EDITORIAL

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Is tenofovir disoproxil fumarate an all-powerful weapon in the treatment of chronic hepatitis B?

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Tenofovir disoproxil fumarate (TDF) belongs to a class of antiretroviral agents known as nucleotide analog reverse transcriptase inhibitors. These drugs target enzymes that are crucial to the replication of human immunodeficiency virus (HIV) and hepatitis B virus (HBV). TDF is prescribed to HIV patients with or without HBV. TDF also shows excellent efficacy in the suppression of HBV replication in treatment-naïve patients with chronic hepatitis B (CHB) [1] and in 2008 it was approved as the primary drug for the treatment of these patients. TDF was recently joined by entecavir (ETV), which also has a high antiviral potency and a high genetic barrier against the emergence of resistance. The two drugs are currently the mainstays of therapy in treatment-naïve CHB patients.

Since the end of the 1990s, many CHB patients have been treated with antivirals despite the low genetic barrier to resistance of these drugs. As a result, there is now a large number of patients with various antiviral mutation including multi-drug resistance, who are difficult to treat. The long-term effective suppression of HBV allows the regression of fibrosis and cirrhosis and delays the development of hepatocellular carcinoma as well as its progression [2,3]. Thus, the emergence of antiviral resistance has significantly reduced the beneficial effects of antivirals. Moreover, effective antiviral therapy using a minimum number of drugs has become a major challenge in the management of CHB patients with antiviral resistance.

The choice of a "rescue therapy" for patients with antiviral-resistant CHB requires the profiling of antiviral drugs to identify those without cross resistance. In clinical practice, patients with drug resistance should be treated with a combination of nucleoside and nucleotide analogues that do not show cross resistance, to prevent the emergence of multidrug resistance that often occurs during sequential monotherapy. However, this approach has had limited success; for example, subsequent adefovir (ADV) resistance during combined lamivudine (LMV) and ADV therapy has a 5-year emergence rate as high as 10.2% in LMV-resistant CHB patients [4]. In addition, the optimal therapeutic strategy for resistance to ADV, ETV, or multi-drug resistance has yet to be determined.

The study of Kim et al. [5] reported in *The Korean Journal of Internal Medicine* thus provides timely information on the optimal therapy for CHB patients with drug-resistant disease. Their study enrolled 52 CHB patients with failure to respond to two or more nucleos(t)ide analogues who were switched to TDF in a monotherapy or combination reg-

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imen. During a median of 34.5 months of TDF-based treatment, the cumulative incidence of achieving a virologic response (HBV DNA < 9 IU/mL) was 74.2% at 24 months and 96.7% at 48 months. A virologic response was associated only with a low baseline HBV DNA level and was not affected by whether TDF was administered as monotherapy or combination therapy or by the presence of mutations associated with resistance to nucleos(t)ide analogues. Furthermore, although six patients experienced viral breakthrough, in all patients the viral load declined below the previous nadir, either spontaneously or following good therapeutic compliance. The authors of the study concluded that TDF, whether as monotherapy or in combination with another nucleoside analogue, is an effective therapy for CHB patients with multiple nucleosi(t)de failure.

Nonetheless, despite the relatively long follow-up duration (median, 35.5 months), the results of that study should be interpreted with caution, because of its retrospective design and the small number (52) of patients enrolled. Moreover, more than half of the patients (53.6%) had either no genotypic mutation (n = 8) or only a LMV mutation (n = 22) and were thus more likely to better respond to TDF.

Cross-resistance data obtained *in vitro* showed full sensitivity to TDF in the presence of LMV and ETV resistance mutations and intermediate sensitivity in the presence of ADV resistance mutations [6,7]. These results encouraged physicians to choose a TDF-based therapy for their CHB patients with resistance to various antiviral agents. Worldwide guidelines currently recommend TDF-based monotherapy or combination therapy as the first-line treatment of patients with antiviral-resistant CHB [6,8,9]. However, sensitivity to TDF is decreased by up to tenfold in patients with dual ADV mutations, such as rtA181V + rtN236T [7]. A European multicenter retrospective study similarly reported that ADV resistance impairs the efficacy of TDF. In that study, 33% of the patients with, but 90% of those without, initial ADV genotypic resistance had HBV DNA levels below the limit of detection (HBV DNA < 400 copies/mL) after 12 months of TDF monotherapy [10]. Thus, the efficacy of TDF-based therapy for antiviral resistance may be less than we have come to expect and the optimal therapeutic strategy for the management of CHB patients with antiviral resistance remains to be determined. The few reports on TDF-based therapy for patients with antiviral resistance are either retrospective studies or were based on a small series of patients. Prospective controlled studies have been conducted but they included patients with a suboptimal response as well as those with confirmed genotypic resistance mutations, which makes it difficult to draw clear conclusions from their findings.

