ORIGINAL ARTICLE

Tenofovir Disoproxil Fumarate Reduces the Severity of COVID-19 in Patients with Chronic Hepatitis B

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Abstract

Background and Aims HIV-positive patients on tenofovir hydroxyl fumarate (TDF)/emtricitabine have a lower risk of COVID-19 and hospitalization than those given other treatments. Our aim was to analyze the severity of COVID-19 in patients with chronic hepatitis B (CHB) on TDF or entecavir (ETV).

Methods Spanish hospital databases ($n = 28$) including information regarding adult CHB patients on TDF or ETV for the period February 1st to November 30th 2020 were searched for COVID-19, defined as a positive SARS-CoV-2 polymerase chain reaction, and for severe COVID-19.

Results Of 4736 patients, 117 had COVID-19 (2.5%), 67 on TDF and 50 on ETV. Compared to patients on TDF, those on ETV showed ($p < 0.05$) greater rates of obesity, diabetes, ischemic cardiopathy, and hypertension. COVID-19 incidence was similar in both groups (2.3 vs. 2.6%). Compared to TDF, patients on ETV more often ($p < 0.01$) had severe COVID-19 (36 vs. 6%), required intensive care unit (ICU) (10% vs. 0) or ventilatory support (20 vs. 3%), were hospitalized for longer (10.8 ± 19 vs. 3.1 ± 7 days) or died (10 vs. 1.5%, $p = 0.08$). In an IPTW propensity score analysis adjusted for age, sex, obesity, comorbidities, and fibrosis stage, TDF was associated with a sixfold reduction in severe COVID-19 risk (adjusted-IPTW-OR 0.17, 95%CI 0.04–0.67, $p = 0.01$).

Conclusion Compared to ETV, TDF seems to play a protective role in CHB patients with SARS-CoV-2 whereby the risk of severe COVID-19 is lowered.

Keywords Hepatitis B · COVID-19 · Tenofovir · Entecavir

Introduction

Since December 2019, more than 307 million people have become infected by SARS-CoV-2 and at least 5 million deaths have been declared by COVID-19 [1]. Despite vaccination, most people remain vulnerable to COVID-19 because of heterogeneity in vaccine administration among countries and emergence of SARS-CoV-2 variants that escape immunization. These facts have fostered research on new antivirals or repurposing of older ones that could be effective against SARS-CoV-2.

Tenofovir disoproxil fumarate (TDF) is a nucleotide analog indicated in the treatment of patients with chronic hepatitis B (CHB) to suppress hepatitis B virus DNA levels [2] and combined with emtricitabine and/or lamivudine in patients with HIV [3]. Three observational studies in HIV-positive individuals conducted during the first pandemic wave found the prevalence of SARS-CoV-2 antibodies,

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and the risks of symptoms, hospitalization, and death by COVID-19 were lower among patients on antiviral regimens that include TDF [4–6]. The results of these studies have been confirmed in a large cohort of HIV-positive individuals after careful adjustment for multiple comorbidities [7]. Protection from SARS-CoV-2 infection or severe COVID-19 by TDF could also be of relevance in patients with CHB. Approximately, 240 million people are living with chronic HBV infection, and some of them are candidates to therapy with nucleot(s)ide analogs, TDF, or entecavir (ETV) [2]. In them, demonstration of a benefit of TDF on COVID-19 could matter in the decision making of CHB therapy.

Most of the published studies of COVID-19 in patients with CHB focus on the incidence and clinical characteristics. Rates of incidence ranging from 0.1 to 12.2% have been found, depending on country's HBV prevalence. Previous liver dysfunction and also COVID-19-related liver injury seem to worsen prognosis [8–13]. Other studies analyze the possible reactivation of CHB during COVID-19 with different results [14, 15]. However, no study has evaluated the potential impact of the nucleotide analog used to treat CHB on COVID-19 outcomes.

We have evaluated in a Spanish nationwide cohort of patients with CHB on treatment with nucleot(s)ide analogs, TDF or ETV, the severity of COVID-19 during the first 10 months of pandemia.

