Case Study in the Management of Patients with HBV-Related Decompensated Cirrhosis

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CASE

A 60 year-old Middle Eastern male with no prior history of chronic hepatitis B is admitted to the intensive care unit in grade II encephalopathy. He is found to be hepatitis B surface antigen (HBsAg)-positive and hepatitis B Core antigen, antibody (Anti-HBc) IgM-negative. His aspartate aminotransferase (AST) is 153, alanine aminotransferase (ALT) is 90IU/L; bilirubin is 1.4mg/dL, and international normalized ratio (INR) is 1.3. He has mild to moderate ascites. He is hepatitis Be antigen (HBeAg)-negative but his hepatitis B virus (HBV) DNA is pending. His blood urea nitrogen (BUN) is 34 and his serum creatinine is 1.5 (upper limit of normal 1.4). What would you do?

(a) No treatment, wait for serum HBV DNA results
(b) Start lamivudine
(c) Start adefovir dipivoxil
(d) Begin evaluation for liver transplantation and start lamivudine
(e) Begin evaluation for liver transplantation and start adefovir

Further studies become available. The patient's HBV DNA is found to be 3.2 x 10^7 copies/mL by a commercially available polymerase chain reaction (PCR). He is Anti-HBe-positive. His INR is repeated (next day) and it is now 1.7. His serum creatinine is 1.6 despite hydration and colloid expansion. Would this change your thinking about how to approach management?

(a) I would start lamivudine because of concerns about nephrotoxicity with adefovir
(b) I would start adefovir as soon as the patient's renal dysfunction improves
(c) I would use adefovir knowing that I could adjust the dose according to creatinine clearance as listed in the package literature
(d) I would not worry about starting adefovir since he is unlikely to have severe significant renal dysfunction

The patient is started on lamivudine. Six weeks later, he no longer has encephalopathy, AST, ALT and serum bilirubin have decreased to normal range, and serum HBV DNA has declined to 1.2 x 10^4 copies/mL. His serum creatinine has stabilized at 1.4, and the patient's INR is now 1.2.

The patient is maintained on lamivudine and does well for 11 months when his AST and ALT increase to 80 and 63, respectively. Serum HBV DNA is now 2.5 x 10^6 copies/mL. Genotyping results show lamivudine resistance (double mutant at positions 180 and 204). His serum creatinine is 1.7. Creatinine clearance is 40mL/minute. Now what would you do?

(a) Stop the lamivudine and start adefovir
(b) Add adefovir to lamivudine maintenance
(c) Add adefovir and consider stopping the lamivudine after two to three months
(d) Maintain the patient on lamivudine alone

NUCLEOSIDE ANALOGS FOR PATIENTS WITH ADVANCED CHRONIC HEPATITIS B

Nucleos(t)ide analogs reduce viral replication by competitive inhibition of HBV DNA polymerase and are the preferred treatment for patients with decompensated cirrhosis. They do not have any direct immunologic activity and only rarely have been associated with flares of aminotransferase levels [1]. Unlike interferon, these agents do not suppress bone marrow function.

Lamivudine use in stable cirrhosis

Long-term data on lamivudine maintenance therapy for advanced hepatitis B have recently been reported [2]. In a study with more than 600 patients with clinically compensated stage 4 or greater fibrosis (Ishak score), lamivudine was compared to placebo in the ability to prevent disease progression. In this study, lamivudine therapy (median treatment exposure 32 months) was shown to significantly reduce disease progression and the risk of hepatocellular carcinoma. In addition, the presence of YMDD mutant HBV reduced, but did not totally nullify the benefit of treatment.

Lamivudine use in decompensated cirrhosis

Lamivudine therapy has been a major breakthrough in the management of patients with decompensated HBV-related cirrhosis due to its potent inhibitory effects on HBV replication and its excellent safety record [3]. Treatment with lamivudine monotherapy before and after liver transplantation has provided proof of concept that viral suppression often improves the clinical status of patients and reduces the risk of recurrent infection after liver transplantation [4]. Lamivudine may also increase the likelihood of transplant-free survival. Investigators at the University of California, San Francisco, for example, have demonstrated that time to death or transplantation was significantly longer (P<001) and transplantation was less frequent (35% vs. 74%) in lamivudine treated patients compared to a historical untreated cohort that was matched for age, sex, and baseline Child Pugh status [5].

