Entecavir Treatment is Safe and Highly Effective in the Patient with de Novo Hepatitis B Infection After Liver Transplantation: Case Report

Karaciğer Naklinden Sonra de Novo Gelişmiş Hepatit B Enfeksiyonu İçin Entekavir Güvenli ve Etkin Bir Tedavi Şeklidir

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ABSTRACT De novo hepatitis B infection (HBV) occurs rarely after liver transplantion (LT) and is associated with severe hepatitis and graft loss. The liver grafts from anti-HBc positive donors are currently the main sources of de novo HBV infection after LT, which is usually defined by the development of positive HBsAg and/or detectable serum or liver HBV DNA in previously HBV naïve recipients. Here we reported the case of a liver transplant recipient with de novo HBV infection who had a favorable outcome after entecavir therapy. The patient received orthotopic liver transplantation because of end-stage cryptogenic cirrhosis and was found to have de novo HBV infection 6 months later. He was treated with entecavir and his serum HBV DNA turned undetectable 6 months later and HBsAg seroconversion was achieved 18 months later.

Key Words: Entecavir; liver transplantation; hepatitis B virus

ÖZET Karaciğer nakli (KN) sonrası de novo hepatit B (HBV) enfeksiyonu nadirdir, genellikle ciddi hepatit ve greft kaybı ile sonuçlanır. KN sonrası de novo HBV enfeksiyonunun en sık nedeni anti HBc pozitif vericiler olup; daha önce HBV enfeksiyonu yönünden naiv alıcılarda HBsAg'nin pozitifleşmesi ve/veya serumda ya da karaciğer biyopsisinde HBV DNA'nın saptanması ile tanımlanmaktadır. Bu yazıda KN sonrası de novo HBV enfeksiyonu gelişen entekavir ile başarılı sonuç elde edilen bir olgu sunulmaktadır. Son dönem kriptojenik siroz nedeniyle ortotopik KN yapılan olguda, karaciğer naklinden 6 ay sonra de novo HBV enfeksiyonu tespit edilmiştir. Entekavir ile tedavi edilen hastada serum HBV DNA 6 ay sonra negatifleşmiş ve 18 ay sonra HBsAg serokonversiyonu sağlanmıştır.

Anahtar Kelimeler: Entekavir; karaciger nakli; hepatit B virüsü

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De novo hepatitis B infection (HBV) in immunocompromised patients mostly progresses to chronic hepatitis and sometimes is associated with high mortality and morbidity.[1,2] De novo HBV is defined as hepatitis B occurring in a recipient who did not have infection before liver transplantation (LT). The incidence of acquiring de novo hepatitis B virus (HBV) infection after LT in patients who are negative for hepatitis B surface antigen is between 1.7 and 3.5%.[3,4] Potential sources of HBV infection after LT include transfusion of blood products, reactivation of an occult HBV infection in the recipient and grafting of organs from HBsAg-negative and antibody to hepatitis core antigen (anti-HBc)-positive

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donors.[3,4] Anti-viral treatment such as lamividune is effective in patients with de-novo hepatit B infection after LT.[5] Tenofovir and entecavir are newer antiviral agents with lower rates of breakthrough and resistance in the setting of therapy for chronic hepatitis B infection.

In this report, we described a case of de novo hepatitis B infection in a liver transplant recipient underwent orthotopic liver transplantation and HBs Ag seroconversion was achieved after 18 months of entecavir (ETV) therapy.

CASE REPORT

A 23 year-old man received deceased donor liver transplantation on September 7, 2006 due to end-staged cryptogenic cirrhosis. He was diagnosed with cryptogenic cirrhosis in 2004. Liver biopsy revealed cirrhosis without any specific type findings. Immunohistochemistry exam of HBsAg was negative. His viral markers including anti-HIV, anti-HCV, HBsAg, hepatitis B surface antibody (HBsAb), hepatitis B e antigen (HBeAg), hepatitis B e antibody (HBeAb), hepatitis B core antibody (HBcAb), and HBV DNA were all negative before orthotopic LT. Alfa 1-antitrypsine, ANA, SMA, LKM, ds DNA were also negative. Cu, cerruloplasmin were within normal limits. He was vaccinated against HBV with a commercial HBV vaccine (Engerix-B, SmithKline Beecham, Reixersart, Belgium) at the standard dose (40 μg) and frequency (3 doses at 0, 1, and 6 months). Unfortunately, the antibody response to the vaccine was not developed.

