Fatal fulminant hepatitis B after withdrawal of entecavir treatment in a patient with HBeAg seroconversion

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To the Editor,

The presence of hepatitis B e antigen (HBeAg) is often associated with ongoing liver disease, whereas HBeAg seroconversion often coincides with loss of serum hepatitis B virus (HBV) DNA, normalization of liver biochemical tests, clinical remission and subsidence of hepatic inflammatory activity (1). Herein we desribe a patient with HBeAg reversion with acute liver failure after discontinuation of entecavir therapy.

A 49 year-old man was admitted to our hospital because of jaundice. Initial physical examination revealed a distended abdomen with ascites and flapping tremors. The laboratory investigations were as follows ; alanine aminotransferase : 252 U/L, aspartate aminotransferase : 245 U/L, prothrombin time (PT) : 22 s, International normalized ratio (INR) : 2.2, albumin : 2.8 g/dL, total bilirubin 25 mg/dL ; hepatitis B surface antigen (HBsAg) and HBeAg positive. Detailed medical history revealed that he had been treated with entecavir 0.5 mg/day for HBeAg positive chronic hepatitis B between 2009 and 2010. Before starting treatment, his abdominal ultrasonography and liver function tests, including PT, albumin level, and albumin/globulin ratio were normal. Treatment was discontinued 48 weeks after HBeAg seroconversion. At that time, his liver function tests were normal, with undecetable HBV DNA levels. He was regularly followed up at 3 and 6 months after discontinuation of therapy. During the follow-up period, HBV DNA levels progressively increased with high levels of serum transaminase. The laboratory examinations of the patient are summarized in Table 1. The patient was hospitalized with the diagnosis of acute liver failure. Abdominal sonography demonstrated a cirrhotic liver and diffuse ascites. Esophagogastroduodenoscopy showed esophageal and fundal varices with portal gastropathy. Entecavir therapy was re-started. On the 15th day of hospitalization he remained severly oliguric and hemodialysis was performed, while entecavir tretament was withdrawn. During the follow-up period the patient's liver functions continued to decline with total bilirubin rising to 32 mg/dl, direct bilirubin : 22 mg/dl, PT : 42 s, INR : 3.9. On the 30th day of hospitalization the patient's clinical condition detoriated and he died due to multiorgan failure.

Table 1. — **HBeAg/Anti HBeAg /HBV DNA status and liver enzyme Levels**

	HbeAg	Anti HBeAg	HBV-DNA (iu/ml)	Liver Enzymes
2009	+	-	64.461.310	AST : 145 (U/L), ALT : 214 (U/L) Total bilirubin : 1,2 mg/dL
2010	-	+	-	Normal
01/2011	-	+	-	Normal
04/2011	-	+	< 15	Normal
07/2011	-	+	9287	Normal
09/2011	+	-	153.193.526	ALT : 252(U/L), AST : 245(U/L), Total bilirubin : 16 mg/dL

ALT : Alanine aminotransferase, AST : Aspartate aminotransferase.

For patients that are HBeAg-positive, durable HBeAg seroconversion is a satisfactory end-point since it has been shown to be associated with improved prognosis (2). Studies have suggested that nucleos(t)ide analogue therapy can be stopped 24 to 48 weeks after HBeAg seroconversion. HBsAg should be checked at 6-month intervals after HBeAg seroconversion (2).

In the present case, the treatment of Hepatitis B was interrupted 48 weeks after the development of HBeAg seroconversion according to the EASL Guideline for treatment. However, after cessation of therapy, HBeAg reversion developed with acute liver failure. Some authors suggest that measurement of HBV DNA after HBeAg seroconversion is a useful method for predicting HBeAg reversion risk (3). In addition, the presence of core promoter mutations was associated with re-emergence of serum HBeAg (4). However, no effective and reliable tests are available to predict HBeAg reversion. For this reason, it may be speculated that in some patients the duration of treatment should be longer than 48 weeks.

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