Renal toxicity and adherence associated with Tenofovir Disoproxil Fumarate in hepatitis B virus

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ABSTRACT

Introduction: Hepatitis B Virus (HBV) is the leading cause of primary liver cancer worldwide. Tenofovir disoproxil fumarate (TDF) is a standard treatment for HBV. Although generally eliminated by renal excretion, prolonged use can lead to nephrotoxicity.

This study aims to analyze the nephrotoxicity caused by TDF in HBV patients. A secondary objective will be to assess treatment adherence.

Methods: This is a descriptive observational study that includes all patients infected with HBV, treated with TDF over four years (2017-2021), and followed for two years after initiating treatment. During this period, renal function was monitored using baseline creatinine and glomerular filtration rate. Adherence was calculated based on dispensation records.

Results: A total of 61 patients were recruited (24 males and 37 females), with a median age of 62 years (range 26-87). During the two-year follow-up after treatment initiation, there was an increase in the average serum creatinine levels to 1.01 ± 0.20 mg/dL (mean eGF 60.2 ± 17.5 mL/min/1.73 m²). Sixteen patients experienced type 1 renal damage, and five patients suffered type 2 renal damage. The average adherence to treatment was 93.7 ± 19.7%.

Conclusions: TDF leads to a deterioration in renal function, which is usually mild and reversible. Nephrotoxicity caused by TDF reaches serious stages in a small percentage of patients. Patients with HBV demonstrate a high rate of adherence to treatments.

Keywords: **Hepatitis B, tenofovir, nephrotoxicity**

Toxicidad renal y adherencia asociadas al Tenofovir Disoproxil Fumarato en la hepatitis B

RESUMEN

Introducción: El Virus de la Hepatitis B (VHB) es la causa principal del cáncer hepático primario a nivel mundial. Tenofovir disoproxil fumarato (TDF) es un tratamiento habitual para el VHB eliminándose por vía renal su uso prolongado puede producir nefrotoxicidad. Este estudio tiene como objetivo analizar la nefrotoxicidad causada por TDF en pacientes con VHB. Como objetivo secundario se estudiará la adherencia al tratamiento.

Métodos: Estudio observacional descriptivo que incluye todos los pacientes infectados por VHB, tratados con TDF durante cuatro años (2017-2021) y con dos años de seguimiento tras el inicio del mismo. Durante este periodo se monitoriza la función renal mediante la creatinina basal y filtrado glomerular. Se calculó la adherencia mediante registro de dispensaciones.

Resultados: Se reclutaron 61 pacientes (24 hombres y 37 mujeres), con una mediana de edad de 62 años (rango 26-87). Durante el seguimiento los dos años posteriores al inicio de tratamiento, se observa un aumento de la media de los valores de creatinina sérica a 1,01 ± 0,20 mg/dL (FGe medio 60,2 ± 17,5 ml/min/1,73 m²). 16 pacientes sufrieron un daño renal de tipo 1 y 5 pacientes de tipo 2. La media de adherencia al tratamiento fue del 93,7 ± 19,7 %,

Conclusiones: TDF produce un deterioro en la función renal que suele ser leve y reversible. La nefrotoxicidad causada por TDF, alcanza estadios graves en un bajo porcentaje de pacientes. Los pacientes con VHB muestran una elevada tasa de adherencia al tratamiento.

Palabras clave: **Hepatitis B, tenofovir, nefrotoxicidad**

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INTRODUCTION

Hepatitis B virus (HBV) is the leading cause of primary liver cancer worldwide, with approximately 350,000 new cases attributable to HBV annually. Hepatocellular carcinoma is more likely in the presence of underlying cirrhosis, but HBV itself has oncogenic properties, and hepatocellular carcinoma can occur in non-cirrhotic patients with HBV infection[1].

More than 240 million patients (approximately 4% of the world's population) are chronic carriers of HBV. Two billion people, one in three, have been in contact with the virus. HBV is not a cytopathic virus and liver injury in chronic hepatitis B is a consequence of the local immune response in the immune clearance phase. Chronic inflammation triggers fibrogenesis and as a result, many patients with chronic hepatitis B have progressive fibrosis, which can progress to cirrhosis1. The spectrum of chronic disease is highly variable, ranging from the inactive carrier to patients with chronic hepatitis, cirrhosis and hepatocellular carcinoma[2].

