Case Report

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Tenofovir alafenamide as a rescue therapy in a patient with HBV-cirrhosis with a history of Fanconi syndrome and multidrug resistance

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Abstract

Tenofovir disoproxil fumarate (TDF) is a recommended first-line therapy for both naïve and experienced patients with chronic hepatitis B (CHB), although reduced estimated glomerular filtration rate (eGFR), hypophosphatemia, hyperphosphaturia and Fanconi syndrome have been reported in some patients. Entecavir (ETV) could be considered as a rescue therapy for TDF-treated patients developing renal dysfunction, though patients with prior history of treatment with lamivudine (LAM) can develop ETV resistance strains, which can lead to potentially severe hepatitis flares. Tenofovir alafenamide (TAF), a new prodrug of tenofovir, has recently been developed to improve the renal and bone safety profile compared to TDF, while maintaining the same virologic efficacy. The recently published 48-week phase III TAF registration studies confirmed the superior safety profile. Here we describe a case of a 75-year-old woman with HBV mono-infection and compensated cirrhosis who developed ETV resistant strains and grade 3 chronic kidney disease after many years of LAM and adefovir (ADV) treatment and a TDF-induced Fanconi syndrome. The administration of 25 mg/day of TAF, granted as part of a compassionate use program, rapidly suppressed viral replication to undetectable levels without worsening renal function or side effects.

Introduction

Tenofovir disoproxil fumarate (TDF) is one of the recommended anti-HBV strategies for both nucleos(t)ide (NUC) naïve and NUC-experienced patients with chronic hepatitis B (CHB), owing to its potent antiviral activity and high barrier to resistance.[1,2] While registration studies showed minimum renal toxicity events (~2%) over seven years of treatment,[3] real life long-term studies have demonstrated that some patients may experience a decline in estimated glomerular filtration rate (eGFR), hypophosphatemia, chronic tubular disease or Fanconi syndrome, a severe acute proximal tubular disease.[4] Apoptosis of tubular cells and inhibition of mitochondrial DNA replication in proximal tubular cells may be involved in the pathogenesis of TDF-induced nephropathy.[5] Risk factors for development of TDF-associated nephrotoxicity include polymorphism in genes encoding proximal tubular transporters, concomitant use of protease inhibitors, pre-existing kidney disease, low body mass index, older age, advanced HIV infection, concomitant HCV infection and concurrent use of other nephrotoxic drugs.[6] International guidelines on HBV management recommended monitoring blood phosphate as a marker of tubular disease,[1–3] although other markers of proximal tubular dysfunction such as the urine beta2-microglobulin-to-creatinine ratio (UBCR) and the ratio of maximum rate of renal tubular reabsorption of phosphate to glomerular filtration rate (TmPO4/GFR) may better serve this purpose given their higher sensitivity and specificity.[4–6]

To overcome the renal and bone safety issues, a new prodrug of tenofovir, TAF, has been developed to reduce systemic exposure to tenofovir, thereby reducing renal tubular exposure. The recently published 48-week phase III randomized trials, which included approximately 20% of patients who had been previously exposed to LAM, ADV or entecavir (ETV), have indeed confirmed that TAF had comparable efficacy to TDF in patients positive and negative for hepatitis B e antigen (HBeAg), but an improved glomerular and tubular safety profile.[7,8] Compared to TDF, patients receiving TAF had a lower decline in eGFR as well as a smaller percentage increase in UBCR (μg/g), which is considered a more sensitive and specific marker of proximal tubular disease.[7,8] Another potential advantage of TAF over other NUCs is that no dose adjustments are required in adults or adolescents (aged at least 12 years and of at least 35 kg body weight) with estimated creatinine clearance (CrCl) ≥15 ml/min or in patients with CrCl <15 ml/min who are receiving hemodialysis. Whether TAF could also be used to switch TDF-treated patients with renal safety issues has not yet been demonstrated, but such studies are ongoing. TAF was approved for the treatment of patients with CHB in the US, Japan in November 2016, and Europe in January 2017. No cases of TAF

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as a rescue treatment for drug resistance and/or renal toxicity have been published.

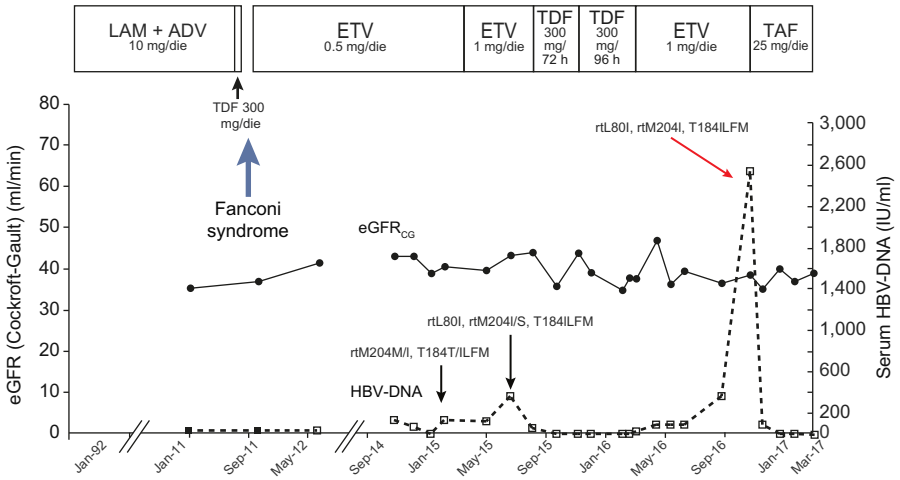
Case report

A 75-year-old Italian female with HBeAg negative compensated HBV-related cirrhosis was referred to our center in February 2015 because of progressive increase of viremia during ETV treatment given as a rescue for Fanconi syndrome during TDF treatment.

