ide analogues (NAs) have been tried instead[6]. Very recently, a multicenter randomized study of adefovir dipivoxil (ADV) substitution for low-dose IM HBIg showed no HBV recurrence for at least 12-mo post-LT[7]. In the following case study, a cirrhotic patient with high HBV levels and fatal liver failure received an emergency orthotopic LT. No HBIg was available; he received only NAs treatment. He achieved a sustained recovery even after the antivirals were discontinued, and even showed that HBs had seroconverted. HBIg-free NAs regimens are widely used in China to prevent LT re-infection, and the following case may be a typical one.

CASE REPORT

A 33-year-old male patient had been HBsAg-positive since childhood, but had had no regular examinations. At this time he had lassitude, lack of appetite, and dark yellow urine for 6 wk. In mid-October of 2003, he was admitted to a local primary hospital, and only treated with conventional herbal medicine to alleviate his symptoms and lower the serum transaminase. His symptoms worsened in a week and he went into a coma for 3 d. He was then transferred to the hepatology unit at Nanfang Hospital on October 20th, 2003. Examination revealed a temperature 38.2℃, blood pressure of 96/60 mmHg, pulse rate at 90/min, and respiration rate at 32/min. The patient was heavy jaundiced and was in a deep coma. Heart and lungs were normal, liver and spleen not palpable, and the abdomen had swelling with ascites. Virological tests were positive for serum HBsAg and HBeAg (EIA, Abbott Lab, Chicago, IL, USA), and 9.04×10^7 copies/mL of HBV DNA (Fluorescent quantitative PCR-based assay with a Roche Amplicor machine using a locally licensed kit). There was no evidence of hepatitis C, hepatitis D, or human immunodeficiency virus infections. Biochemical tests revealed alanine transaminase (ALT) 120 U/L, aspartate transaminase (AST) 157 U/L, albumin 32 g/L, total bilirubin 211 μmol/L, direct bilirubin 110 μmol/L, prothrombin time 49 (normal < 13) sec, alfa fetal protein 172 (normal < 10.9) ng/mL, serum urea and creatinine normal.

Emergency management included tracheal incubation ventilation, artificial liver support and plasmapheresis, and LMV 100 mg was administered daily by gastric tube. Two days after admission, the patient received an orthotopic LT.

The explant liver was tenacious with grey yellow cross sections. Microscopy showed hepatocyte ballooning degeneration and confluent necrosis, diffusing pseudo-lobule with generously fibrous connective tissue.

The virological features and the clinical course are shown in Figure 1. Immunosuppressive therapy began with 15 mg of corticosteroid daily in the first week, which was then lowered to 5.5 mg daily, and tacrolimus was adjusted to maintain a serum level of 12-14 ng/mL during the first year. The dosages of both drugs were decreasedannually. There was no HBIg available, and simple LMV use continued, and we had no choice but to use LMV as the HBV prophylaxis and treatment regimen at that time. Serum HBV DNA was 1.72×10^4 copies/mL and HBeAg cleared at the second week of treatment, but HBsAg was still positive. At the end of the first month post-LT, HBV DNA was 7.68×10^3 copies/mL. The patient's liver chemistry gradually returned to normal.

Three months later, the patient complained of lassitude and nausea. His ALT was at 121 U/L and HBV DNA was 5.25×10^3 copies/mL. There was no evidence

of cytomegalovirus infection. Histological examination of the biopsied transplanted liver revealed moderate inflammation and mild fibrosis. ADV 10 mg/d was added to the treatment regime not long after the hepatitis flared, but serum HBV DNA was still detectable, and the ALT levels remained abnormal during 10 mo of combined LMV and ADV therapy.

Then in the following 2 years (from June 2004 to December 2006) the patient suffered bacteremia of aerugo pseudo-monosporangium, hepatophyma and cholangitis successively. He received multiple treatments, hepatotoxic antibiotics were carefully avoided, and the infections were finally cured.

