



Editorial

Is alanine aminotransferase flare-up in nucleos(t)ide analogue treatment of chronic hepatitis B a promising, rather than a devastating, sign?

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See Article on Page 154

Hepatitis B is the most common cause of chronic viral hepatitis in the world, and an estimated 257 million people are living with a current hepatitis B virus (HBV) infection, which is defined as being HBsAg positive. In 2015, 887,000 deaths were due to hepatitis B, mostly from complications such as cirrhosis and hepatocellular carcinoma.¹ The initial antiviral therapy for chronic hepatitis B (CHB) was interferon, which functioned as an immune modulator to enhance the host immunity against HBV. However, its clinical efficacy was suboptimal; the rate of virological response defined as HBeAg seroconversion was 15-32%.^{2,3} Since the first oral nucleoside analogue (NUC) for CHB, lamivudine, was approved in 1998, it has shown a rapid virologic suppression, but long-term treatment with lamivudine has induced the development of drug-resistant variants.^{4,5} The clinical practice guidelines suggested entecavir (ETV) and tenofovir dipivoxil fumarate (TDF) as the first line oral NUCs because these drugs showed high antiviral efficacy and high genetic barrier for drug resistance.⁶⁻⁸ Owing to effective oral

NUCs, the long-term outcome of patients with CHB dramatically improved, and many patients escaped liver-related mortality.⁹

Nevertheless, some patients with CHB showed elevated alanine aminotransferase (ALT) levels during NUC therapy, which made clinicians concerned about aggravation of liver function and failure of antiviral treatment. In the era of interferon therapy, this phenomenon was also observed during the early stage of treatment. Flink et al. presented two types of ALT flares in patients with CHB treated with peg-interferon α -2b, in which ALT flare following a decrease in HBV DNA was associated with high treatment response, compared with ALT flare following an increase in HBV DNA (58% versus 20%).¹⁰ For lamivudine, acute ALT flare was related to high HBeAg loss or seroconversion. In contrast, late ALT flare during treatment implied the occurrence of drug resistance mutation and biochemical breakthrough following virological breakthrough.⁵

According to a study by Seo et al.¹¹, 7 of 181 CHB patients (3%) showed early ALT flare ($>10\times$ ULN) without viral breakthrough during administration of TDF, and all of them recovered without decompensation and were able to maintain virological response.

Abbreviations:

ALT, alanine aminotransferase; CHB, chronic hepatitis B; ETV, entecavir; HBV, hepatitis B virus; NUC, nucleos(t)ide analogue; TDF, tenofovir dipivoxil fumarate

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Table 1. Proportion of on-treatment alanine aminotransferase elevation among patients with chronic hepatitis B in major clinical trials dealing with nucleos(t)ide analogues

	Grade 3 (ALT >5-10×ULN) and 2×baseline value	Grade 4 (ALT 10×ULN) and 2×baseline value
Entecavir		
Chang et al. (2006) ^{14*}	37/354 (10%)	12/354 (3%)
Lai et al. (2006) ^{15†}	6/325 (2%)	3/325 (<1%)
Tenofovir disoproxil fumarate		
Marcellin et al. (2008) ^{12‡}	13/426 (3%)	11/426 (3%)
Chan et al. (2016) ^{13‡}	36/292 (13%) [§]	

ALT, alanine aminotransferase; ULN, upper limit of the normal range.

*Entecavir 0.5 mg/day for a minimum of 52 weeks in HBeAg-positive CHB; †Entecavir 0.5 mg/day for a minimum of 52 weeks in HBeAg-negative CHB; ‡Tenofovir disoproxil fumarate 300 mg/day for 48 weeks in HBeAg-positive CHB; §This included grade 3 and 4 ALT elevation.

Although TDF is one of the highly potent NUCs that induce rapid reduction of viral load, a few subjects taking TDF showed early ALT flare without transient decompensation.^{12,13} This trend was also similar to cases treated with ETV (Table 1).^{14,15} Therefore, early ALT flare on NUCs seems to be a good predictor of treatment response in NUC therapy for CHB.

This phenomenon can be explained as an immune reconstitution phenomenon. In HIV/HBV co-infected patients with a normal liver function profile and high HBV viral load, highly active anti-retroviral therapy introduced acute hepatitis after the CD4+ T-cell count was recovered. This is representative of immune reconstitution inflammatory syndrome, in which the cytopathic lysis of HBV-infected hepatocyte occurs through recovered immunity from medication.¹⁶ In HBV-mono infected patients, the high viral load was associated with suppression of the adaptive immune system through CD4+ and CD8+ T-cell mediated reactions. Boni et al. showed that during the early period of lamivudine treatment in HBeAg-positive CHB patients with high a viral load, CD4+ T-cell proliferation was elevated since the commencement of NUC therapy. Two of 12 patients showed ALT elevation during treatment.¹⁷ This study suggested that restoration of the antiviral immune mechanism by suppression of high viremia on NUCs was associated with host-related cell lysis of HBV-infected hepatocytes.

However, it is prudent to closely monitor the liver function in the early course of NUC therapy in the patients with CHB, especially in the case of decompensated cirrhosis, acute liver failure, or acute on chronic liver failure. In these cases, there is a high risk of mortality by severe necroinflammation by immune reconstitution. Fujiwara et al. showed that steroid therapy was effective during the early period of NUC therapy in severe acute hepatitis B¹⁸; however, this strategy was not validated in a large patient population.

In conclusion, Seo et al.¹¹ showed that early ALT flare on highly potent NUC was relatively safe and led to successful virological responses in compensated CHB patients. In addition, to achieve partial immune reconstitution by NUCs, additional immune therapy is expected to completely eliminate HBV in the liver in further investigations.

Conflicts of Interest

Nae-Yun Heo received lecture fees from Gilead Sciences and Bristol-Myers Squibb.

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