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Efficacy and tolerance of a combination of tenofovir disoproxil fumarate plus emtricitabine in patients with chronic hepatitis B: A European multicenter study

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ABSTRACT

Background and aims: The combination of tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) is used extensively to treat HIV infection and also has potent activity against hepatitis B virus (HBV) infection. The aim of this study was to assess the efficacy and tolerance of TDF + FTC in patients with chronic hepatitis B (CHB).

Methods: Seventy eight consecutive CHB patients from five European centers were included. All started a TDF + FTC combination between October 2005 and March 2010. Virological, biochemical, and clinical data were recorded during follow-up. Tolerance was also monitored. Patients were classified into either treatment simplification (TS), where efficacy of the previous treatment was obtained at TDF + FTC initiation, and treatment intensification (TI), where the previous line of therapy had failed.

Results: TDF + FTC was given as a TI to 54 patients (69%) and as a TS to 24 (31%). Among patients with TI, 83% were males. The median baseline HBV-DNA was 4.4 $\log_{10}$ IU/mL, and median alanine-transaminase (ALT) was 1.10 × ULN. Sixty percent were HBeAg positive, 47% had significant fibrosis (⩾F3 Metavir equivalent), and 29% had confirmed cirrhosis. Median treatment duration was 76 weeks (interquartile range 60–116). Kaplan–Meier analysis showed that, 48 weeks after TI, the probability of being HBV-DNA becoming undetectable was 76%, and reached 94% at week 96. No viral breakthrough occurred. Patients with TS (87% males, median baseline HBV-DNA 1.1 $\log_{10}$ IU/mL, median ALT 0.79 × ULN, 33% HBeAg positive, 61% with significant fibrosis) were treated for a median duration of 76 weeks. In this subgroup, all patients but one remained HBV-DNA undetectable and no ALT flare-up occurred during follow-up. Creatinine levels did not show kidney-function deterioration in either group of patients.

Conclusions: After a median follow-up of >76 weeks, the TDF + FTC combination showed encouraging antiviral efficacy and a good safety profile in all patients with CHB. TDF + FTC may represent an interesting clinical option to simplify therapy and increase the barrier to resistance, which should be assessed in the long term.

1. Introduction

Hepatitis B virus (HBV) is the leading cause of liver cancer and frequently leads to cirrhosis and liver failure (Lavanchy, 2004). The goal of nucleos(t)ide analog treatment is to suppress viral replication, to halt liver-disease progression, and to prevent the onset of complications. Management of antiviral therapy should be based on precise virological monitoring that enables early diagnosis of

Abbreviations: ADV, adefovir; ALT, alanine aminotransferase; CHB, chronic hepatitis B; ETV, entecavir; FTC, emtricitabine; HBV, hepatitis B virus; HIV, human immunodeficiency virus; TDF, tenofovir; ULN, upper limit of normal.

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a partial response and also treatment failure (EASL, 2009; Liaw et al., 2005; Sorrell et al., 2009).

Virological response is defined by a decline in HBV-DNA levels during therapy (Locarnini et al., 2004) and different profiles of response may be distinguished. The initial response is characterized by a decrease of at least 1 $\log_{10}$ IU/mL in viral load by week 12. This definition was chosen as it exceeds variability in HBV-DNA assays and spontaneous variations of viral load during the course of infection. Primary non-response is defined as the result of either poor-treatment compliance or inadequate antiviral potency of the drug (Si Ahmed and Zoulim, 2009). Current guidelines have focused on patients with a partial virological response, defined as a decline in HBV-DNA greater than 1 $\log_{10}$ IU/mL from baseline, but a detectable viral load at week 24 (for lamivudine- or telbivudine-based therapy) or week 48 (for adefovir, entecavir, tenofovir) (EASL, 2009). In these cases it is recommended to switch or to add a more potent with a complementary cross-resistance profile.

Virological breakthrough was defined by an increase of at least 1 $\log_{10}$ IU/mL compared to the lowest value during treatment, and was confirmed by a second test in a treatment-compliant patient (Lok et al., 2007; Ahmed et al., 2000). Persistent viremia has been identified as a risk factor for a worse outcome and is associated with a greater risk of resistance (Lai et al., 2007; Yuen et al., 2001; Zoulim, 2004). Early adaptation of treatment is recommended, at least at the time of a virological breakthrough or in cases of insufficient viral suppression in compliant patients. The addition of a complementary drug is the preferred strategy.

