pISSN 2287-2728
eISSN 2287-285X

CMH

https://doi.org/10.3350/cmh.2017.0045
Clinical and Molecular Hepatology 2017;23:219-221

Editorial

Is tenofovir monotherapy a sufficient defense line against multi-drug resistant hepatitis B virus?

Yun Bin Lee[1], and Jeong-Hoon Lee[2]

[1]Department of Internal Medicine, CHA Bundang Medical Center, CHA University, Seongnam; [2]Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, Korea

Keywords: Chronic hepatitis B; Multi-drug resistance; Entecavir; Tenofovir; Rescue therapy

See Article on Page 230

Clinical resistance to tenofovir disoproxil fumarate (TDF) did not develop in any patient after 8 years of TDF treatment in a phase III clinical trial for treatment-naïve patients with chronic hepatitis B (CHB).[1] Potent efficacy and high barrier to resistance of TDF have been established, even in patients who have been previously treated with nucleos(t)ide analogues (NUCs) or have NUC-resistant hepatitis B virus (HBV) variants. We previously reported that TDF-based rescue therapy was effective in patients harboring lamivudine (LAM)-resistant or multidrug-resistant HBV variants.[2,3] Moreover, two randomized controlled trials evaluating the efficacy of TDF monotherapy in patients infected with HBV variants resistant to adefovir (ADV) and entecavir (ETV) were conducted, and non-inferior antiviral efficacy compared with TDF plus ETV combination therapy was demonstrated.[4,5] On the basis of *in vitro* and *in vivo* data, there was concern that HBV susceptibility to TDF may be reduced in patients with HBV strains with substitutions conferring ADV resistance (rtA181T/V and rtN236T), but TDF has shown antiviral efficacy dispelling such concern. Thus, recently updated international guidelines recommend switching to TDF or tenofovir alafenamide as the first-line treatment option for patients with HBV variants resistant to ETV.[6,7] However, no long-term data have been driven from clinical practice to assess the antiviral efficacy of TDF monotherapy in patients with ETV resistance.

In this issue of Clinical and Molecular Hepatology, a Korean real-world study by Jeon, et al. indicates that TDF monotherapy was as effective as TDF plus LAM or ETV combination therapy for the treatment of patients infected with HBV strains resistant to both LAM and ETV.[8] Seventy-three patients with resistance to LAM and ETV were treated with TDF-based rescue therapy for at least 6 months. During a median TDF-based treatment period of 37 months, 63 of 73 patients (86.3%) achieved virologic response, defined as undetectable HBV DNA by quantitative polymerase chain reaction assay (<12 IU/mL). Virologic response rates in patients treated with TDF alone (n=12) were comparable to those in patients treated with TDF plus LAM (n=19) and TDF plus ETV (n=42) (88.4%, 94.7%, and 84.2%, respectively, at 24 months; P=0.200). On multivariate analysis, lower baseline HBV DNA level was an independent predictive factor of virologic response achieved by TDF-based rescue therapy (hazard ratio [HR]=0.723;

Abbreviations:

ADV, adefovir; CHB, chronic hepatitis B; ETV, entecavir; LAM, lamivudine; NUC, nucleos(t)ide analogue; TDF, tenofovir disoproxil fumarate

Corresponding author : Jeong-Hoon Lee
Department of Internal Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel. +82-2-2072-2228, Fax. +82-2-743-6701
Email: pindra@empal.com or JHLeeMD@gmail.com
http://orcid.org/0000-0002-0315-2080

Received : Aug. 17, 2017 / **Accepted :** Aug. 21, 2017

P<0.001). However, we must consider the possibility of a type II error underlying Jeon, et al. study, which results from a sample size that is not large enough to detect small differences between TDF monotherapy and TDF-based combination therapies. In addition, baseline HBV DNA level, which was the only independent factor predictive of virologic response, differed significantly among the three groups (*P*=0.021). The proportion of HBeAg-positive patients was lower, albeit non-significant (*P*=0.096), in the TDF monotherapy group (66.7%) than in the TDF plus LAM combination therapy group (89.5%) and in the TDF plus ETV combination therapy group (90.5%). Therefore, a real-world study with a larger sample size and/or a sufficiently long-term follow-up is needed to demonstrate the non-inferior efficacy of TDF monotherapy compared to TDF-based combination therapy. To adjust for treatment selection bias, which is an inevitable challenge of retrospective studies, statistical methods (e.g., propensity score analysis) may be adopted. Nevertheless, Jeon, et al. study is worthy of consideration as a real-world study of ETV-resistant CHB patients from Korea and advocates the switching-to TDF monotherapy as recommended by the international guidelines.[6,7]