The major downside of lamivudine has been the high rate of resistance when used for longer than one year, and this appears to have greater clinical consequences in patients with diminished parenchymal reserve. Accordingly, the timing of initiation of lamivudine treatment

was a key issue in the past because patients with long waiting times for liver transplantation might develop resistance while awaiting surgery. Fortunately, this is no longer the case because patients with lamivudine resistance can be treated with adefovir dipivoxil or tenofovir isofumarate [6, 7]. HBV DNA and serum aminotransferase levels often remain lower than baseline after the emergence of lamivudine resistance, but without specific treatment histological responses have been shown to eventually become blunted in clinically stable patients [8]. Some reports suggest that progressive liver injury and liver failure occur more commonly when drug resistance occurs after liver transplantation, and this may be due to the viral enhancing effects of anti-rejection therapy [9].

Adefovir dipivoxil use in stable or decompensated cirrhosis

This is an oral prodrug of adefovir, a nucleotide analog with antiviral activity against both wild-type and YMDD mutant HBV. The remarkable thing about this drug is that resistance is rare, occurring in 2% of patients after two years of continuous use and approximately 4% of patients after 3 years [10]. Adefovir (10mg) can be used safely and effectively in patients with YMDD mutant HBV irrespective of whether the patient has clinically stable cirrhosis, decompensated cirrhosis or recurrent hepatitis B after liver transplantation (Figure 1) [6, 11, 12]. The decrease in HBV DNA levels has been associated with a favorable effect on Child Pugh status as well as improvement in biochemical parameters of liver function.

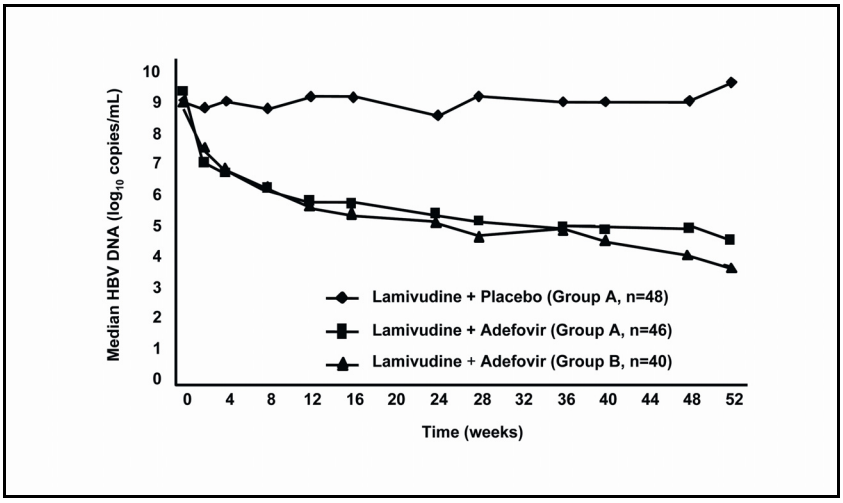

Figure 1: Virological and biochemical profiles of three groups of patients with YMDD mutant HBV who were either maintained with lamivudine alone (♦) or lamivudine and adefovir (■ and ▲). Group B patients (n=40) either had decompensated cirrhosis or recurrent hepatitis B after liver transplantation. Group A patients (n=94) were clinically stable.

Nephrotoxicity has been observed when adefovir is used in higher doses (30mg or more) than is currently recommended for hepatitis B (10mg). Thus, there may be some concern about the long-term administration of this agent in patients with concomitant renal dysfunction, particularly in patients who are treated after liver transplantation. While dose reduction according to the package insert based on creatinine clearance is advised, it is not known if this interferes with the ability of the drug to maintain viral suppression. In a recently reported study in which 324 patients were treated with adefovir before or after liver transplantation, changes in renal status were confirmed in 13% of patients [6]. Most of these patients had pre-existing renal dysfunction or were taking potentially nephrotoxic medications, however, making it difficult to attribute the change in renal function to adefovir therapy.

Other agents

There are several nucleoside analog drugs under development that have antiviral activity against YMDD mutant as well as wild type HBV [13]. Early clinical trials with entecavir look promising [14]. As this nucleoside has no known nephrotoxicity, it may play a particularly important role in the future management of renally compromised patients with lamivudine resistant HBV. Tenofovir is a drug which is chemically related to adefovir but is considerably less likely to be nephrotoxic at the effective dose (300mg). It may have even greater antiviral efficacy against lamivudine resistant HBV than adefovir [7]. Recently, the author treated a decompensated cirrhotic patient with tenofovir. The patient had marked improvement (Child Pugh C conversion to A) after just 4 months of therapy, and continued to do well with maintenance therapy (Figure 2). It is clear that in the relatively near future a number of therapeutic options will become available for lamivudine resistant patients with decompensated cirrhosis.