With the availability of drugs that exhibit potent antiviral activity and have a high barrier to resistance, antiviral drug resistance is becoming a more manageable issue. Therefore, all the current guidelines have identified the persistence of viral replication, even at low levels, as a major target to prevent disease progression and to prevent the emergence of resistance (Zoulim and Locarnini, 2009).

Tenofovir disoproxil fumarate (TDF) plus emtricitabine (FTC) is used extensively to treat HIV infections. Both drugs also exhibit potent activity against hepatitis B virus (HBV) (Gish et al., 2002, 2005; Jenh and Pham, 2010; Lim et al., 2006). Their combination (Anonymous, 2004) may be clinically relevant in increasing the barrier to resistance of TDF and alleviate the risk of antiviral drug resistance (Zoulim and Locarnini, 2009). The objective of this study was to assess the efficacy and tolerance of the TDF + FTC combination for chronic hepatitis B (CHB) in a cohort of patients followed in five European clinical centers.

2. Materials and methods

2.1. Patients

Patients with chronic hepatitis B, treated with a combined TDF + FTC therapy, were consecutively recruited from five European Centers, which were all members of the European Network of Excellence VIRGIL (vigilance against viral resistance): Hospices Civils de Lyon, France; Erasmus MC, Rotterdam, Netherlands; Hospital Vall d'Hebron, Barcelona, Spain; Hôpital Cochin, Paris, France; Hannover Medical School, Hannover, Germany. All patients started the TDF + FTC combination between October 2005 and March 2010. Patients were classified into two groups: treatment simplification, i.e., two drugs in one pill per day, when efficacy of the previous line of therapy has been obtained before initiation of TDF + FTC, and treatment intensification (TI), when the previous line of therapy had failed. Patients were included in the analysis if they received the TDF + FTC combination for at least 12 weeks and they had no co-infection with HIV or HCV. Previous treatment history was recorded and coded as simple ($\leqslant$1 molecule for $\leqslant$1 year) or complicated (>1 molecule and/or treatment duration >1 year), in accordance with the European Association for the Study of the Liver (EASL) guidelines (EASL, 2009).

2.2. Patient follow-up

All patients were regularly monitored within their routine clinical follow-ups. Virological, biochemical, clinical, and tolerance data were assessed locally during the follow-up. The primary endpoint of interest was virological response, defined as HBV-DNA being undetectable (assessed by real-time PCR), according to the technique used. Secondary endpoints were time when HBV-DNA became undetectable, clinical improvement, alanine-transaminase (ALT) normalization, tolerance assessed by creatinine level during follow-up, and HBsAg and HBeAg loss and/or seroconversion. Renal-function impairment was defined as an increase in creatinine level >1.5 times the baseline value.

2.3. Statistical analyses

Normally distributed variables were presented as the mean+/− standard deviation, whereas skewed variables were presented as the median and interquartile (25–75%) range. Categorical variables were studied using the two-sided chi-square test or Fisher's exact test when necessary, whereas quantitative variables were analyzed using analysis of variance (ANOVA) or the non-parametric Kruskal–Wallis test as appropriate. A Kaplan–Meier analysis was performed to assess the probability of HBV-DNA being undetectable and for ALT normalization over time after TDF + FTC initiation. Follow-up times were calculated from the date of TDF + FTC initiation to the date of event or censorship. Cumulative probabilities were compared between subgroups using the log-rank test. HBV-DNA values were dichotomized according to the 4 $\log_{10}$ IU/mL cut-off based on published data that showed clinical relevance (Mommeja-Marin et al., 2003; Si Ahmed and Zoulim, 2009). Age was analyzed by comparing patients below or above 40 years, a cut-off age above which HBV complications has been reported to increase (Sorrell et al., 2009). Statistical analysis was performed using SPSS v.17.0 for Windows. All statistical tests were two-sided and a p-value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

Seventy-eight consecutive CHB patients were included. All started on combined TDF + FTC therapy between October 2005 and March 2010. This TDF + FTC combination was given as treatment-intensification to 54 patients (69%) and as treatment simplification to 24 (31%) patients. Within the whole study population, 85% of patients were males, and the mean age was 49 years ±15 (Table 1). Median duration of follow-up was 76 weeks in both groups. Two patients had a co-infection with the hepatitis delta virus. The proportion of patients with significant fibrosis at baseline (Metavir score $\geqslant$ F3) was slightly higher in the treatment-simplification group (61.1%) than in the treatment-intensification group (46.7%), although this difference was not statistically significant (p = 0.30). Sixty percent of patients within the treatment-intensification group were HBeAg positive at baseline versus 33% of patients within the treatment-simplification group (p = 0.028).