He underwent deceased donor liver transplantation in 2006. The liver donor was a healthy young man who died from a traffic accident without HBV. The donor was tested for HBsAg, anti-HCV and HIV and was found to be negative for all. Anti-HBs titer and anti-HBc (IgG) tests were not performed. Postoperatively LT patient received steroid and tacrolimus-based immunosuppression. The patient developed acute cellular rejection associated with an increase in alkaline phosphates, ALT and AST on 7th day of liver transplantation. He was treated with pulse steroid (1 g/3 days). Mycophenolate mofetil (MMF) was added on tacrolimus treatment. He recovered well with normalized liver function tests and was followed up every 2-4 weeks at early stage post-LT.

During the follow-up, tacrolimus was discontinued because his serum creatinine levels went up and rapamycine was started. Despite feeling well in April 2007, he was found to have positive serologies for HBsAg, HBeAg and anti-HBc, during routine testing, and the HBV DNA level was 1,92 x 10^8 IU/mL. He was negative for anti-HDV and Anti-HCV. Liver enzymes including serum ALT, AST levels were within normal limits. We diagnosed de novo hepatitis B without biochemical abnormalities. Antiviral therapy with high dose ETV (1 mg/day) by mouth was started, as the patient was immune compromised.

Serum HBV DNA became negative by PCR after six months of ETV therapy however HbeAg was still positive. ETV was continued with satisfactory antiviral efficacy, as shown by persistently undetectable HBV DNA and normal liver enzymes during long-term follow-up (Figure 1). In August 2007, he developed the second acute cellular rejection because he stopped taking immunosuppressive medications. Liver biopsy showed that severe acute cellular rejection without severe necrosis or hepatitis. HBsAg immunostaining was negative either. Pulse steroid i.v. (1 g three days) was given, biochemical resolution was revealed.

HBeAg was found to be negative after 12 months of ETV therapy but seroconversion was not occurred. HBsAg seroconversion was achieved at 18 months of ETV treatment. HBsAg seroconversion was sustained with serum Anti-HBs titer reaching 80 IU/ml. Than the patient was vaccinated with HBV vaccine at standard dose and frequency, and anti-HBs titer reached to 180 IU/ml. Entecavir treatment was sustained up till now, as the patient is immune compromised. The long-term safety of ETV therapy was satisfactory. No side effect was seen due to ETV therapy. During the long-term follow-up, there was no evidence of HBV reactivation.

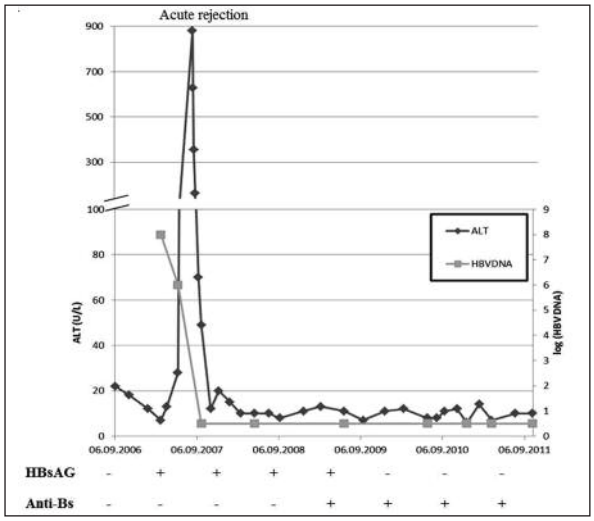

FIGURE 1: The whole course of de novo hepatitis B after orthotopic liver transplantation (OLT). At 7 months post-OLT, the recipient was found with positive hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), and HBV DNA in serum. HBV DNA turned undetectable after 6 months of entecavir (ETV) therapy.

DISCUSSION

We are presenting the case of de novo HBV infection after LT with favorable outcome after entecavir therapy. The patient was found to have de novo HBV infection at 7 months after LT. The origin of de novo HBV infection could not be revealed. In our country, blood donors are required to have negative HbsAg, HCV and HIV. However Anti-HBc, anti-HBs are not tested in the most centers. Also the current policy of the Turkish Organ Procurement Organization requires testing organ donors only for HBsAg.