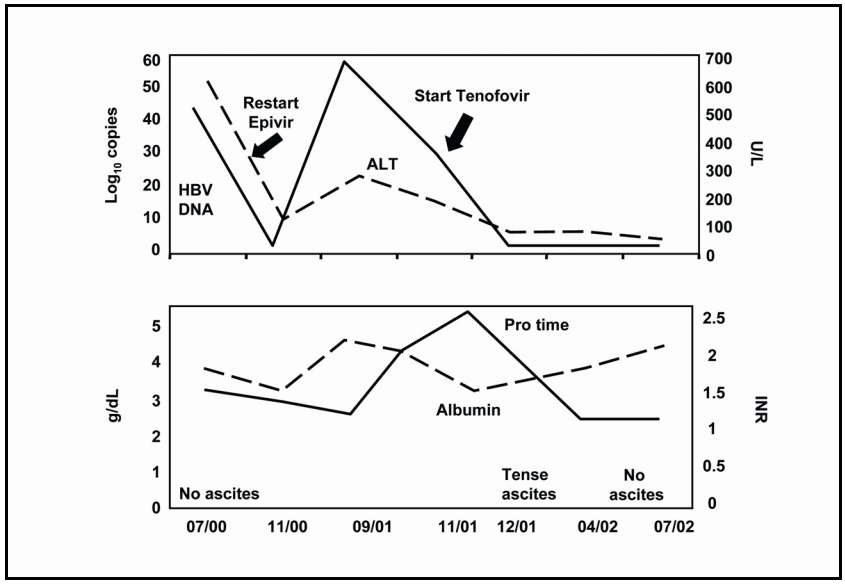

Figure 2: Virological and biochemical events in a 39 year-old nurse with decompensated cirrhosis due to HBeAg-positive chronic hepatitis B. The patient had been formerly treated successfully with lamivudine for two years and had stopped taking this nine months earlier. At the time of the reactivated hepatitis, lamivudine was restarted unsuccessfully. The patient continued to worsen and was started on tenofovir because adefovir was not yet available. Within 4 months, the patient had dramatic virologic, biochemical, and clinical improvement, going from Child Pugh C to A status. The patient died of unrelated causes two years later.

CASE DISCUSSION

There are several reasons to have instituted nucleoside analog therapy in the current case. First and foremost, is the potential for clinical stabilization. Despite the patient's severe encephalopathy he had a relatively low MELD score (15) upon presentation and was likely to be transplanted several months or more in the future. This interval provided time for continued viral suppression and clinical improvement. The literature supports the concept that the degree of

clinical improvement may reduce the need for transplantation [4, 6]. The second reason for treatment with a nucleoside analog is reduction in risk of recurrent hepatitis B. Lamivudine has been shown, for example, to reduce the risk of recurrent hepatitis B infection by approximately 40% [4]. Thus, the key question in the current case is not whether to use nucleoside analog therapy but which one to use as initial therapy? The emerging renal dysfunction in this patient makes lamivudine a better initial choice than adefovir. Tenofovir would also have been a reasonable (although more expensive) choice for first line therapy due to a lack of nephotoxicity at the 300mg dose, low resistance profile, and the probable need for long-term antiviral suppression in this patient with HBeAg-negative chronic hepatitis B.

Once resistance to lamivudine develops, as in this case, lamivudine should be continued in combination with a second nucleotide like adefovir or tenofovir. This is based upon the observation that a significant number of such individuals will have an ALT flare which is probably due to rapid emergence of wild type HBV. In one study in which lamivudine resistant patients received adefovir monotherapy, 37% of patients had an ALT flare of 5-10 times the upper limit of normal soon after discontinuing lamivudine [15].

Such flares have not been observed when patients are maintained on adefovir in combination with ongoing lamivudine maintenance therapy [12, 15].

CONCLUSIONS AND PERSPECTIVES

Cirrhosis due to infection with HBV is associated with decreased survival, but interferon can be dangerous in patients with relatively mild hepatic decompensation and should not be used once liver failure has emerged. Treatment of patients with advanced hepatitis B has been made simpler and safer with nucleoside analog therapy. Lamivudine resistance can be overcome with adefovir, but the potential for nephrotoxicity may make it difficult to use this agent in patients who are renally compromised. In the future, the development of alternative nucleoside analogs with greater antiviral potency, a low rate of viral resistance, and even better safety profiles will further improve our options in treating these seriously ill patients.

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