3.2. Analysis of changes in HBV-DNA levels during therapy

In the treatment-intensification group, median HBV-DNA level at initiation of TDF + FTC was 4.4 $\log_{10}$ IU/mL and all patients were HBV-DNA positive. Among patients with available HBV-DNA

Table 1
Patients' characteristics at the start of tenofovir (TDF) plus emtricitabine (FTC) therapy (n=78).

	Treatment intensification (n = 54)	Treatment simplification (n = 24)	p
Demographics			
Male (n (%))	45 (83.3)	21 (87.5)	0.75
Mean age (years) ± SD	47.8 ± 15.8	51.8 ± 14.0	0.29
Median BMI (kg m^{-2}) [IQ range]	23.7 [21.5–25.4]	23.9 [21.8–28.5]	0.48
BMI > 25 (%)	45.0	26.7	0.15
Previous treatment history (complicated, n (%))	48 (88.9)	23 (95.8)	
Median TDF + FTC duration (weeks) [IQ range]	76 [60–116]	76 [52–120]	0.58
Median ALT (×ULN) [IQ range]	1.10 [0.64–1.95]	0.79 [0.53–1.11]	0.04
Significant fibrosis (Metavir ⩾ F3, %)	46.7	61.1	0.30
Proven cirrhosis (%)	28.9	38.9	0.44
Virological			
Median HBV-DNA (log_{10} IU/mL) [IQ range]	4.4 [3.0–5.8]	1.1 [1.1–1.1]	<0.001
HBeAg positive (%)	60.4	33.3	0.028
Co-infections (n)			
Delta	1	1	0.53
Genotype, n (%)			
A	11 (28.9)	4 (26.7)	1
B	6 (15.8)	1 (6.7)	0.66
C	5 (13.2)	4 (26.7)	0.25
D	11 (28.9)	5 (33.3)	0.75
E	4 (10.5)	1 (6.7)	1
F	1 (2.6)	0 (0)	1
Non available	16	9	

IQ, interquartile (25–75%); SD, standard deviation.

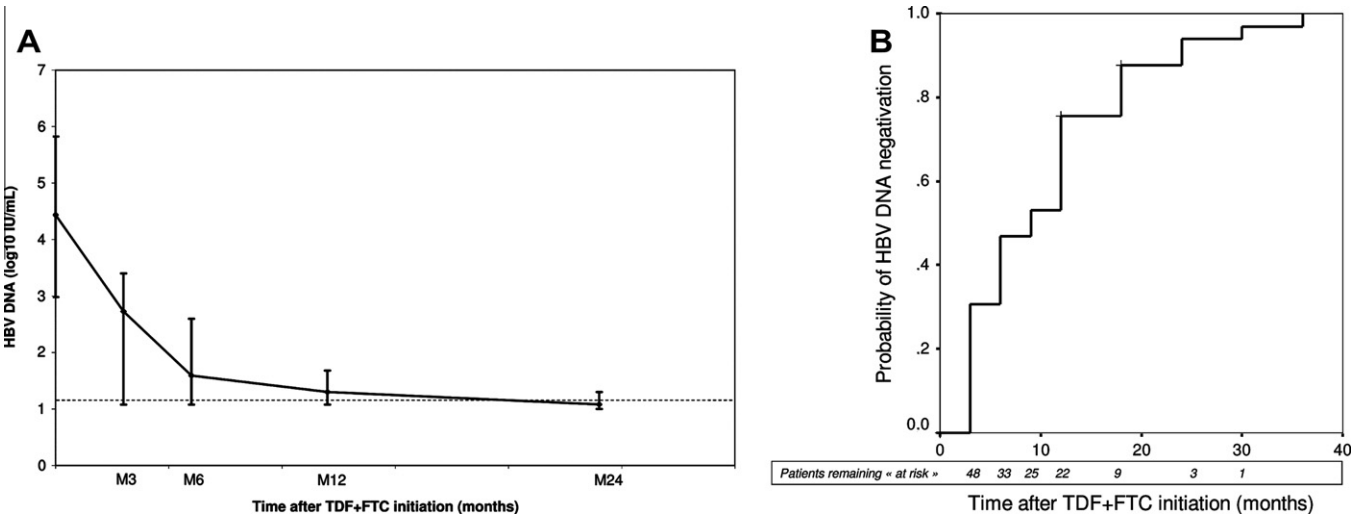

Fig. 1. (A) HBV-DNA kinetics (median with interquartile range) after TDF + FTC initiation in patients with treatment intensification (n = 54). (B) Kaplan–Meier analysis in patients with treatment intensification (n = 54).

