Switching from TDF to TAF - perhaps not as simple as we thought

Although antiviral therapies for chronic hepatitis B infection (CHB) have been available for over two decades, there is still no curative treatment[1] and most patients with CHB are put on long-term oral antiviral therapy. Benefits of antiviral therapy might be bombarded with treatment-associated toxicities, especially the existing pool of CHB patients are aging with increasing number of comorbidities. Tenofovir disoproxil fumarate (TDF) is a prodrug of tenofovir, which in high plasma levels will lead to kidney and bone toxicities over long-term use. Tenofovir alafenamide (TAF) is another prodrug of tenofovir but with greater plasma stability than TDF. In the 2 head-to-head comparative studies of TAF vs. TDF in treatment-naive viremic CHB patients, the pooled results at week 96 showed that TAF is equally effective as TDF in virological suppression. Compared to TDF-treated patients, TAF-treated patients experienced smaller decline in estimated glomerular filtration rate (eGFR), and smaller reduction in bone mineral density (BMD).[2-4]

It was previously not known whether the antiviral efficacy could be maintained if TDF-treated non-viremic CHB patients are to be switched to TAF. In this issue, Lampertico P *et al* showed that switching TDF-treated CHB patients (median treatment duration 4 years, half had prior oral antiviral therapy, ~15% compensated cirrhosis, median eGFR ~90ml/min) to TAF is equally effective to maintain virological suppression. At week 48, only one patient from each group (TAF: 1/243, TDF: 1/245) had serum HBV DNA ≥20 IU/mL. Switching to TAF led to eGFR change of +0.94 ml/min compared -2.74 ml/min for those continuing TDF. In addition, switching to TAF led to BMD increment at both spine and hip compared to BMD reduction for those continuing TDF.

TAF is a safer alternative for TDF, but its toxicities still exist. There were 2/243 (0.8%) patients switching to TAF and 1/245 (0.4%) patients continuing TDF who had eGFR decline to <50ml/min during the study period. Both switching to TAF and continuing TDF group demonstrated an increase in the proportion of patients >grade 1 proteinuria (TAF group: from 7% at baseline to 14% at week 48; TDF group: from 7% at baseline to 22% at week 48), although less so for switching to TAF. In addition, the magnitude of eGFR change need to be interpreted with caution. Taking into account the background natural decline of eGFR of about 1ml/min/year in the general population,[5] the improvement of eGFR peaking at week 24 (up to +5mL/min) for switching to TAF and subsequent downsloping to approaching zero (+0.94ml/min) towards week 48 is somewhat unexpected. More data from the extension study (open label TAF) is needed to confirm that the improvement of eGFR in the switching to TAF group is not transient after long term TDF use.

The rates of treatment-induced HBsAg seroclearance at week 48 in this study were 0% (0/243) for TAF group and 2% (5/245) for TDF group (p=0.028). Despite matching the baseline HBsAg level (both groups: 2.9 $\log_{10}$IU/mL), the mean rate of decline of HBsAg in the TAF group was relatively low at 0.07 $\log_{10}$IU/mL after 48 weeks of treatment, compared to 0.10 $\log_{10}$IU/mL for TDF group (p=0.15). The authors explained that out of the 5 TDF patients with HBsAg loss, 4 of them had low levels of HBsAg (<1 IU/mL) at baseline. The HBsAg seroclearance rates for patients with higher baseline HBsAg titre in both groups are thus anticipated upon longer

treatment duration to prove that switching to TAF allows similar chances of achieving functional cure.

Switching to TAF led to increase in fasting lipid parameters, and these changes were not seen in those continuing TDF which is known to exert 'lipid-lowering effect'.[6] At week 48, the median total cholesterol and low-density lipoprotein cholesterol increased by 19 and 16 mg/dL (i.e. 0.49 and 0.41 mmol/L), respectively. These could be significant increments for the aging patient population with increasing number of cardiovascular comorbidities who need stringent lipid targets. Concurrent adjustment of lipid-lowering strategies may be required.

The study population were good pill-takers with baseline median eGFR of ~90ml/min, normal baseline serum phosphate levels (3.2-3.3mg/dL), and had tolerated TDF for 4 years. They are not representative of many candidates whom are considered for TAF switch in real life, as such consideration is usually based on unacceptable treatment-related adverse events. An ongoing trial (NCT03180619) includes patients with eGFR 15-59ml/min, or <15ml/min on hemodialysis, or patients with Child Pugh class B cirrhosis. This will definitely provide insights in the efficacy and safety of TAF in CHB patients with significant renal and hepatic impairment to further broaden the clinical use of TAF.

Conflict of interest: none to declare.

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