The rate of chronicity following acute HBV infection is greater than 95% among patients infected at birth. This risk decreases with increasing age of acquisition of infection and is less than 5% in those infected in adulthood. Chronic hepatitis B is usually asymptomatic. The most common symptom is fatigue, but sleep disturbances, difficulty concentrating and pain in the right hypochondrium are often present[1]. The goals of treatment are to suppress viral replication in a sustained manner[2], to reduce the histological activity of chronic hepatitis and to reduce the risk of cirrhosis and hepatocellular carcinoma[1]. HBV infection cannot be completely eradicated due to the persistence of covalently bound closed circular DNA in the nucleus of infected hepatocytes but should be reduced to undetectable concentrations (< 10 - 15 IU/ml)[1]. As a result, treatment aims to achieve persistent loss of HBsAg with or without the appearance of anti-HBs and to maintain undetectable HBV-DNA levels in HBeAg-positive patients in whom seroconversion is not achieved and in HBeAg-negative patients[2]. Long-term treatment with nucleoside/nucleotide analogues is indicated in most chronic hepatitis B patients. The nucleoside analogue entecavir and the nucleotide analogue tenofovir are the most potent drugs with a high barrier to resistance and are recommended as first-line monotherapies. When HBeAg-positive patients undergo seroconversion and become seronegative or HBeAg- negative patients lose HBsAg, treatment should be continued for at least 6-12 additional months. In all other cases, treatment should be maintained for life, and adherence to treatment is extremely important[1].

Tenofovir disoproxil fumarate (TDF) is a prodrug of tenofovir, which potently inhibits the reverse transcriptase of Human Immunodeficiency Virus (HIV) and HBV[3]. TDF is renally eliminated by glomerular filtration, with 20-30% being transported to the cells of the proximal tubule. TDF is associated with nephrotoxicity on the proximal tubule, altering the processes of secretion and reabsorption of substances such as creatinine, causing its accumulation in the plasma[4].

Acute Renal Failure (ARF) is defined as a decrease in the kidneys' ability to eliminate nitrogenous waste products, occurring within hours to days[5].

Glomerular filtration rate (GFR) is widely accepted as the best indicator of renal function. However, GFR is difficult to measure and is commonly estimated by plasma levels of endogenous filtration markers such as creatinine. The KDIGO Clinical Practice Guidelines classify acute kidney injury into three stages based on the increase in serum creatinine relative to baseline and urine volume.

When it comes to chronic diseases, such as HBV infection, non-adherence to treatment is a prevalent and relevant problem in clinical practice. It is estimated that 20-50% of patients do not take their medication correctly, although this percentage varies according to the pathology. According to the World Health Organization (WHO), the consequences of inadequate adherence are diverse: therapeutic failure, inefficiency of treatment, emergence of resistance, worsening of the patient's clinical condition, increase in emergency room visits and hospitalizations, treatment abandonment, etc. Non-adherence is a complex, multifactorial process, influenced by factors that vary with the patient's clinical situation, concomitant treatment, personal environment and healthcare environment.

Methods for adherence assessment have traditionally been classified as direct and indirect. Direct methods refer to the determination of drug concentrations in biological fluids or the measurement of clinical outcomes. Indirect methods include "practitioner assessment", which tends to overestimate adherence, and "prescription and dispensing records", "medication overcount" and "questionnaires" or patient self-reported adherence[6].

The present study aims to analyse the nephrotoxicity caused by TDF in HBV patients. Adherence to treatment will be studied as a secondary objective.

METHODS

Descriptive observational study including all HBV-infected patients treated with TDF for four years (2017-2021) and with two years of follow-up after baseline in a university hospital complex with referral units. Patients for whom computerized analytical data were not available were excluded from the study. Demographic data were collected (sex, age), diagnosis, start of treatment, end of treatment (end of study date if the patient was still on treatment at that time), duration of treatment, baseline serum creatinine in the last year before starting treatment (baseline creatinine) and estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. To stage acute renal failure, the difference between baseline creatinine and the highest creatinine value in the two years after initiation of treatment was calculated. Stage 1 was defined as > 0.3 mg/dL or 1.5-1.9 times baseline creatinine, stage 2 as 2-2.9 times baseline creatinine and stage 3 as > 4.0 mg/dL or 3 times baseline creatinine. At the end of the study, the recovery of renal function was assessed using the serum creatinine and eGFR values of the last analysis performed.

Treatment adherence was calculated in terms of units prescribed and dispensed over the entire course of treatment, as indicated by the following formula: percentage (%) medication possession rate = number of total units dispensed/number of total theoretical units prescribed on that time interval × 100.

The end-of-study viral load determined by the quantitative real-time COBAS® TaqMan® technique was recorded and a detectable viral load of more than 20 copies/

mL was defined as detectable viral load. The sources of information for data collection were the pharmaceutical dispensing software Farmatools® and the electronic medical record Jara®. Statistical processing of the data was performed with SPSS® v.26.

RESULTS

A total of 61 patients (24 men and 37 women), with a median age of 62 years (range 26-87), were included in the study. 51 (83.6%) patients were receiving TDF for active treatment of chronic hepatitis B and 10 (16.4%) as antiviral prophylactic treatment for HBV reactivation due to immunosuppressive treatment or immunosuppressive therapy with anti-CD20 antibodies. The median duration of treatment with TDF was 53.5 ± 32.4 months. All patients began treatment with one TDF tablet every 24 hours.