Recently, several well-controlled randomized studies of TDF-based regimens have been reported [11-13]. Their aim was to determine the optimal therapeutic strategy for CHB patients with confirmed antiviral resistance mutations.

Fung et al. [11] compared TDF monotherapy with combined TDF and emtricitabine therapy in CHB patients with genotypic LMV resistance. After 2 years of treatment, the rate of undetectable HBV DNA (HBV DNA < 400 copies/mL) was 89% in the TDF monotherapy group (n = 141) and 86% in the combination therapy group (n = 139). The difference was not statistically significant and no novel mutations were detected. The authors concluded that the antiviral effect of TDF monotherapy was satisfactory and comparable to that of combined TDF and emtricitabine therapy [11].

A randomized controlled study involving five Korean medical centers was carried out in patients with ADV resistance receiving TDF-based therapy [12]. Patients with documented ADV resistance mutations and serum HBV DNA > 60 IU/mL were randomized to receive TDF monotherapy (n = 50) or a combination of TDF + ETV (n = 52) for 48 weeks. The results showed that at week 48, 62% of the patients in the TDF monotherapy group had HBV DNA < 15 IU/mL compared to 63.5% of those in the combination therapy group. Viral breakthrough occurred in only one patient in each group and in both cases was attributed to low compliance. No novel mutation was documented. This study suggested that in CHB patients with ADV resistance, TDF monotherapy yields a virologic response similar to that achieved with TDF + ETV for at least 48 weeks. It should be noted that 29% of the patients in that study harbored double ADV resistance mutations (rtA181T/V + rtN236T) and 84% also had resistance mutations to LMV and/or ETV; i.e., multidrug resistance. Nevertheless, the antiviral effect was sufficiently strong in both regimens. The only concern not resolved in that study was in the subgroup

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analysis of patients with double ADV resistance mutations, in whom the decrease in serum HBV DNA tended to be slower in the TDF monotherapy group (–2.42 $\log_{10}$ IU/mL) than in the TDF + ETV group (–3.45 $\log_{10}$ IU/mL). Although the difference was not statistically significant ($p = 0.09$), long-term follow-up data are needed for these difficult-to-treat patients.

Thus far, only one randomized controlled trial has been performed in patients with ETV resistance who were treated with a TDF-based therapy [13]. The 90 patients with documented ETV resistance mutations and serum HBV DNA > 60 IU/mL were randomized to receive TDF monotherapy (n = 45) or combined TDF and ETV (n = 45) for 48 weeks. At week 48, 71% of the patients in the TDF monotherapy had HBV DNA < 15 IU/mL compared to 73% in the TDF + ETV group. Viral breakthrough occurred in only one patient, in the TDF monotherapy group, and was attributed to low compliance. No novel mutations were documented. Based on these results, the authors concluded that in CHB patients with ETV genotypic mutations the high virologic response to TDF is similar to that achieved with TDF + ETV during 48 weeks of treatment.

The results of Kim et al. [5] provide further support for the findings of those randomized controlled studies [11-13] suggesting a similar antiviral efficacy of TDF monotherapy and TDF plus nucleoside analogue combination therapy for CHB patients with one or more resistance mutations. However, there are also several reports showing that the antiviral effect of TDF monotherapy is limited in patients with ADV mutations, especially ADV double mutations [10,12]. Furthermore, considering the frustrating and disappointing experience in the previous era of antivirals with a low genetic barrier, the potential development of TDF resistance after several years of treatment in patients with persistent viremia in spite of TDF monotherapy or combination therapy cannot be ruled out.

In conclusion, while TDF-based therapy is a promising approach and is currently the best option in the management of CHB patients with antiviral resistance, we do not have sufficient data to conclude that TDF is the all-powerful drug suggested by some studies. Long-term follow-up data from well-designed trials will allow physicians to select the best therapeutic options for their patients with antiviral-resistant CHB.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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