Patients and Methods

Study Design and Patients

This industry-independent and observational retrospective study was conducted according to STROBE statement. The databases of 28 Spanish hospitals of patients with CHB on TDF or ETV were searched for cases of COVID-19 between 1st February and 30th November 2020. All databases were cross-checked with in-hospital pharmacy registries to ensure the inclusion of all CHB patients on antiviral treatment.

Inclusion criteria were (i) age above 18 years; (ii) CHB defined as HBsAg positive for at least six months; (iii) antiviral treatment with TDF or ETV at the time of COVID-19 diagnosis; and (iv) SARS-CoV-2 infection defined by a positive PCR result of nasopharyngeal swab test done both in primary and hospital care. Patients with more than one antiviral drug or coinfected with HIV, HCV, or HDV were excluded.

For each confirmed case, age, sex, comorbidities as obesity, diabetes mellitus, arterial hypertension, and ischemic cardiopathy were registered. COVID-19 clinical features, management, hospital stay, and outcomes were collected by medical history. Liver fibrosis was assessed from the most recent liver elastography or liver biopsy available.

Data were anonymized and collected from medical records by each local investigator and were centrally compiled and analyzed. The study was approved by all ethics committees of the participating institutions. Individual written informed consent was waived by ethic committees due to the study design and purposes.

Definitions

Severe COVID-19 was defined according to the World Health Organization criteria: severe pneumonia (respiratory rate > 30 breaths/min, or oxygen saturation < 94% on room air), acute respiratory distress syndrome (PaO2/FiO2 < 300), sepsis, or septic shock [16]. COVID-19 clinical severity was classified as outpatient, hospital admission, or intensive care unit (ICU) admission [16]. Ventilatory support was defined as non-invasive mechanical ventilation or orotracheal intubation requirements. Length of hospitalization was calculated in days from the date of hospital admission to the date of discharge or death.

Statistical Analysis

Qualitative variables are expressed as frequency counts and percentages. Quantitative variables are expressed as the median and 1st–3rd quartile. Proportions were compared using the χ^2 or Fisher's exact test, and continuous variable were tested using parametric (t test) and non-parametric test (Mann–Whitney U test) when appropriate. To calculate the propensity score of receiving TDF, we fitted a logistic model including age, sex, obesity, arterial hypertension, diabetes mellitus, ischemic cardiopathy, HBeAg presence, detectable HBV DNA, and advanced fibrosis [17]. Then, we used inverse probability of treatment weighting (IPTW) propensity score method to compare COVID-19 severity between patients receiving TDF or ETV. We assessed the balance of covariates by an overidentification test and by calculating raw and weighted standardized differences. Need for intensive care unit (ICU) and ventilatory support, and mortality were explored by bivariate analysis due to the low number of events. Significance was set at $p < 0.05$. Data were analyzed using the SPSS Statistics package version 22.0 (SPSS Inc, Chicago, IL).

Results

Baseline Characteristics of COVID-19 Cases

The databases of the participating hospitals included 4736 patients with CHB, 1864 of on ETV (39%) and 2872 on TDF (61%). The search identified 117 cases of COVID-19 (8-month incidence = 2.5%, 95%CI 2.1–2.9%)

(Supplementary Table 1). Seventeen patients (14.5%) were obese, and 24 (20.5%) were previously diagnosed with diabetes mellitus, 34 (29.1%) with arterial hypertension, and 9 (7.7%) with ischemic cardiopathy. Fifty out of the 117 patients (42.7%) were on ETV and 67 on TDF (57.3%), and the median treatment duration was of 60 (24.5–107) months. Twenty-one patients were HBeAg positive, and 22 had detectable HBV DNA. Twenty-eight (23.9%) patients presented advanced fibrosis (F3 or F4). COVID-19 hospitalization was needed in 46 patients (39.3%), 22 (18.8%) presented severe COVID-19, and 5 of them required ICU admission (4.3%). Twelve patients (10.3%) received ventilatory support and 6 (5.1%) died.

Comparisons Between Groups of Treatment

Compared with patients on TDF (Table 1), those on ETV were older, and had significantly ($p < 0.05$) greater rates of obesity, diabetes, ischemic cardiopathy, and arterial hypertension. There were no significant differences between groups in HBeAg status, detectable HBV DNA, or treatment duration. Advanced fibrosis was non-significantly more frequent in patients on ETV (32 vs. 18%, $p = 0.06$).