After many years of LAM+ADV combination therapy and two months of TDF treatment (Fig. 1), the patient was hospitalized in September 2011 because of Fanconi syndrome, characterized by severe tubulopathy, hypophosphatemia, high urinary phosphate, hypouricemia (1.8 mg/dl, normal value [nv] 2.4–5.7 mg/dl), high urinary uric acid (fractional excretion [FE] 46%), significant glycosuria (680 mg/24 h, nv 30–90 mg/24 h) and proteinuria (680 mg/dl, nv 2–12 mg/dl, predominantly tubular [albuminuria 140 mg/day, nv <30 mg/24 h, and FE beta2-microglobulin 82%]); creatinine clearance (eGFR) was 37 ml/min, modest metabolic acidosis was observed (pH 7.3, HCO_3^- 18 mmol/L). Blood phosphate was at the lower limits, while parathormone (PTH), serum calcium, vitamin D, serum and urine immunofixation were within the normal range. Following the improvement of renal function after TDF discontinuation, ETV 0.5 mg/day was started and strict nephrological follow-up for chronic kidney disease (CKD) stage 3 was recommended.

The patient was referred to our Liver Unit in February 2015 because of a virologic breakthrough during ETV treatment. Concomitant comorbidities were diabetes mellitus, arterial hypertension and osteopenia; concurrent therapies were sodium bicarbonate, potassium phosphate, acetylsalicylic acid, calcitriol, vitamin D, insulin, losartan. Resistance testing (INNOLiPA HBV Multi-DR; Innogenetics, Fujirebio Europe, NV Ghent, Belgium) detected wild-type and mutant virus populations in positions 184 and 204 (rtM204M/I, T184T/ILFM). Between March 2015 and November 2016, several attempts were made to control viral replication with different therapeutic strategies (Fig. 1). While TDF efficiently suppressed viral replication but worsened renal function, ETV preserved renal function but failed to control viremia (Fig. 1), despite good compliance to treatment. The resistance profile progressively evolved to a more complex pattern on July 2015 (rtL80I, rtM204I/S, rtT184T/ILFM; indeterminate results for rtL180, rtA181, rtN236) and on November 2016 (rtL80I, rtM204I, rtT184ILFM; indeterminate results for rtL180, rtA181, rtN236) when HBV DNA peaked for the first time above 3 $\log_{10}$ IU/ml during treatment with ETV 1.0 mg/day.

In the absence of any alternative therapeutic approach among the registered and commercially available anti-HBV drugs, TAF was requested for compassionate use. The patient started TAF at the dose of 25 mg/day on 12 November 2016 after full baseline assessment of renal safety parameters, including proteinuria ([urinary protein/urinary creatinine] × 1000, urine protein-to-creatinine ratio [UPCR], normal value <200 mg/g); ([urinary albumin/urinary creatinine] × 1000, urine albumin-to-creatinine ratio [UACR], normal value <30 mg/g); UBCR normal value <300 µg/g; TmPO4/GFR ratio and bone variables such as spine and hip Dual-X-ray Absorptiometry (DEXA) scans, FRAX® tool and the Italian FRAX-derived version (DeFRA), vitamin D and PTH levels (Table 1). While glomerular proteinuria was within the normal range (urinary protein 17 mg/dl), $eGFR_{CG}$ was low (38 ml/min) and tubular proteinuria (UBCR 28,475 µg/g) and phosphaturia were elevated ($TmPO_4$/GFR 0.68). She had osteopenia at the femoral neck and a 10-year probability of major osteoporotic fracture of 14% and 10% according to FRAX and DeFRA, respectively.



Blood calcium (mg/dl)/urinary calcium (mg/dl)		10/8	10/4	10/15	10/9	10/7	10/8	10/13
Blood phosphate (mg/dl)/$TmPO_4$/GFR		3/0.59	3/0.72	3/0.55	3/0.67	3/0.72	3/0.68	3/0.66
Urinary creatinine (mg/dl)/urinary phophate (mg/dl)		36/30	28/24	50/67	44/44	91/84	55/45	44/32
Urinary protein (mg/dl)/UPCR (mg/g)		10	6	11	19/432	32/352	17/310	13/295
UBCR (µg/g)	>50,000				25,000	17,556	28,578	34,241
Acid uric blood (mg/dl)/urine (mg/dl)					3/26	4/49	4/35	3/39
Microalbuminuria (mg/L)/UACR (mg/g)					36/82	54/59	33/60	22/50
Glycosuria by urine dipstick analysis (mg/dl)	>1,000				neg	0.05	0.1	neg

Fig. 1. Biochemical, virologic and renal parameters, and previous anti-HBV treatment history before and during TAF treatment.
ETV, entecavir; HBV, hepatitis B virus; LAM, lamivudine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TmPO4/GFR, maximum rate of renal tubular reabsorption of phosphate to glomerular filtration rate; UPCR, urine protein-to-creatinine ratio; UBCR, urine beta2-microglobulin-to-creatinine ratio; UACR, urine albumin-creatinine ratio.

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