information after 48 weeks of combination therapy, 80% (33/41) had undetectable HBV-DNA and this proportion increased to 94% (15/16) at 96 weeks. Kaplan–Meier analysis indicated that the probability of being HBV-DNA undetectable at 24 weeks was 47%, reaching 76% at 48 weeks, and 94% at 96 weeks (Fig. 1).

Time to undetectable HBV-DNA was shorter in patients with baseline HBV-DNA below 4 log_{10} IU/mL compared to those with a viral load above 4 log_{10} IU/mL (log-rank test gave $p < 0.001$; see Fig. 2). However, no significant difference was observed according to HBeAg status at baseline, previous treatment history (simple vs complicated), age, gender, or ethnicity.

In the group with treatment simplification, all patients but one remained HBV-DNA undetectable during follow-up. In one patient, relapse occurred between 72 and 96 weeks of follow-up, shortly after the patient deliberately stopped TDF + FTC therapy.

3.3. Analysis of clinical endpoints

No ALT flare occurred during follow-up for all patients. Two patients with decompensated cirrhosis at inclusion improved during the treatment-intensification follow-up. Four patients with treatment-intensification and cirrhosis decompensated during follow-up. Two of them already had an HCC at TDF + FTC initiation (one died), one developed HCC during follow-up and one had a cholestatic hepatitis associated with denutrition. HBV-DNA was undetectable at decompensation in three of these four patients.

Interestingly, HBe seroconversion was observed in three patients, who were HBeAg positive and received TDF + FTC intensification, at week 4, 16, and 112, respectively. HBs seroconversion was observed in only one patient in the treatment intensification group after 28 weeks of combination therapy.

