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REVIEW ARTICLE

Adefovir as a Novel Drug for the Treatment of Chronic Hepatitis B in Patients with End-Stage Renal Disease and Kidney Recipients

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Administration of adefovir dipivoxil (ADV) has been shown to provide an increased rate of hepatitis Be (HBe) seroconversion. It is also effective in the treatment of HIV. Because of its significant nephrotoxicity after 24 weeks of the treatment, this drug is no longer used for management of HIV. However, hepatitis B virus is inhibited with lower doses of ADV. The drug can even be used safely in those with renal impairment. This review provides new aspects of treatment of hepatitis B using ADV, especially in patients with renal dysfunction as well as renal transplant recipients. We showed that ADV can be used as a safe drug in renal transplant recipients.

Keywords: **Adefovir, Hepatitis B, Kidney Transplantation, Renal Failure**

Introduction

Infection with hepatitis B virus (HBV) is a major cause of liver disease among renal transplant recipients and is associated with high morbidity and mortality [1-7]. Immunosuppressive therapy in renal transplant recipients increases HBV replication which may be associated with aggravated hepatic injury [8]. The increased HBV replication may in turn, cause emergence of *de novo* resistance to antiviral drugs. It has been demonstrated that HBV infection significantly decreases both patient and graft survival. Nowadays, multiple antiviral drugs including lamivudine and adefovir are available and provide hopeful therapeutic regimens so that kidney transplantation in those with end-stage renal disease (ESRD) who are positive for hepatitis B surface antigen (HBsAg) should no longer be postponed [9]. In this review, we gathered the most current information on adefovir and its use in ESRD and renal transplant recipients.

Methods

In this review, the research team searched the websites of the National Library of Medicine of the US as well as the Iranian published data to find studies on "renal transplantation" and "adefovir" in an unlimited manner. After gaining access to the full text published manuscripts, two researchers

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independently, evaluated the reliability, validity and relevance of the studies retrieved.

Adefovir at a glance

Adefovir is a nucleotide analog of adenosine monophosphate (dAMP). It is a selective reverse transcriptase inhibitor of HBV-DNA replication. Adefovir dipivoxil (ADV) is an oral prodrug of adefovir which is used against HBV and some other viruses [1, 10-14]. It is excreted in the urine through glomerular filtration and tubular secretion, unchanged [15]. ADV became an approved treatment for HBV in the United States in September 2002 and in the European Union in March 2003. Although there is no strong evidence about secretion of adefovir into milk, mothers are prohibited from breast feeding their infants while receiving the drug.

ADV is accepted at a dose of 10 mg/day for treatment of patients with chronic HBV infection who have evidence of active viral replication, increased alanine transferase (ALT) levels and biopsies demonstrating active liver inflammation and fibrosis [16]. Short-term treatment with ADV leads to a rapid decrease in liver enzyme levels as well as viral load. Besides, prothrombin time becomes normal and HBV-DNA becomes negative and undetectable in polymerase chain reaction (PCR). A decrease in serum HBV-DNA of -3.5 to -4.6 $\log_{10}$ copies/mL (Roche Amplicor Monitor) at the end of the first year of the treatment has been reported [13, 14, 17, 18]. The level of DNA suppression depends on prolonged therapy [10, 19]. It is observed that the liver function may remain stable and even improved slightly [10].

Adefovir and new horizons for treatment of lamivudine-resistant HBV

ADV has been demonstrated to be safe and efficient in patients with lamivudine-resistant (LR) HBV [1, 2, 10, 11, 13, 14, 16-21]. In patients with LR hepatitis B, a comparison of combination therapy of lamivudine+ADV with ADV alone did not show considerable differences in achievement of virologic response, prevention of ADV resistance and ALT normalization [22]. On the other hand, another report demonstrated that continuing lamivudine therapy is not necessary while switching to ADV [23]. The issue of continuing or discontinuing lamivudine in patients with LR hepatitis B receiving ADV remains to be more investigated. Within the early course of the treatment, the antiviral efficacy of ADV in LR patients has been reported to be slower and less potent than that with lamivudine in nucleoside-naive patients [24]. In more than 70% of patients with LR hepatitis B, ADV has been demonstrated to suppress viral replication [25]. Pattern of lamivudine-resistant YMMD mutation is common and a combination therapy of ADV and lamivudine is known to be safe and efficient in treating patients with YMMD mutation [26, 27]. In HBeAg-negative patients with LR chronic hepatitis B, adding ADV to lamivudine has been reported to be effective in suppressing HBV replication that can be maintained at least for three years with no evidence of ADV resistance development [28] It was also reported that ADV could be used without lamivudine in treating YMMD mutants if the patient did not receive lamivudine for a long time [13]. Although non-YMDD LR HBV has been diagnosed [29], our knowledge on usage of ADV in LR hepatitis B is limited to YMDD mutants. LR hepatitis B is a major problem among renal transplant recipients with chronic hepatitis B. ADV has recently been demonstrated to be successful in post-renal transplant patients with chronic LR HBV infection [30]. Unfortunately, there has not been enough evidence on usage of adefovir in YMMD in renal transplantation.

