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Long-term efficacy and safety of switching from lamivudine + adefovir to tenofovir disoproxil fumarate in virologically suppressed patients

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ABSTRACT

Background and Aim: Tenofovir disoproxil fumarate (TDF) is recommended as first-line monotherapy for nucleos(t)ide (NA)-naïve chronic hepatitis B (CHB) patients and as a second-line rescue therapy for NA-experienced patients with a previous treatment failure. However, data regarding the efficacy of TDF monotherapy in patients with lamivudine resistance (LAM-R) successfully treated with LAM + adefovir (ADV) are limited. Herein, the efficacy and safety of switching from LAM + ADV to TDF monotherapy in clinical practice have been evaluated.

Methods: Sixty LAM-R HBeAg-negative CHB patients treated with ADV add-on therapy and stable viral suppression, were switched to TDF monotherapy and prospectively evaluated for virological response, liver and renal function, and bone mineral density.

Results: During a median period of 57 months of TDF monotherapy, all patients maintained a virological response, four of whom cleared HBsAg (6.6%) and discontinued treatment. Monitoring of renal function showed no case of the Fanconi syndrome, no significant alterations of median serum creatinine, eGFR and phosphate levels, although a reduction of TDF dosage was required in five patients (8.3%). Despite the stable virological suppression, five cirrhotic patients and one CHB patient developed hepatocellular carcinoma.

Conclusions: Our results demonstrate the efficacy of switching to TDF monotherapy in virologically suppressed CHB patients receiving long-term LAM + ADV therapy, with a low rate of adverse events.

1. Introduction

Lamivudine (LAM), the first oral nucleoside analogue (NA) approved for treatment of chronic hepatitis B (CHB), has been the only oral antiviral available for many years; consequently, patients have been treated with this drug and a significant number developed resistance (LAM-R) [1]. Moreover, because of its low cost, this drug continues to be used in many countries, and the pool of patients who have developed resistance to LAM continues to increase.

Optimal management of patients with resistance to LAM alone, or to both LAM and adefovir dipivoxil (ADV), and even more those with multidrug resistance, still presents a problem for the clinician [2,3]. The therapeutic options for patients with LAM-R have changed significantly in recent years. ADV add-on strategy was the initial rescue therapy for LAM-R patients [4]; however, ADV is no longer recommended due to its low potency, the high rate of resistance and the risk of nephrotoxicity. After its approval, tenofovir disoproxil fumarate (TDF) has been increasingly used as rescue therapy for patients with LAM-R or ADV-R, either as mono- or combination therapy [5–8].

A recent randomized study has demonstrated that TDF monotherapy is as effective as the TDF + emtricitabine combination for maintaining viral suppression in LAM-R patients [9]. Moreover, TDF monotherapy has also proved to be superior to continuous add-on therapy in CHB patients with suboptimal response to LAM + ADV [10] and equally efficacious as the TDF + LAM combination in LAM-R patients who failed LAM + ADV combination therapy [11]. However, all these studies have a short follow up and data on the long-term efficacy of TDF treatment in patients with LAM-R CHB successfully treated with LAM + ADV are limited. In this study, the long-term efficacy and safety of switching from LAM + ADV to TDF monotherapy in LAM-R HBeAg-negative CHB patients with stable viral suppression have been evaluated in clinical practice.

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Table 1
Resistance patterns of mutations in the reverse transcriptase region in 35 of 60 LAM-R patients.

Mutation patterns	No. of patients
rtL180M, rtM204I	11
rtL180M, rtM204V	15
rtL80I, rtM204I	5
rtL80V, rtM204I	2
rtM204I	2

rt = Reverse transcriptase region.

2. Methods

2.1. Study population

From November 2010 to April 2011, 60 Italian consecutive HBeAg-negative CHB patients with LAM-R, successfully treated with ADV add-on strategy (10 mg/day orally) in two Apulian referral centers (Bari, Foggia), were included in this observational cohort study.

All patients had at least 24 months of stable virological suppression with LAM + ADV treatment and were directly switched to TDF monotherapy.

One patient assumed ADV at a reduced dosage due to a Stage-III chronic kidney disease and therefore was switched to TDF on alternate days.

Patients with decompensated liver cirrhosis and HIV co-infection were excluded.

All 60 LAM-R patients showed a virological breakthrough during LAM monotherapy and the presence of LAM-mutations was confirmed by genotypic test for 35/60 patients (Table 1).

Our study cohort has also been object of a previous publication which focused on bone and kidney toxicity induced by nucleos(t)ide analogue therapy [12].

2.2. Study objectives and endpoints

The primary endpoint of this study was to evaluate the maintenance of undetectable HBV (hepatitis B virus) DNA during TDF monotherapy in LAM-R patients virologically suppressed with ADV + LAM therapy and thus, the primary endpoint was an undetectable HBV DNA level with real-time quantitative polymerase chain reaction during TDF treatment. The secondary endpoints were: the loss of hepatitis B surface antigen (HBsAg) or seroconversion, the safety of TDF and its tolerability.

