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Editorial

Is the tenofovir based therapy almighty for previous treatment failure in chronic hepatitis B?

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During the past decade, management of drug resistant chronic hepatitis B (CHB) has been a major issue.[1,2] A series of new antiviral agents has been developed, which provided new treatment options as well as new resistance issues. Hence, to avoid multidrug resistance,[2] combination of antiviral agents without cross resistance has been recommended.[3] However, combination of the less potent drug did not produce a better efficacy while the incidence of additional resistance has decreased.[3-5] A more potent drug was needed for a better antiviral response. Tenofovir disproxil fumarate (TDF) is a nucleotide analogue which has a strong antiviral effect in treatment naïve as well as treatment experienced CHB patients for a long term periods.[6,7] Also its therapeutic efficacy is much improved than that of adefovir (ADV).[7] Therefore it is natural that combination therapy containing TDF show higher response rates than ADV-based therapies for management of drug resistance.

Previously, TDF plus ETV therapy was evaluated in Western countries,[8] and subsequently in Korea as well (Table 1).[9-11] This combination therapy showed a better virologic response compared with ADV plus ETV therapy in refractory or suboptimal responders to lamivudine (LMV) plus ADV combination in a retrospective study conducted in Korea (at 12 month, 84.8% vs. 26.7%, respectively, $P<0.001$).[11] The study included 58.7% of multidrug resistant CHB patients. Single arm studies of TDF-ETV combination were reported with a retrospective and a prospective design in Korea.[9,10] Virologic response was achieved in approximately 80% of patients within a year. Furthermore, the antiviral efficacy was not influenced by the type of prior therapies and baseline resistance mutations in both studies.[9,10]

In the current issue, Kim et al. introduced an interesting data regarding management of suboptimal responders to ETV-ADV combination therapy.[12] They observed the patients for a long term period up to 3 years after initiating ETV-ADV combination therapy for LMV, ADV, and/or ETV resistance. In addition, the authors evaluated the responses of TDF based therapy which was introduced in case of refractory to the ETV-ADV combination. Among 48 patients enrolled, 12 patients achieved virologic response within 3 years, and 26 patients switched to the TDF based therapies due to suboptimal response despite long term ETV-ADV combination therapy. Ten patients received TDF monotherapy, of whom 9 achieved virologic response while 9 patients received TDF combination therapy (TDF-LMV in 7 and TDF-ETV combination in 2 patients), of whom 8 achieved virologic response. The authors subsequently performed in vitro susceptibility test using replicons

Abbreviations:

ADV, adefovir; CHB, chronic hepatitis B; ETV, entecavir; LMV, lamivudine; TDF, tenofovir

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Table 1. Representative published data of tenofovir-based therapies from Korea for multiple treatment failures

Target population (n)	Design	Treatment duration	Key Findings	Author Ref. No.
LMV+ADV-R (28), LMV+ETV-R (45), and LMV+ADV+ETV-R (20)	RC	13 months	Cumulative VR rates at 6 mon were 55.7%, 75.0%, and 65.0%, respectively, by TDF-ETV combination. A lower baseline HBV DNA level was an independent factor for VR, but resistance type was not.	Lee[9]
Mixed of LMV, ADV, ETV-R (64)	PC	48 weeks	VR rate was 85.9% by TDF-ETV combination therapy. The combination is highly efficacious.	Park[10]
Suboptimal responder to LMV+ADV (63)	RC	12 months	VR rates were 84.8% vs. 26.7% by TDF-ETV vs. ADV-ETV, respectively. TDF-ETV combination showed better response rate.	Park[11]
Mixed of LMV, ADV, ETV-R (52)	RC	18 months	VR occurred in 72% vs. 78% of TDF-LMV vs TDF-ETV group, respectively. No difference between the groups.	Kim[14]
LMV-R+ADV-R (43) and LMV-R+ETV-R (113)	RC	15 months	Cumulative VR rates were 81.4% (ADV-R) and 84.1% (ETV-R) by TDF monotherapy. Multiplicity of resistance did not influence the VR.	Lee[15]
LMV+ETV-R (90)	RCT	48 weeks	VR rates were 71% vs. 73% in TDF monotherapy vs. TDF-ETV combination groups. Efficacy of TDF monotherapy was comparable that of TDF-ETV combination therapy.	Lim[17]
LMV+ADV-R or LMV+ADV+ETV-R (102)	RCT	96 weeks	VR rate was 64% in TDF monotherapy group and 63.5% in TDF-ETV combination followed by TDF group. TDF monotherapy provided high VR rate comparable to TDF-ETV combination therapy.	Lim[18]

LMV, lamivudine; ADV, adefovir; ETV, entecavir; TDF, tenofovir; R, resistance; PC, prospective cohort; RC, retrospective cohort; RCT, randomized controlled trial; mon, month; VR, virologic response.

obtained from 4 patients. Interestingly, albeit weak, replication was detected in the case of TDF monotherapy while no replication was observed under TDF-ETV combination therapy.

In this study, the response rate of ETV-ADV therapy was relatively low (12 out of 48 patients in 3 years) in the patients with multiple lines of treatment failure as expected, and it is consistent with previous report.[13] When comparing the TDF based therapies for ADV-ETV suboptimal responders, TDF monotherapy was efficacious and seemed not to be inferior to the TDF based combination therapies (90% vs 89%, respectively).

As mentioned above, the high efficacy of TDF-based combination therapy has been reported from Korea.[9-11,14] However, several additional data comparing TDF monotherapy and TDF-ETV combination therapy highlighted that monotherapy is as efficacious as combination therapy even for multiple drug resistance (Table 1).[15-18] For example, virologic response was achieved in 71% of patients with TDF monotherapy while in 73% of patients with TDF-ETV combination therapy (P>0.99) after 48 weeks in the presence of ETV resistance.[17] Likewise, in another prospective study which included ADV-resistant CHB patients, virologic response rate was 62% in the TDF monotherapy group after 96 weeks while 63.5% in the sequential 48-week TDF-ETV combination therapy and subsequent 48-week TDF monotherapy group (P=0.88).[18] Also, type of resistant mutation did not significantly affect the outcome under TDF monotherapy.[15,16] In contrast, there is a discrepancy between Kim et al's.[12] in vitro study finding and these clinical data, in terms of incomplete suppression of mutant HBV by TDF monotherapy. The HBV mutant clones retained no known TDF-resistant mutation, but efficacy of TDF was limited. The sequences denoted only LMV-resistant mutations together with several multiple site amino acid substitutions of which the significance has not been proved. As we still don't have experience of TDF resistance in HBV mono-infected patients, so it would be worth evaluating effect of individual substitutions on viral replication fitness under various antiviral agents including TDF. Otherwise, it would be difficult to acknowledge the role of the substitutions found in the clones.

Clinical course of patients with drug resistance is troublesome, not only because of decreased virologic response, but also because of lack of serologic response. Most of the patients included in Kim et al.[12] study were HBeAg positive, i.e. 97.9% in overall patients. As they mentioned, response guided therapy using HBsAg as well as HBeAg quantification could be helpful. In addition, immune responses may need to be boostered in a separate manner. For example, combination of pegylated interferon,[19] toll like receptor agonist,[20] therapeutic vaccine,[21] or other new emerging therapy might be helpful. Otherwise, end point of treatment will

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not be able to be reached in CHB patients who have experienced multiple drug resistance.

Conflicts of Interest

The author has no conflicts to disclose.

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