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LETTER TO THE EDITORS

Tenofovir disoproxil fumarate rescue therapy for HBV recurrence in two liver transplant recipients with previous multiple nucleo(s/t)ide treatment failures

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Dear Sirs,

Treatment with combinations of hepatitis B immunoglobulin (HBIG) and nucleos(t)ide analogues (NUCs) has reduced the risk of hepatitis B virus (HBV) recurrence in liver transplantation (LT) recipients to less than 10% [1,2]. However, antiviral drug-related mutation significantly decreased the efficacy of NUCs. Therefore, an efficient antiviral agent is desirable in the condition of HBV recurrence, which would improve the patient outcome [3]. Tenofovir disoproxil fumarate (TDF) is a newer antiviral agent with profound efficacy, rapid onset of action, and a high genetic barrier [4]. Recently, TDF was found to be effective in preventing HBV recurrence after LT [5,6]. Furthermore, TDF retained significant activity against HBV in heavily pretreated patients with high rates of genotype resistance [7]. To our knowledge, there have been no reports describing the use of TDF as rescue therapy for patients with HBV recurrence after LT. Herein, we described the favorable outcomes of TDF in two recipients with HBV recurrence after LT following previous multiple NUC treatment failures.

A 66-year-old Asian man was diagnosed as HBV-related cirrhosis in July 2007 and was prescribed with entecavir (ETV) 0.5 mg/day by mouth for positive serum HBV DNA, which led to a complete virologic response (<1000 copies/ml). However, ETV was stopped 2 months later because of an allergy rash. In April 2008, the patient was transferred to our center for a hepatocellular carcinoma (HCC), and the serum HBVDNA level was 3.5×10^4 copies/ml. Then, lamivudine (LAM) 100 mg/day by mouth was started. On May 2008, LT was performed successfully when the serum HBVDNA has already turned to be negative. Post-transplantation prophylaxis regimen was LAM plus HBIG intramuscularly injection to keep the HBIG titer be above 100 IU/ml.

No clinical complications occurred until April 2012. Although both HBsAg and HBVDNA were negative, it was difficult to maintain the targeted HBIG titer. As a result, HBV recurrence was suspected and LAM was replaced by ETV 0.5 mg/day from May 2012 with no rash observed (TDF was unavailable until 2013 in our hospital). Unfortunately, HBsAg became to be detectable in July 2012 and HBIG was discontinued. One month later, the HBVDNA was 8.83×10^3 copies/ml and the genetic sequencing showed the rtM204I mutation (Fig. 1). Then, adefovir (ADV) was added which reduced HBVDNA to <500 copies/ml 6 months later. The patient's condition remained stable until June 2013 when the serum HBVDNA became positive with a deteriorated liver function. As rescue treatment, ADV was replaced by TDF 300 mg/day by mouth.

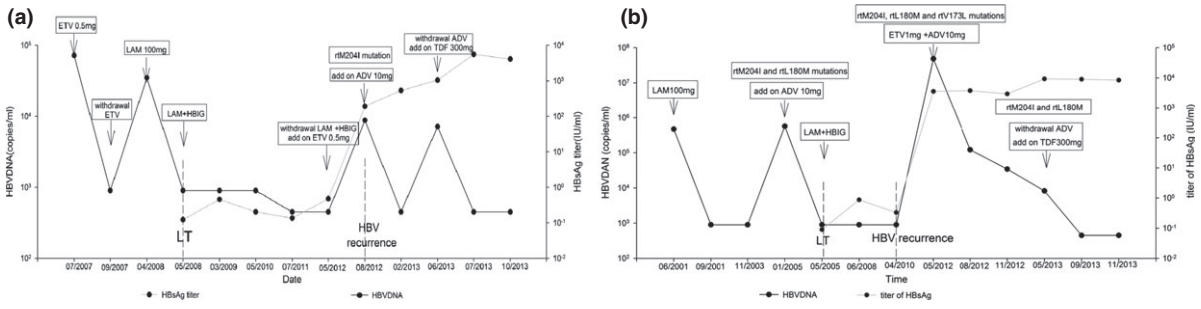

Figure 1 Change in HBV DNA and titer of HBsAg in case 1(a) and case 2(b).