The incidence of COVID-19 in patients on TDF or ETV was similar (0.023 vs. 0.026, $p = 0.44$). ETV patients more often ($p < 0.01$) had severe COVID-19 (36% vs. 6%), required ICU (10% vs. 0), ventilatory support (20% vs. 3%), had longer hospitalization (10.8 ± 19 vs. 3.1 ± 7 days), or died (10% vs. 1.5%, $p = 0.08$).

Severe COVID-19 Analysis

Univariate analysis indicates that severe COVID-19 was significantly ($p < 0.05$) more frequent in patients who were older [*odds ratio* (OR) age > 60 years 3.79 (95%CI 1.43–10)], had diabetes mellitus [OR 3.69 (95%CI 1.34–10.16)], or were on ETV [OR 8.85 (95%CI 2.76–28.3)] (Table 2). Inverse probability of treatment weighting propensity score showed that TDF treatment reduced by sixfold the risk of severe COVID-19 (adjusted OR 0.17, 95%CI 0.04–0.68, $p = 0.013$). Supplementary Table 2 and the overidentification test ($p = 0.97$, the null hypothesis that the covariates were balanced cannot be rejected) show that covariates were well-balanced after IPTW matching.

Discussion

In this study, we have addressed the incidence and severity of COVID-19 in a large nationwide cohort of 4736 patients with CHB on ETV or TDF during the first pandemic wave. Our results show that after adjustment for multiple comorbidities and severity of chronic liver disease, TDF treatment

Table 1 Characteristics of the patients with COVID-19 infection on ETV or TDF

Variable	ETV ($n = 50$)	TDF ($n = 67$)	p value
Demographics and epidemiologic characteristics			
Age (years)	58 (48–69)	53 (46–61)	0.03
Male sex	30 (60%)	50 (75%)	0.11
Obesity	11 (22%)	6 (9%)	0.06
Arterial hypertension	22 (44%)	12 (18%)	< 0.01
Diabetes mellitus	16 (32%)	8 (12%)	0.01
Ischemic cardiopathy	7 (14%)	2 (3%)	0.03
Chronic hepatitis B characteristics			
Advanced fibrosis (F3-F4)	16 (32%)	12 (18%)	0.07
HBeAg positive	10 (20%)	11 (16%)	0.42
Detectable HBV DNA	13 (26%)	9 (13%)	0.09
Treatment duration (months)	60 (53)	78 (59)	0.11
COVID-19 infection characteristics			
Incidence	0.026	0.023	0.44
Severe COVID-19	10.8 (36%)	3.1 (6%)	< 0.01
Management			
Outpatient	21 (42%)	50 (75%)	< 0.01
Inpatient (ward)	24 (48%)	17 (25%)	0.02
ICU	5 (10%)	0	0.01
Oxygen therapy			
No need	18 (36%)	4 (6%)	< 0.01
Basic therapy	26 (52%)	55 (82%)	0.1
Ventilatory support	14 (28%)	10 (15%)	< 0.01
Hospitalization length (days)	10.8 (19)	3.1 (7)	< 0.01
Death	5 (10%)	1 (1.5%)	0.08

Results are expressed as median (1st–3rd quartile), mean (SD) and n (%)

p value, assessed by χ^2 or t test

ETV: Entecavir, *TDF* Tenofovir, *HBV* Hepatitis B virus, *DNA* deoxyribonucleic acid, *ICU* intensive care unit

exerts a protective effect for severe COVID-19 infection when compared with ETV.

Molecular studies have set the experimental basis for a beneficial impact of TDF on COVID-19. The coronaviruses are single-strand RNA viruses whose replication requires a RNA-dependent RNA polymerase. Both HIV and HBV incorporate TDF in their polymerases, which stops viral replication [18]. Molecular docking and in vitro studies indicate that TDF inhibits SARS-CoV-2 RNA polymerase [19–21]. Moreover, TDF/emtricitabine reduces viral loads in nasal swabs of preclinical models [22]. TDF also has immunomodulatory effects, including decreased production of interleukin-8 and -10 [23], both have been shown to predict COVID-19 severity. Interestingly, tenofovir alafenamide (TAF) lacks activity against SARS-CoV-2 in a cell model, has weaker immunomodulatory effects, and reaches tenfold

