Real-World Experiences with Tenofovir Disoproxil Fumarate: Is this the “B-Ticket”?

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The preferred options for treatment of chronic hepatitis B viral (HBV) infection in countries without resource constraints are peginterferon, entecavir, or tenofovir disoproxil fumarate (TDF) [1, 2]. For most clinicians, peginterferon is infrequently considered due to the greater complexity of monitoring, higher frequency of adverse effects and patient preference, which narrows the treatment options to TDF or entecavir. In the registration trials of treatment-naïve patients with chronic hepatitis B, both TDF and entecavir demonstrated high rates of on-treatment HBV DNA suppression and low rates of viral resistance coupled with excellent safety [3, 4]. Given that TDF and entecavir have been approved therapies for HBV for more than a decade, data derived from “real-world” cohort studies have helped fill knowledge gaps regarding the use of these drugs in clinical practice. In the case of TDF, the issues of particular interest include: (1) the efficacy of TDF across a wider spectrum of patients including those less adherent than patients in clinical trials, and (2) the risks associated with longer-term use of TDF, especially the frequency of viral resistance and the risk of renal and bone toxicity.

Patients participating in clinical trials are a select group—typically healthier than many patients in the clinic, with fewer comorbidities and higher rates of adherence. The registration trials for TDF required a estimated glomerular filtration rate (eGFR) >70 ml/min, absence of anemia, neutropenia, and liver decompensation or presence of unstable comorbidities [3]. In practice, patient complexity can be greater, comorbidities not always optimized,

and adherence less assured. Understanding how antivirals perform under these less than ideal circumstances is important. The ideal “real-world” study would prospectively enroll consecutive patients and account for all patients at study end, provide intent-to-treat as well as per-protocol analyses, and include details of treatment failures, including reasons for treatment discontinuation. The “real-world” cohorts included in this issue of *Digestive Diseases and Sciences*—GEMINIS from Germany [5] and VIREAL from France [6]—partially meet these high standards. Regardless, some important practical messages can be gleaned from their analyses.

The VIREAL and GEMINIS cohorts enrolled >800 patients from diverse practice settings who were newly initiated on TDF therapy [5, 6]. Treatment-naïve and experienced subjects were included, with a substantial proportion of the treatment-experienced patients transitioning from another nucleos(t)ide analog therapy to TDF and having low or undetectable HBV DNA levels at the time of TDF initiation. Hypertension, diabetes, renal disease, cardiovascular diseases, and other comorbidities were present in ~40 % of patients [5] with up to 28 % having eGFR <90 ml/min [6]. Although the intent of the study was to follow patients for 3 years, both cohorts suffered from patient attrition, leading to incomplete reporting of virologic and safety data. The primary measure of treatment effectiveness was HBV DNA suppression (HBV DNA <69 IU/ml), achieved by >88 % of those completing 3 years of treatment. Importantly, no resistance was detected. The vast majority of virologic breakthroughs were transient, suggesting that adherence was possibly the cause. Although these results were encouraging, with 25 % of the cohort lacking complete follow-up, the interpretation of efficacy was less informative than desired. It is conceivable that poor response to therapy or adverse effects contributed to these losses, with consequent

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overestimation of the therapy's benefits. Alternatively, it is possible that those with the best responses, i.e., achievement of HBeAg or HBsAg loss, were among those lost to follow-up, with consequent underestimation of treatment benefits.

Although the achievement of “on-treatment” HBV DNA suppression is an important marker of treatment efficacy for those receiving nucleos(t)ide analogue (NA) therapy, an even more desirable treatment outcome is the achievement of HBsAg seroconversion. The term “functional cure” has been coined to describe patients who achieve HBsAg seroconversion plus persistently undetectable HBV DNA in blood, representing a state of sustained immunologic control. Currently available NA therapy infrequently results in HBsAg loss, especially in patients who are HBeAg negative at the start of treatment. In the VIREAL cohort, the overall rate of cumulative HBsAg loss at 3 years was 3 %, whereas in the GEMINI cohort, the 3-year cumulative rate of HBsAg loss was 6 % in HBeAg-positive and 3 % in HBeAg-negative patients. These cumulative rates are likely overestimates, as 40–60 % of the treatment-experienced patients in these cohorts started TDF with low or undetectable HBV DNA levels due to prior NA therapy, and this total duration of NA treatment was not accounted for in the cumulative estimates of HBsAg loss. Nonetheless, the overall message from these “real-world” cohorts is that although HBV DNA suppression was achievable in the vast majority of patients with TDF therapy, HBsAg loss was a rare event, highlighting the need for new treatment strategies that more frequently result in HBsAg loss.

The VIREAL and GEMINI cohorts provide valuable data with regard to TDF safety, especially as it relates to renal consequences. In the recently published AASLD guidelines, there was insufficient evidence of harm to recommend one drug over another with regard to the effects of TDF versus entecavir on renal and bone health [1]. Nevertheless, renal events related to TDF were acknowledged. Treatment guidelines recommend adjustment of NA dosing according to the eGFR and, in the case of TDF, renal safety measurements, such as creatinine clearance and serum phosphorus, prior to and at least annually during treatment. In the VIREAL and GEMINI cohorts, the mean eGFR declined by −3.86 and −3.50 ml/min, respectively, over 3 years. Similar findings were reported from another “real-world” cohort from Taiwan, with the greatest decline in eGFR occurring in the first year [7]. Of note, cases of renal failure and renal tubular dysfunction leading to discontinuation of TDF occurred in each of the “real-world” cohorts, underscoring the importance of monitoring for serious but thankfully rare renal adverse events. While largely reassuring, a TDF treatment exposure of 3 years is contextually quite brief; more safety data beyond the 3- to 5-year mark are accordingly needed.

In summary, these two prospective cohort studies highlight several important clinical messages: (1) TDF resistance was not observed, an immensely reassuring observation that reflects the high barrier to resistance of TDF, even with suboptimal adherence; and (2) TDF is effective in patients with a wide range of prior NA treatment experience. VIREAL and GEMINI reported no evidence of reduced responsiveness in those who had received prior NA treatment, in contrast to a prospective study from Taiwan, in which adefovir resistance and prior suboptimal response to entecavir were linked with lower virologic responses to TDF [7]. Thirdly, with regard to renal safety in these more complex “real-world” patients, the minority (3–5 %) experienced a decline in eGFR with treatment exposures up to 3 years. Prior adefovir treatment, lower baseline eGFR, and TDF dosing in excess of that recommended were suggested as potential factors contributing to renal risk. These data reinforce the need for monitoring and dose adjustment of TDF in patients with reduced eGFR. With the anticipated approval of tenofovir alafenomide (TAF), a phosphonate prodrug of tenofovir that efficiently delivers active drug to hepatocytes, thereby reducing systemic tenofovir exposures, the renal concerns are likely to be reduced [8]. Nevertheless, in clinical scenarios where medication costs may influence use of TAF versus TDF, these “real-world” cohorts using TDF identify patients at higher risk of renal toxicity and thus might be targeted for TAF a priori.

Looking forward, the era of long-term or indefinite NA suppressive therapy will likely come to an end. Increasingly, clinical studies evaluating a finite duration of NA therapy are being undertaken [9]. With new therapeutic targets identified [10], future HBV therapy is likely to be more individualized and utilize sequential or combinations of drugs that target specific host and viral pathways to achieve functional cure. With these future therapies, reports from high-quality “real-world” cohorts will continue to inform practice by providing safety and effectiveness data across diverse treatment settings and in a broader array of patients.

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