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Editorial

Switch to tenofovir-based therapy or to continue adefovir-based therapy in CHB patients with suboptimal response to adefovir-based combination?

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See Article on Page 443

Hepatitis B virus (HBV), a major cause of liver disease, has infected approximately 2 billion people worldwide, and more than 350 million are chronically infected.[1] Persistent viral replication increases the risk of progression to liver cirrhosis, development of hepatocellular carcinoma (HCC) and liver-related death.[2-4] Therefore, the goals of antiviral therapy are to improve quality of life and survival by preventing progression of the disease to cirrhosis, HCC and death[5,6] These goals can be achieved if HBV replication can be suppressed completely. Recent clinical studies showed that long-term suppression of HBV replication using anti-viral agents in patients with CHB can prevent progression to liver cirrhosis, hepatic failure and the development of HCC.[2-5,7-9]

Lamivudine (LAM), adefovir dipivoxil (ADV), telbivudine (Ltd), entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are available nucleos(t)ide analogues (NAs) for treating CHB patients worldwide. However, long-term treatment with NAs other than ETV and TDF increase the risk of drug resistance up to 80% because of low antiviral efficacy and low genetic barrier,[10-14] Therefore, most guidelines recommend peg-interferon, ETV, or TDF in treatment-naïve patients.[5,15]

ADV add-on therapy has been widely used as a rescue therapy for patients with LAM-resistant CHB before TDF was not available.[6,16] However, suboptimal response has been commonly observed in patients receiving ADV-based therapy.[17-19]

TDF, one of very potent antiviral agent with a high genetic barrier, showed excellent virologic response (VR), defined as serum HBV DNA level undetectably by sensitive PCR method, in NAs-naïve[20,21] and NAs-resistant patients.[22-26] Clinical efficacies of TDF therapy in NA-naïve and experienced patients are summarized in Table 1. In NA naïve patients, a significantly higher proportion of patients receiving TDF than of those receiving ADV had reached VR at 48 weeks (Table 1). Almost all patients who received TDF therapy showed VR without any evidence of resistance at seven year.[14] In patients with LAM-resistant patients receiving TDF or TDF/emtricitabine (FTC), VR achieved in 89.4% and 86.3% at 96 weeks of therapy, respectively,[24] without any evidence of TDF resistance during 5 years of follow-up.[27] TDF also showed high

Abbreviations:

ADV, adefovir dipivoxil; CHB, chronic hepatitis B; ETV, entecavir; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LAM, lamivudine; TDF, tenofovir disoproxil fumarate; VR, virologic response

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Table 1. Summary of randomized controlled trials to evaluate the anti-viral efficacy of tenofovir-based therapy in patients with NAs-naïve or experienced patients

Authors	Study populations	Intervention	Primary efficacy end point	Virologic response
Marcellin et al. (2008)[20]	NAs-naïve	TDF vs. ADV HBeAg (+) (n=266) HBeAg (-) (n=375)	HBV DNA level <69 IU/mL at 48 week	76% vs. 13% in HBeAg (+) patients 96.8% vs. 71.2% in HBeAg (-) patients
Fung et al. (2014)[24]	LAM -resistant	TDF (n=141) vs. TDF/FTC (n=139)	HBV DNA level <69 IU/mL at 96 week	89.4% vs. 86.3 % (*P*=0.43)
Lim et al. (2016)[25]	ADV-resistant (100% LAM-resistant)	TDF (n=50) vs. TDF/ETV (n=52)	HBV DNA level <15 IU/mL at 48 week	62% vs. 63.5% (*P*=0.88)
Lim et al. (2016)[26]	ETV-resistant	TDF (n=45) vs. TDF/ETV (n=5)	HBV DNA level <15 IU/mL at 48 week	71% vs. 73% (*P*=0.99)
Berg et al. (2010)[23]	Suboptimal response to ADV (73% of the patients had received prior LAM therapy)	TDF (n=53) vs. TDF/FTC (n=52)	HBV DNA level <69 IU/mL at 48 week	81% vs. 81% (*P*=ns)
Yang et al. (2015)[31]	Suboptimal response to ADV/LAM (prior LAM resistance patients)	TDF (n=28) vs. continue ADV/LAM (n=31)	HBV DNA level <200 IU/mL at 48 week	96.43% vs. 29.0% (*P*<0.001)
Lee et al. (2016)[30]	Suboptimal response to ADV-based combination therapy due to NA resistance (LAM-resistant 9, Ldt-resistant 14, ETV-resistant 9)	TDF +NA (n=16) vs. continue ADV+NA (n=16)	HBV DNA level < 60 IU/mL at 48 week	81.3% vs. 56.3% (*P*<0.001)