Table 2 Comparisons between patients with mild and severe COVID-19 infection

Variable	Mild COVID-19 ($n=95$)	Severe COVID-19 ($n=22$)	OR (95%CI) Uni-variate analysis	OR (95%CI) IPTW
Age	53 (45–61)	63 (54–71)	3.8 (1.4–10)*	0.98 (0.95–1.01)
Male sex	64 (67%)	16 (73%)	0.8 (0.2–2.1)	0.35 (0.14–0.88)[+]
Obesity	11 (11%)	6 (27%)	2.9 (0.9–8.9)	0.65 (0.18–2.40)
Arterial hypertension	24 (25%)	10 (45%)	2.5 (0.9–6.4)	0.37 (0.14–0.97)
Diabetes mellitus	15 (16%)	9 (41%)	3.7 (1.3–10)*	0.40 (0.12–1.37)
Ischemic cardiopathy	6 (6%)	3 (14%)	2.3 (0.5–10)	0.44 (0.07–2.82)
HBeAg positive	19 (20%)	2 (9%)	0.4 (0.1–1.9)	1.15 (0.32–4.14)
Detectable HBV DNA	17 (18%)	5 (23%)	1.3 (0.4–4.1)	0.43 (0.12–1.54)
Advanced fibrosis	20 (21%)	8 (36%)	2.3 (0.8–6.4)	0.69 (0.24–1.95)
ETV treatment	32 (34%)	18 (82%)	8.85 (2.8–28)*	0.17 (0.04–0.68)[+]

Results are expressed as median (1st–3rd quartile) and *n* (%)

OR odds ratio, *HBV* Hepatitis B virus, *DNA* deoxyribonucleic acid, *ETV* entecavir

*$p < 0.05$, assessed by χ^2 or *t* test

[+]$p < 0.05$, assessed by IPTW propensity score analysis

lower extracellular concentrations and mucosal penetrations than TDF, which justify that HIV individuals on TAF fared no better than the general population from COVID-19 [4].

Our results indicate that TDF exerts protective effects in CHB patients with COVID-19. This was shown by the lower ICU admission, ventilatory support need, hospitalization length, and deaths in patients on TDF compared to those on ETV. This conclusion has been reached after adjustment for relevant covariates, including comorbidities, by means of the IPTW method. These results agree with those studies that have shown lower COVID-19 severity in HIV patients on antiviral regimens that include TDF [4–7]. In contrast, we did not observe that TDF reduced COVID-19 incidence in patients with CHB compared to those on ETV. Conclusions regarding incidence in retrospective observational studies are rather inaccurate and biased by differences in health provision behavior. Specifically, studies of TDF in HIV patients were limited to the first months of the pandemic when PCR testing was restricted to hospitals and mild COVID-19 cases recommended not to come to hospitals, having lower access to PCR testing. In contrast, our study extended observations through 2020, an interval when mild COVID-19 was diagnosed in hospitals and in outpatient clinics, a factor that could have attenuated the differences between treatment groups.

The strengths of our study include its national scope, relatively long-time interval, and analysis and adjustment for a variety of potential risk factors and comorbidities. However, several limitations should be acknowledged. The study is retrospective and we cannot discard some bias in patient selection and residual confounding. We also should consider that limitation of PCR testing to hospitals in the first months of the pandemic could have contributed to underestimate mild COVID-19 cases. Conclusions regarding mortality in our cohort are limited by the short number of deaths. Finally, our results involve alfa SARS-CoV 2 variant, so our findings deserve further investigations with newer variants like delta or omicron.

As the SARS-CoV-2 pandemic keeps going, a protective effect of TDF from severe COVID-19 in patients with CHB could be of interest in certain situations in which TDF might be considered the preferred treatment option of CHB: (i) patients with advanced liver disease in whom vaccines are likely to be suboptimal, (ii) patients with recent CHB diagnosis who are about to initiate antivirals, since it is unlikely to switch long-term treatments, and (iii) immunosuppressed patients who need antivirals to prevent HBV reactivation.

In conclusion, the results of this nationwide study indicate that compared to ETV, TDF exerts a protective effect in CHB patients infected with SARS-CoV-2, with less risk of severe COVID-19.

Declarations

Conflict of interest None.

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