In our country, the prevalence of HBsAg and anti-HBc positivity in the adult population is 2.97% to 5.2% and 25% to 30%, respectively.[6] Many transplant physicians reported that they did not accept anti-HBc-positive donors in naïve HBV recipients. Given the shortage of organ donors, the application of such a policy in geographic areas with a high prevalence of anti-HBc in the general population would represent the loss of an unacceptably large number of livers.[1]

De novo HBV infection has been reported to occur in 0.3-48% of liver transplant patients without a known history of HBV infection.[7-9] The use of post-transplant prophylaxis with hepatitis B immunoglobulin (HBIG) and/or lamividune reduces overall probability of de novo infection in both HBV naïve and anti-HBs and or anti-HBc positive recipient of anti-HBc positive donors.[5] Although our patient was known to have no history of HBV infection, donor HBV status was not known except HbsAg negativity. Therefore, anti-HBV prophylaxis after liver transplantation was not started. The possibility of donor with occult HBV infection was not excluded. So we changed our policy as all donors are tested for anti-HBs, anti-HBc and if one of these markers is positive, PCR-HBV DNA is performed to detect occult HBV infection especially in the HBV-naïve recipients. However HBV infection remains a major public health problem in our country.

HBV vaccination should be offered to all naïve HBV patients as soon as possible after diagnosis of non-HBV chronic liver disease, preferable at an early stage when the immune system is still functional. However, it has been reported that liver transplant candidates show poor antibody response to standard HBV vaccination.[10] For that reason additional anti-HBV prophylaxis will be needed in case of LT with grafts from known anti-HBc positive donors. Before transplantation, our patient was vaccinated against HBV with a commercial HBV vaccine at the standard dose and frequency but the antibody response to the vaccine was not developed.

Once de novo HBV infection was established, he was treated with ETV. He was asymptomatic at the beginning and during the therapy, and no evidence of hepatic decompensation caused by de novo HBV infection was observed.

Data in the literature regarding survival rates in patients with de novo HBV infection are controversial. Some investigators have suggested that LT with anti-HBc-positive donors is associated with a slight decrease in survival, whereas others have found that de novo HBV infection does not adversely affect long-term patient survival (Table 1).[4,7,11-13]

Many studies have shown that prophylaxis with hepatitis B immunoglobulin and/or lamivudine, are highly effective in the prevention of de

novo HBV infection.[3,4] However, use of more potent nucleoside analogs, such as entecavir or tenofovir with low resistance profiles may be suggested today.[4-14,15] Several investigators have also reported that lamividune and/or adefovire therapy for LT recipients with de novo HBV infection is effective.[5,16,17]

In this setting, it is essential that Organs Procurement Organizations make information on donor anti-HBc status available to liver transplant physicians before orthotopic LT. This would allow an appropriate matching between donors and recipients and would help reduce the incidence of de novo HBV infection after LT. Moreover, when de novo HBV infection occurs, lamividune, entecavir, tenofovir therapies are highly effective for controlling HBV replication. Entecavir, with low resistance profile and high anti-viral potency, has the advantage of being non-nephrotoxic.

TABLE 1: The course of de novo hepatitis B virus infection after liver transplantation.

The incidence of de novo HBV infection	HBV therapy	Course of de novo HBV infection	First author, year (Ref.)
18.9% 39 studies 149/788 HBcAb+ donor grafts	LAM/ADV	3-year survival 67–100%	Cholongitas 2010[4]
19.7% 13/66 HBcAb+ donor grafts (247 LT) DNHB without LAM prophylaxis was 31.3%, with prophylaxis was 10.8%	- LAM - LAM resistance: ETV and/or ADV	No DNHB-related mortality or graft loss.	Lee 2015[11]
23.9% 11/46 HBcAb+ donor grafts	ADV combined with LAM	Two (2/11) presented severe liver dysfunction, 2-year survival rate 4.2%.	XI 2013[12]
14.1% 9/64 HBcAb+ donor grafts (1013 LT)	TDF/ADV	Survival rates and the graft survival rates were 92.2% and 69.2% at 1 and 5 years, No graft losses or deaths	Bohorquez 2013[13]

LT: Liver transplantatin; DNHB: de novo hepatitis B; LAM: Lamivudine; ETV: Entecavir; TDF: Tenofovir; ADV: Adefovir

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