Sometimes, patients receiving adefovir at doses of 10 mg/day for chronic hepatitis B have a "suboptimal" virological response (*i.e.*, a slow and moderate decrease in viral replication). Increasing the dose of ADV to 20 mg/day has recently been reported to be beneficial and safe in patients with LR HBV and a suboptimal response to adefovir at the dose of 10 mg/day [31]. For prediction of virologic response of ADV in patients with LR hepatitis B, ALT levels prior to the treatment, a viral load at three months of therapy, and viral decline by >3 $\log_{10}$ from the baseline value at three months were reported to be considerably associated with the HBeAg seroconversion within 12 months of therapy [32]. Tenofovir might be an effective therapeutic agent for HBV-infected patients with LR and suboptimal response to ADV [33]. Further investigations are needed to determine the most appropriate therapeutic protocol to overcome suboptimal virologic response in patients receiving ADV.

What complications have been reported?

Safety of ADV has also been proved in immunodeficient patients such as HIV-positive ones

as well as cirrhotic patients before and after liver transplantation [34]. There is no contraindication for administration of adefovir except known hypersensitivity to it or the ingredients in its formulation. Initially, no resistance has been reported in patients who were placed on ADV for up to 36 weeks [35]. In 2003-04, a very low resistance of 0, 2% and <4% were reported at years one, two and three of treatment, respectively [13, 14, 17, 18]. Compared to LR patients, the emergence of resistance against ADV has been reported slower in naive patients. Recently, adefovir has been demonstrated to be with a low resistance profile approximately 3%, 9%, 18%, and 28% after two, three, four, and five years, respectively [36]. Two factors including a high pretreatment HBV-DNA and unacceptable initial viral response (HBV-DNA ≥4 $\log_{10}$ copies/mL after six months of therapy) have been reported to be associated with ADV resistance [37]. Due to probability of ADV resistant mutants, using long-term ADV in patients with LR hepatitis B was challenging. In a recent report, no adefovir resistance has been shown in patients who were treated with a long-term combination of lamivudine+ADV with no history of ADV monotherapy [38]. Consequently, a combination therapy with lamivudine+adefovir may be protective against the emergence of adefovir resistance.

Hepatic side effects of ADV have been demonstrated. Liver complications such as hepatic failure, liver dysfunction and an increase in aminotransaminases were reported. Lactic acidosis and severe hepatomegaly with steatosis have been reported in patients with risk factors such as female gender, obesity and prolonged treatment with ADV. In addition, one successfully treated hemodialysis patient with fibrosing cholestatic hepatitis through ADV has been reported [15]. Hepatitis exacerbation has been seen following ADV discontinuation in up to 25% of patients and usually during 12 weeks after discontinuation of the drug according to clinical studies. Thus, hepatic function should be monitored closely at regular intervals after discontinuing ADV (*e.g.*, for up to 12 weeks).

Nephrotoxicity as well as underlying renal impairment may occur at higher daily dosages of ADV for treatment of HBV (30 mg) or HIV infection (60 and 120 mg) compared to the recommended doses (18). Furthermore, renal insufficiency and renal failure have been demonstrated in those who received ADV. No significant complication has been seen with adefovir in renal insufficiency except hypophosphatemia which could be compensated with oral phosphate supplements [4]. Prolonged treatment of HBV infection with ADV, even in recommended dosages (10 mg/day), may also lead to nephrotoxicity [2]. It is recommended to monitor renal function during ADV therapy and adjust dosages when necessary [12-14, 19]. So, the serum creatinine level has to be monitored monthly.

