Antiviral Research 92 (2011) 90–95

Contents lists available at ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

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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ARTICLE INFO

Article history:
Received 22 March 2011
Revised 29 June 2011
Accepted 4 July 2011
Available online 13 July 2011

Keywords:
Chronic hepatitis B
Tenofovir
Emtricitabine
Combination therapy

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.

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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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doi:10.1016/j.antiviral.2011.07.003

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

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