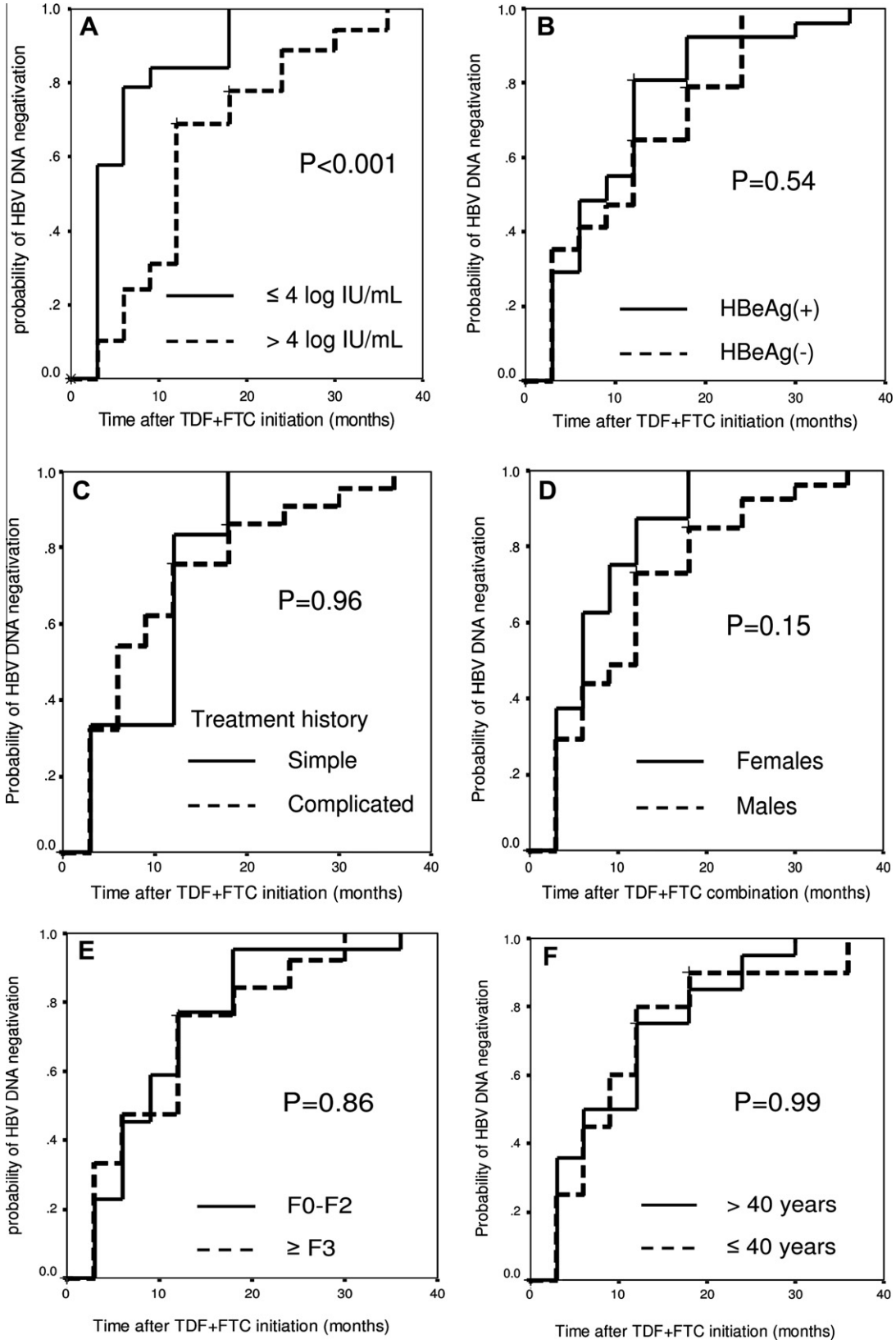

Fig. 2. Kaplan–Meier analysis giving the probability of HBV-DNA negativity according to HBV-DNA level at baseline (A), HBeAg status at baseline (B), previous treatment history (C), gender (D), fibrosis at baseline (E), and age (F).

3.4. Safety

Creatinine levels did not show kidney-function deterioration in either group of patients (Fig. 3). Only one of the 78 patients had an increased creatinine level that was greater than 1.5 times the baseline value. Creatinine level in this patient increased from 92 μmol/L at baseline to 149 μmol/L at 24 weeks, but decreased back to normal value (76 μmol/L) at 48 weeks.

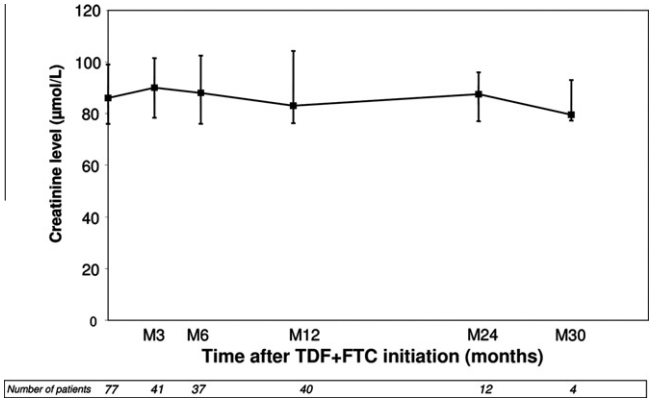

Fig. 3. Median creatinine level, over time, in all patients ($n = 77$). Error bars indicate the interquartile range.

4. Discussion

To our knowledge, we have reported one of the largest clinical experience studies on the combination of TDF + FTC for the treatment of CHB besides clinical trials. Based on unselected patients, this longitudinal multicenter cohort study could be considered as representative of what is usually seen in routine clinical practice. Patients' baseline characteristics are indeed similar to previously reported data from field-practice experience. Age, gender, and significant fibrosis distributions were no different from what has been reported by Levrero et al. (2010) in a study that included 85 consecutive TDF-treated patients with a suboptimal response to adefovir (ADV) after 48 weeks of ADV ± lamivudine. These baseline characteristics are also similar to those of nucleos(t)ides-naive patients from an Italian cohort treated with entecavir (ETV) (Lampertico et al., 2010a) and are similar to naïve or previously treated patients undergoing TDF therapy (Lampertico et al., 2010b).