The mean baseline creatinine was 0.75 ± 0.18 mg/dL which means a mean baseline eGFR of

84.0 ± 18.5 ml/min/1.73 m^2. During the two-year follow-up after the start of treatment, mean

serum creatinine values increased to 1.01 ± 0.20 mg/dL (mean eGFR 60.2 ± 17.5 ml/min/1.73 m^2). Regarding the staging of acute renal failure, in the two years after starting TDF, 16 (26.2%) patients had type 1 and 5 (8.2%) patients had type 2 renal impairment. The mean final serum creatinine value was 0.95 ± 0.26 mg/dL (mean eGFR 68.5 ± 22.0 ml/min/1.73 m^2). The dosage regimen of TDF was adjusted to the renal function of the patients according to the technical data sheet. At the end of the study, 20 (32.8%) patients reverted to baseline renal function, with serum creatinine andeGFR values close to those at baseline.

The mean adherence to treatment was 93.7%, with 51 (83.6%) patients adhering more than 80%. ± 19.7%. Fifty-eight (95.1%) patientshad a negative viral load at the end of the study.

DISCUSSION

According to the European Association for the Study of the Liver (EASL 20177) clinical practice guidelines for the management of HBV infection, the treatment with a nucleoside analogue such as TDF, with a high barrier to resistance, is an indicator of long-term efficacy because it achieves undetectable levels of viral DNA in most patients as well as a favourable safety profile. However, the renal damage associated with TDF is known from studies carried out in HIV patients with this treatment and is associated with a related decrease in eGFR of 9.8 mL/min/1.37 m^2 in 5 years[8,9].

As regards HBV, in a study of 273 patients who were receiving treatment with TDF, the eGFR level 24 months after starting treatment was 3.99 mL/min/1.73 m^2 lower than its baseline value[10]. Nevertheless, in this study the average eGFR at 2 years of treatment is considerably more significant, decreasing approximately 24 mL/min/1.73 m^2. This discordance may be due to the difference in the total duration of treatment of the studies, unequal and insufficient sample sizes, and the interindividual variability of the patients analysed. Some authors argue that older age, male sex, cirrhosis or baseline renal disease are independent factors but predisposing to suffer acute kidney damage. However, these studies have limitations because of the small sample size, the short duration of treatment or the calculation of eGFR by means of the MDRD equation[11,12]. In this study, risk factors predisposing to nephrotoxicity were not collected, which could mean a bias in our results. Nevertheless, Koklu et al. state that if they excluded patients with risk factors predisposing to nephrotoxicity from their analysis, the renal damage produced by TDF was reduced although it did not disappear[10]. In the case of pathologies with chronic treatments, it is essential to monitor their adherence, as both efficacy and safety are affected by taking or not taking the medication[13].

The ideal method for estimating adherence should be sensitive and specific, providing a quantitative and continuous measure, reliable, reproducible, capable of detecting changes in adherence over time, applicable in different situations, as well as quick and inexpensive. The data obtained from pharmacy dispensing records is an indirect method, feasible in health systems where dispensing data is available, relatively inexpensive and it allows the establishment of routine and computerised records with longitudinal monitoring of patients 6. It is the method most extensively used by hospital pharmacy services, where each dispensing is easy to record and there is direct contact with patients. However, one of its main limitations is that medication dispensing is not necessarily associated with correct adherence. To analyse adherence, it is recommended to study at least three-month periods in early phases of treatment and six-month periods in more advanced stages[6].

In this study, all medication dispensed at each visit was recorded. Despite the known lack of adherence to treatment in chronic pathologies without symptomatology that makes the patient's quality of life worse, in our case we observed high levels of adherence throughout the study. To confirm these data, a direct method was used, which was the determination of HBV viral load, and its results only supported the data obtained from the dispensing registers, as in the study by Allard N et al.[14] Adherence rates to treatment are high and this concept has been assessed using two different methods that complement each other.

Limitations of the study were the small sample size which does not allow for subgroup analysis,

e.g. to differentiate between patients who were treated for a certain period (due to initiation of immunosuppressive treatment) from patients on chronic treatment (chronic Hepatitis B). On the other hand, to assess adherence to treatment, it could have been complemented with other methods such as validated questionnaires.

The results obtained lead us to conclude that TDF produces a deterioration in the renal function of some patients, which is usually mild and sometimes reversible. Nephrotoxicity caused by TDF reaches severe stages in a low percentage of patients. HBV patients show a high rate of adherence to treatment as reflected by a negative viral load at the end of the study.

Conflicts of Interest: The authors declare not to have conflicts of interest and there is no organisation that founds the research.

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