ADV, adefovir dipivoxil; ETV, entecavir; TDF, tenofovir disoproxil fumarate; TDF/FTC, TDF/emtricitabine; LAM, lamivudine; NAs, nucleos(t)ide analogues.

rate of VR in patients with ETV resistance.[26] In a randomized controlled trial conducted by Lim et al.[26] the proportion of patients with HBV DNA <15 IU/mL was high in patients who received TDF and TDF+ETV groups (71% vs. 73%; *P*=0.99). In patients with ADV-resistant patients with prior LAM resistance, the proportion of patients with HBV DNA <15 IU/mL was not significantly different between the TDF-TDF and TDF/ETV-TDF groups at weeks 48 (62% vs. 63.5%; *P*=0.88) and 96 (64% vs. 63.5%; *P*=0.96), suggesting that TDF monotherapy or combination therapy is effective even in patients with NAs-resistant patients.

There are several studies to evaluate the antiviral efficacy of TDF monotherapy or combination in patients with suboptimal response to ADV with or without prior resistance to LAM.[23,28,29] Berg, et al. conducted a randomized controlled trial to compare the anti-viral efficacy of TDF-based therapy for patients with CHB who had a suboptimal response to ADV (73% of the patients had received prior LAM therapy). A TDF monotherapy and TDF+FTC combination therapy showed similar VR at 48 week (81% vs. 81%).[23] Cho et al. reported that the rate of VR was about 86.5 % through TDF monotherapy or TDF-based combination therapy in CHB patients with suboptimal responses to ADV plus LAM combination therapy.[28] Park et al. reported that the rate of VR was significantly higher in patients receiving TDV+ETV than in those receiving ADV+ETV for 12 months (84.8% vs. 26.7%, *P*<0.001).[29] However, little randomized controlled trials are available to compare between to switch into TDF-based therapy or to continue ADV-based therapy in CHB patients with suboptimal response to ADV-based therapy.

In the current issue, Lee et al.[30] conducted a randomized controlled trial to compare the antiviral efficacy comparing between switching to TDF+NAs therapy and continuing current ADV+NA therapy in patients with suboptimal response to ADV-based therapy. They clearly showed that TDF+NAs therapy provide better VR compared to continue ADV+ NA who showed suboptimal response to ADV-based therapy (87.5% vs. 37.5% at 48 weeks, *P*=0.002).

However, there are several limitations of the study. First, even though the study was designed as a randomized controlled trial, the sample size was very small to conclude the results. Second, in this study, there was no TDF monotherapy group because TDF monotherapy and TDF+NAs combination therapy did not show any difference in VR in NA-experienced patients (Table 1). In addition, Yang et al.[31] compared the antiviral efficacy between switching to TDF monotherapy and continuing ADV+LAM combination therapy in patients with suboptimal response to ADV+LAM (prior LAM resistance patients) therapy. TDF monotherapy showed higher VR compared with continuing ADV+LAM combination therapy (96.43% vs. 29.0%; *P*<0.001). ADV monotherapy in patients with

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LAM resistance increase the risk of drug resistance.[17-19] Therefore, there is a concern about selective pressure on pre-existing resistant mutant viruses.[32] However, clonal analysis revealed that there is no significant selective pressure on pre-existing ADV or LAM resistant strains in during NA monotherpay patients with CHB and suboptimal response to ADV therapy who receiving TDF or TDF+FTC combination therapy.[33]

In conclusion, considering the result from current study[30] and previous studies,[23-26,31] TDF with or without NAs might be very effective to treat the patient with suboptimal response to ADV-based therapy.

Conflicts of Interest

The author has no conflicts to disclose.

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