In post-renal transplant patients with LR hepatitis B, ADV was used and caused a minor worsening of the renal function and a decrease in urine output in few patients [39]. In 2005, a study was done by Fontaine, *et al.*, [30] on 12 patients with LR hepatitis B including 11 post-transplant patients and one on hemodialysis. They all had YMMD mutation after lamivudine therapy except one who did not respond to lamivudine. Thereafter, they were all placed on ADV at an initial dose of 10 mg/day. At the end, HBV-DNA decreased and renal function improved significantly, without any renal complications except mild hypophosphatemia. Some severe complications were seen due to underlying diseases-not ADV-including edema and proteinuria of 11 g/day, acute pyelonephritis, erysipelas, hepatocellular carcinoma, nausea, myalgia, asthenia and hyperurecemia [23].

Using ADV in patients with co-infection of HBV/HIV is challenging. Using ADV for treating HBV infection in HIV-infected patients may lead to HIV resistance. Dosage of ADV used for treating HBV infection is not adequate for suppressing HIV-RNA [13, 21]. Nowadays, checking HIV antibody is recommended in all patients before placing them on ADV. Some low incidence complications were retrieved from literature. Dermatologic complications like itching and rash; gastrointestinal complications including abdominal pain, diarrhea, flatulence, indigestion, nausea, vomiting and dyspepsia as well as neurologic complications like asthenia and headache have been reported. Besides, respiratory complications including cough, pharyngitis, sinusitis and fever were observed.

Using adefovir in renal insufficiency and renal transplantation

Although data about usage of ADV in renal insufficiency is scarce [15], it is not contraindicated on the condition that the dose of the drug is adjusted. Since ADV is eliminated through kidney, a dose adjustment is essential in renal insufficiency to prevent drug accumulation and renal complications [15]: 10 mg/day if the creatinine clearance is greater ≥50 mL/min; 10 mg/48 hr if the creatinine clearance is between 20 and 50 mL/min; 10 mg/72 hr if the creatinine clearance is between 10 and 19 mL/min and 10 mg/week following

dialysis, in hemodialysis patients [4]. It is proposed to use adefovir in post-renal transplant patients with LR HBV infection [1, 11, 12, 16, 20].

The experience on using ADV in renal transplant recipients is limited and further studies are warranted [40]. There was a report by Peters, *et al.*, [40] in 1999 about an asymptomatic HBV carrier who underwent renal transplantation in 1997. HBV infection was reactivated in a few months after renal transplantation, so the patient was placed on lamivudine. However, due to resistance to lamivudine, severe hepatic damage occurred. Therefore, liver was also transplanted in 1998. Lamivudine was discontinued and hepatitis B immunoglobin (HBIG) and ADV were started. As a result, liver enzyme levels were normalized, serum creatinine was decreased back to the normal range and HBV-DNA became negative [13].

Another case reported by Garcia, *et al.*, [10] in 2005 reported a 47-year-old man with ESRD and asymptomatic HBV infection who underwent renal transplantation in 1995. The outcome was favorable until 2000, when due to increased serum transaminase and HBV-DNA concentration, the patient was placed on lamivudine 100 mg/day. After two years, moderate to severe renal dysfunction was seen and liver enzymes kept on rising. In 2003, due to liver function deterioration and evidence of cirrhosis, lamivudine was discontinued and ADV was started. Short-term treatment with ADV led to a rapid decrease in liver enzyme levels and viral load. Besides, prothrombin time became normal and HBV DNA became negative and undetectable by PCR. It was observed that liver function stayed stable, even improved slightly, with a little decrease in serum creatinine level [10]. In a study performed by de Silva, *et al.*, [39] in 2006 on six post-renal transplant patients with LR hepatitis B infection, ADV was started for all of them. Their renal function was monitored every month and liver function every three months. Besides, HBV serology and HBV-DNA were checked every three months and every six months, respectively. Worsening of renal function, elevated serum creatinine and decreased urine output were seen in one of them, whereas the others showed favorable results [39].

Recommendations

1) Considering the dose adjustment, ADV seems to be safe in patients with chronic hepatitis B and some degrees of renal dysfunction. 2) Usage of ADV with or without lamivudine may be considered as a rescue in patients with LR HBV infection. 3) The results of utilizing ADV for treatment of hepatitis B in renal transplant recipients are encouraging. 4) Although low incidence of resistance against ADV has been initially reported, the frequency of ADV-resistant mutants seems to be increased. To overcome the new phenomenon of ADV resistant HBV, further surveillance and more appropriate usage are recommended.

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