Jeon, et al. study did not include ADV-experienced patients or patients with resistance to ADV. As aforementioned, if patients have experienced and failed ADV treatment or if genotypic resistance to ADV has emerged prior to TDF treatment, HBV susceptibility to TDF may be decreased, which may, in turn, attenuate the antiviral activity of TDF. When the virologic response rates after TDF treatment were compared between NUC-experienced and NUC-naïve patients, ADV-experienced patients showed lower virologic response rates compared to NUC-experienced but ADV-naïve patients (68.8% versus 89.1%). Furthermore, previous exposure to ADV was determined to significantly influence virologic response after TDF treatment in multivariate analysis (HR=0.37; *P*=0.003).[9] Even though TDF monotherapy was as effective as TDF plus ETV combination therapy in ADV-resistant patients in the previous study, we would need more long-term follow-up data to confirm the antiviral efficacy of TDF against ADV-resistant HBV strains.[5]

We have two therapeutic options for patients harboring HBV variants resistant to ETV—whether to switch to TDF monotherapy or add TDF on ETV. Previous study findings, including those of Jeon, et al. study, have pointed towards TDF monotherapy as an uncontroversial option taking into consideration the lower cost and potential risk of adverse events, as well as the non-inferior efficacy compared to ETV plus TDF combination therapy. However, antiviral resistance to any NUC can emerge, even if ETV or TDF has high barrier to resistance. It is clear that the barrier of tenofovir against resistance is very high, but HBV quasispecies perpetually evolve and acquire drug-resistant strains. The barriers to potent antiviral drugs can eventually collapse if the drug-resistant HBV strains are selected under antiviral pressure during long-term antiviral therapy; therefore, we should be alert and prepared with carefully selected treatment strategies. The most critical adverse event of treatment with any antimicrobial agent is the emergence of drug resistance. It is worth noting that TDF may be an exception to this rule and provide a last line of defense against drug resistance.

Conflicts of Interest

The authors have no conflicts to disclose.

REFERENCES

1. Marcellin P, Gane EJ, Flisiak R, Trinh HN, Petersen J, Gurel S, et al. Long term treatment with tenofovir disoproxil fumarate for chronic hepatitis B infection is safe and well tolerated and associated with durable virologic response with no detectable resistance: 8 year results from two phase 3 trials. Hepatology 2014;60(Suppl 1):313A-314A.
2. Lee YB, Jung EU, Kim BH, Lee JH, Cho H, Ahn H, et al. Tenofovir monotherapy versus tenofovir plus lamivudine or telbivudine combination therapy in treatment of lamivudine-resistant chronic hepatitis B. Antimicrob Agents Chemother 2015;59:972-978.
3. Lee YB, Lee JH, Lee DH, Cho H, Ahn H, Choi WM, et al. Efficacy of entecavir-tenofovir combination therapy for chronic hepatitis B patients with multidrug-resistant strains. Antimicrob Agents Chemother 2014;58:6710-6716.
4. Lim YS, Lee YS, Gwak GY, Byun KS, Kim YJ, Choi J, et al. Monotherapy with tenofovir disoproxil fumarate for multiple drug-resistant chronic hepatitis B: 3-year trial. Hepatology 2017 Mar 30. [Epub ahead of print].
5. Lim YS, Byun KS, Yoo BC, Kwon SY, Kim YJ, An J, et al. Tenofovir monotherapy versus tenofovir and entecavir combination therapy in patients with entecavir-resistant chronic hepatitis B with multiple drug failure: results of a randomised trial. Gut 2016;65:852-860.
6. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016;63:261-283.
7. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370-398.
8. Jeon HJ, Jung SW, Park NH, Yang Y, Noh JH, Ahn JS, et al. Efficacy of tenofovir-based rescue therapy for chronic hepatitis B patients with resistance to lamivudine and entecavir. Clin Mol Hepatol

https://doi.org/10.3350/cmh.2017.0045

2017;22:230-238.
9. Chung GE, Cho EJ, Lee JH, Yoo JJ, Lee M, Cho Y, et al. Tenofovir has inferior efficacy in adefovir-experienced chronic hepatitis B patients compared to nucleos(t)ide-naive patients. Clin Mol Hepatol 2017;23:66-73.