Unfortunately, even combined with ADV, the LMV resistance developed 24-mo into treatment, and t mutations of rtM204V and rtL180M were detected by means of sequencing. The HBV DNA had increased to 1.01 $\times$ 10^5 copies/mL and acute exacerbation occurred, with ALT elevating up to 468 U/L. Antivirals were switched to 1.0 mg of entecavir daily. HBV DNA was undetectable 12-mo after and HBsAg was negative 60-mo after LT and NAs therapy. On December of 2008, anti-HBs sero-converted, and all liver function tests were normal. After another year, , with antivirals being discontinued for 12 mo, the patient had achieved a sustained recovery.

DISCUSSION

The patient with HBV-related cirrhosis and liver failure was near death, characterized by intense ascites, severe encephalopathy, and markedly prolonged prothrombin time. With liver disease at such an advanced stage, emergency LT might be seen to be the only treatment option[8]. LMV was used simply to prevent graft reinfection, but HBIg was not available in an urgent situation. He had high levels of serum HBV DNA pre-LT, and even after the removal of the infected liver, HBV usually still replicated persistently outside the liver, which has been shown to be common in such patients[9]. Thus, about three months later, the graft liver reinfected and hepatitis B flared. Without effective treatment, his prospect of survival was low. ADV was then added his treatment regime, but low virus replication and mild hepatitis still persisted for more than a year, suggesting that in immunosuppressive conditions, the drug combination was still not strong enough[10]. In addition, LMV resistance occurred even with ADV treatment, resulting in HBV rebound and worsening of the disease symptoms, which is uncommon in a non-transplant patient[11]. After changing to entecavir with double the normal dosage, and decreasing the immunosuppression to minimal maintaining doses, the patient's clinical status substantially improved. In the fifth year of NAs therapy post-LT, the patient had achieved anti-HBs seroconversion and even having been off antivirals for 12 mo, remained well.

Currently, combined NAs and IM low-dose HBIg therapy is widely adopted as the most effective strategy against HBV recurrence post-LT[5,6,12]. Free-HBIg NAs therapy has also been investigated and some facts may give new insights. When NAs are used as a part of a prophylaxis regimen, the effect of low-dose IM HBIg is equivalent to that of high-dose IV HBIg[5,6], and maintaining LMV treatment alone always results in a low risk of HBV recurrence, regardless of HBIg discontinuance.Moreover, even one week of HBIg combined with lamivudine regimen at the beginning of the treatment had an equivalent effect, compared with a long-term high-dose HBIg regimen for preventing hepatitis B recurrence[13]. It is suggested that with adequate treatment of potent NAs, concomitant indefinite passive immunization may not be essential[14]. Some studies have compared complete HBIg-free NAs monotherapy (without a short initial HBIg phase) with combined therapy, describing 2-4 year recurrence rates of about 15%-40%, higher than those of the combination therapy[15-19].

In fact, a major factor for recurrence was related to the high resistance to LMV[20], therefore the inclusion of ADV might be a better strategy[7,10]. However, because of the negative influence of immune suppression, the potential for NAs resistance and HBV reinfection in the long-term cannot be excluded. The LT recipients treated with NAs may have higher resistance rates in shorter periods, and fewer viral clearance effects even for lower viremia, and these affect the progression of the disease[20]. Therefore, NAs of more potency and less resistance (telbivudine, entecavir, and tenofovir) are to be preferred. Although there are few studies of these newer antivirals being used as HBV prophylaxis updates[21,22], in accordance with wide use in patients with chronic hepatitis B, they should still replace LMV within prophylaxis regimens in LT patients. With the properties they have, it could be expected that more successful HBIg-free regimens could be established, but most up- to- date studies have been limited by short-term follow-ups. To date, no reliable conclusions have been drawn as to whether treatment based on combination medication is superior to NAs monotherapy. It is therefore important that more control studies with long-term follow-ups are undertaken.

ACKNOWLEDGMENTS

The authors thank Dr. Yuyang Wang, University of Western Ontario, Canada, for his excellent work on language polishing.

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S- Editor Zhang HN **L- Editor** Herholdt A **E- Editor** Liu N