2.3. Follow up of participants

After switching to TDF, patients were followed for a median period of 57 months (range 5–63) and evaluated at each visit for efficacy of treatment, compliance with study medication and adverse events. During the first year, serum ALT levels, creatinine, serum phosphate, urinalysis and HBV DNA levels were monitored every three months, and every six months thereafter. Serum ALT (upper limit of normal (ULN): 40 U/L), creatinine, and phosphorus levels were tested by routine automated techniques. HBV DNA was assessed by real-time PCR assay (linear dynamic detection range: 13 IU/ml–1×10^9 IU/ml; Abbott Laboratories, Chicago, Illinois, USA). HBsAg serum levels were measured by protocol at baseline and yearly thereafter, using a commercial chemiluminescent immunoassay (Architect HBsAg quantitative, Abbott Diagnostics, Wiesbaden Germany).

Cirrhotic patients underwent surveillance for hepatocellular carcinoma (HCC) development by monitoring serum α-fetoprotein levels and abdominal ultrasound every six months.

Table 2
Baseline demographic, clinical and virologic characteristics of 60 patients treated with TDF.

Male, *n* (%)	48 (80)
Age, median yr (range)	58 (33–81)
BMI, median Kg/m^2 (range)	25.87 (19–40)
Overweight, BMI >25 <30, *n* (%)	30 (50)
BMI >30, *n* (%)	5 (8.3)
HCV coinfection, *n* (%)	1 (1.6)
HDV coinfection, *n* (%)	1 (1.6)
HBeAg negative, *n* (%)	60 (100)
Undetectable HBV DNA, *n* (%) (<13 IU/ml)	60 (100)
Prior ADV + LAM duration, median, mo (range)	63 (24–96)
Liver cirrhosis, *n* (%)	26 (43.3)
- Child A, *n* (%)	26 (100)
- Esophageal varices, *n* (%)	8 (30.7)
- HCC, *n* (%)	5 (8.3)
Concomitant diseases, *n* (%)	22 (36.6)
- Hypertension, *n* (%)	12 (54.5)
- Hypothyroidism, *n* (%)	4 (18.2)
- Glomerulonephritis, *n* (%)	1 (4.5)
- Diabetes, *n* (%)	3 (13.6)
- Depression, *n* (%)	3 (13.6)
- Chronic renal impairment[a], *n* (%)	1 (4.5)
Reduced TDF dose, *n* (%)	1 (1.6)

n = Number of patients; BMI = Body mass index; mo = Months; ADV = Adefovir dipivoxil; LAM = Lamivudine; HCC = Hepatocellular carcinoma.
[a] Stage-III chronic kidney disease (CKD).

Renal function was assessed by calculating the eGFR (extimated Glomerular Filtration Rate) using the chronic kidney disease epidemiology collaboration (CKD-EPI) formula. Bone mineral density (BMD) measurements of the lumbar spine and femoral neck were determined *via* dual-energy X-ray absorptiometry (DXA) at the start of TDF and every 2 years thereafter. Loss of BMD was as a 5% reduction of BMD in spine and neck after 2 years of TDF treatment. Serum 25 hydroxyvitamin D [25(OH)D] levels were measured at TDF switching and a supplementation was offered in case of deficiency.

Written informed consent to participate was provided by all patients.

2.4. Statistical analysis

Data were expressed as median and range for discrete variables and as counts and percentages for qualitative variables. The cumulative incidence of virological breakthrough was assessed by the Kaplan–Meier method. All data were analyzed using the SPSS statistical software package (version 12; SPSS, Inc., Chicago, IL, USA).

3. Results

Sixty HBeAg-negative LAM-R chronic hepatitis B patients treated with ADV + LAM combination therapy virologically suppressed for at least 24 months were switched to TDF monotherapy.

The baseline clinical and demographic characteristics are shown in Table 2. Median age was 58 years (range 33–81), 48 were males, all patients were HBeAg-negative, anti-HBe positive; a genotypic resistance test was performed in 35/60 patients and a genotype D was documented in all 35 patients. A histological diagnosis of cirrhosis was present in 20/60 patients; six additional patients had biochemical and ultrasonographic signs of cirrhosis. Esophageal varices were present in 8/26 patients with cirrhosis.

At switching to TDF monotherapy, diagnosis of previous HCC was present in five cirrhotic patients. A coinfection with HDV or HCV was present in two patients; all patients were negative for HIV co-infection. In 22/60 patients (36.6%) the presence of comorbidities (arterial hypertension, diabetes, depression, hypothyroidism, renal impairment) was reported, requiring concomitant