The majority of our patients had a previous complicated treatment history. Only seven patients (belonging to the treatment-intensification group) had a simple history defined as no previous treatment ($n = 4$) or treatment with a single molecule ($n = 3$) during a maximum of 1 year. Our study, conducted in CHB patients from five European centers, shows that the probability of viral suppression increased over time to reach 76% after 48 weeks of treatment with the TDF + FTC combination and 94% after 96 weeks, thereby suggesting that TDF + FTC should be maintained beyond 48 weeks of therapy in patients with persistent viral replication.

In a recent randomized study that included 105 treatment-experienced patients with ADV failure and that compared a TDF monotherapy with a TDF + FTC combination, viral suppression was equivalent in both treatment arms and was achieved in 81% of subjects by week 48 (Berg et al., 2010b) and in 82% of patients by week 168 (Berg et al., 2010a). During a large multicenter long-term-resistance surveillance study in TDF-treated patients (Heathcote et al., 2011), 51of 641 patients (8%) were viremic (>400 copies/mL) after week 72 and were eligible for an add-on comparison strategy (Snow-Lampart et al., 2010). Of these 51 patients, 13 (25%) remained on the TDF monotherapy whereas 38 (75%) also received FTC. Remaining on TDF monotherapy appeared to be as effective as adding FTC to ongoing TDF with, respectively, 69% and 61% of patients achieving viral suppression by week 192. Moreover, no viral resistance occurred during this period (Snow-Lampart et al., 2011).

These studies suggest that both strategies (TDF monotherapy or TDF + FTC) give similar results in terms of viral suppression. Of particular note, a recently published randomized study conducted at 39 sites worldwide, in patients with decompensated CHB liver disease with no history of previous treatment with ADV, TDF, or ETV, reported that viral suppression was obtained by week 48 in 70% of patients treated with TDF, 73% of patients treated with ETV, and 88% of patients treated with a TDF + FTC combination therapy (Liaw et al., 2011). However, this phase II study was designed to assess safety, and was not powered to assess virological efficacy. It was, therefore, not possible to determine whether the TDF + FTC combination was superior or not in terms of viral suppression in this patient population.

In our study, time to viral suppression was shorter in patients with a low baseline viral load, which underlines the importance of early adaptation of treatment in cases of treatment failure, even in the absence of detectable mutation or biochemical breakthrough.

Our study failed to correlate viral response with known co-morbidity factors (Fig. 2b–d), probably because our study population was mainly composed of difficult-to-treat patients. Our descriptive data on clinical endpoints are limited. Although it will take longer before the clinical benefits can be assessed, we have observed only four cases of decompensated cirrhosis with clinical impairment (one patient died from HCC), which is less than what was observed with a placebo or lamivudine (Liaw et al., 2004), or in a cohort of decompensated cirrhosis patients undergoing lamivudine treatment (Fontana et al., 2002). On the other hand, two patients with decompensated cirrhosis at baseline showed significant clinical improvement. Interestingly, Liaw et al. reported that TDF, ETV, and TDF + FTC were well tolerated in patients with decompensated cirrhosis, with improvement in biochemical and clinical parameters (Liaw et al., 2011). Six patients died (all deaths not being considered related to study drugs) and six underwent a liver transplantation.

The main safety issue of nucleotide analogs is kidney dysfunction, especially with proximal tubulopathy (Labarga et al., 2009; Woodward et al., 2009). At the time of the study's design, we focused on late markers estimated by the stability of serum creatinine. Except for one patient, our data did not suggest any kidney function impairment. Future studies assessing safety should also measure early markers of tubular dysfunction as well as co-morbidities, which may also play a major role.

In conclusion, our results indicate that, in difficult-to-treat patients with a high exposure to antiviral drugs, a combination of TDF + FTC can reach a very high rate of viral suppression after 48 weeks of therapy, which further increased after 96 weeks. Several international guidelines still recommend treatment adaptation if viral suppression is not reached at 1 year. However, in the present study, HBV-DNA kinetics beyond 48 weeks of therapy strongly suggests maintaining treatment since no breakthrough has occurred. Several other studies confirm that, in cases of partial virological response, maintaining treatment allowed HBV-DNA to become undetectable over time (Zoutendijk et al., 2011).

Thus, in our study, performed in the clinical practice with patients heavily exposed to antivirals, the TDF + FTC combination showed antiviral efficacy and a good safety profile in all patients, and may represent an interesting clinical option to increase barriers to resistance. Long-term follow-up will determine whether the objective of viral suppression can be reached in all these difficult-to-treat patients.

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