One month later, his serum HBVDNA concentration turned to be undetectable, and his liver function recovered.

Another 55-year-old Asian man was diagnosed with HBV-related cirrhosis in 2001, while the serum HBVDNA level was 4.7×10^5 copies/ml with normal liver function. Then, LAM 100 mg/day by mouth was started which rapidly induced a complete virological response. In January 2005, the serum HBVDNA level was 5.7×10^5 copies/ml, with the rtM204I and rtL180M mutations. As a result, ADV 10 mg/day was added. Unfortunately, his liver function showed persistent deterioration and he underwent LT on April 13, 2005. After LT, HBIG and LAM were given as described as patient 1.

After LT, the patient had no further clinical complications until May 2012, when the titer of HBsAg was 3553 IU/ml and the HBV DNA was 4.83×10^7 copies/ml. Genetic sequencing demonstrated the rtM204I, rtL180M, and rtV173L mutations. Therefore, ETV 1 mg/day plus ADV 10 mg/day were prescribed. Serial testing of HBV DNA quantification showed a decline trend (Fig. 1). However, in May 2013, the HBsAg titer showed a significant increase with increased liver enzymes. After evaluating the risks associated with further drug mutation and graft function deterioration fully, we replaced ADV by TDF. One month later, complete virological response, decline in HBsAg titer, and normal graft function were observed.

Although HBIG combined with NUCs (mainly LAM) after LT has been the most effective prophylaxis regimen for HBV recurrence in clinical practice until now, HBV recurrence was associated with graft loss, HCC recurrence, and significantly decreased survival rate in LT recipients [8,9]. Furthermore, recent studies have found that high preoperative HBV DNA load ($>10^5$ copies/ml), HBV mutation, and HCC in the explant liver were independent risk factors for HBV recurrence following LT [10]. In our study, both recipients were at high risk of HBV recurrence after LT (one with HBV mutations and the other with HCC); therefore, there is no surprise that HBV recurrence occurred after LT despite the combination prophylaxis regimen. In fact, TDF (if available) instead of EVT should have been added in patient 1 when HBV recurrence was suspected; ADV should have been continued in patient 2 after operation because LAM-related mutation was identified before LT. In the recent years, the prevalence of antiviral agent resistance mutations seems to be increasing worldwide. Thus, it is suggested that those patients who having risk factors for HBV recurrence after LT should be treated with the combination therapy of HBIG and an antiviral agent with a high genetic barrier, such as TDF or ETV, to reduce the risk of prophylaxis failure.

In the setting of HBV recurrence, the first-line salvage antiviral regimens always are LAM plus ADV or ETV monotherapy in our center, which is similar to other center in Asia [8]. In fact, LAM-related mutation was detectable in majority of recipients when HBV recurrence was diagnosed, which could significantly reduce the efficacy of ETV. In our study, both patients experienced HBV on-treatment virological breakthrough despite having received ETV combined with ADV. Consistent with previous studies on nontransplant patients, ETV is not an optimal option in the setting of LAM-related mutation emerged in patients after LT. TDF improved outcome in patients with spontaneous reactivation of HBV, presenting as acute-on-chronic liver failure [3]. Besides, it also showed efficient antiviral effects when applied for prophylaxis against HBV recurrence following LT [5], which was consistent with our present report.

In our study, patient 1 coexisted with severe liver injury and patient 2 was accompanied with an increased titer of HBsAg. Fortunately, complete virological response was observed immediately after TDF was added on, with dramatically recovered liver function in patient 1 and decreased HBsAg titer in patient 2. More importantly, our findings suggest that TDF can rescue a graft from failure after reinfection and resistance to other NUCs, because rapid HBV suppression was beneficial for avoiding severe complications after LT, including graft loss and further development of mutation. Given the limited experience in treatment of HBV recurrence after LT with TDF, further multicenter and larger sample studies are needed to evaluate the efficacy and safety of TDF treatment in such clinical settings.

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Conflicts of interest

No conflict of interest exits in the submission of this manuscript, and manuscript is approved by all authors for publication.

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