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Research Article

Prospective Study to Assess Progression of Renal Markers after Interruption of Tenofovir due to Nephrotoxicity

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Background. Prospective studies about the reversibility of tenofovir disoproxil fumarate- (TDF-) related renal impairment remain scarce. *Methods*. This is an observational prospective study including all patients that presented at our HIV Unit who interrupted TDF owing to nephrotoxicity. We assessed the evolution of renal parameters after discontinuation of this drug. *Results*. We included 59 patients, who were followed up for 72 weeks. Most were male (41, 69.5%), median (IQR) age was 53 (44; 58) years, and median time receiving TDF-containing regimens was 55.4 (28; 87.7) months. Most patients were receiving PI-based treatments (67%). At the final visit, most of the subjects showed complete recovery (35, 59.3%) or improvement (13 subjects, 22%). Significant improvements were observed in creatinine levels (from 84.9 [73.8; 97.5] to 78 [69.6; 91] μmol/L, $p = 0.013$), estimated glomerular filtration rate (eGFR, CKD EPI equation, from 87.7 [67; 99] to 89.9 [73.6; 99.3] mL/min/1.73 m^2, $p = 0.017$), and number of patients with eGFR <60 mL/min/1.73 m^2 (from 9 [15.3%] to 1 [1.7%], $p = 0.031$). A trend toward significance was observed in abnormal urine proteinuria/creatinine ratio (from 22 [37%] to 8 [13.6%], $p = 0.057$). *Conclusions*. Our results corroborate the high frequency of complete or partial renal recovery in patients receiving TDF-containing regimens who discontinued therapy owing to nephrotoxicity.

1. Introduction

Nephrotoxicity associated with tenofovir disoproxil fumarate (TDF) has been well characterized in clinical and study cohorts [1, 2], although prospective studies assessing TDF-related renal toxicity in clinical practice are scarce. Very often, discontinuation of TDF does not lead to complete reversibility of renal damage [3, 4]. The principal aim of this prospective study was to assess changes in laboratory values in a cohort of patients who interrupted TDF owing to nephrotoxicity.

2. Materials and Methods

2.1. Study Design and Patients. We conducted an observational prospective study including all patients that presented at our HIV Unit who interrupted TDF owing to TDF-related nephrotoxicity.

The patients had received a TDF-containing regimen for at least 3 months. All patients had normal renal laboratory values at baseline of TDF-including treatment, presented nephrotoxicity during treatment, and discontinued TDF owing to abnormal laboratory values. In order to fully evaluate changes in renal laboratory values, we chose to follow up patients for 18 months (72 weeks) after interruption of TDF, based on the median time to normalization of renal values in a previous study (17 months) [4].

The study was approved by the Institutional Review Board (code EO-12-036). All patients provided their written informed consent.

2.2. Objectives. The primary objective of the study was to assess changes in renal markers when TDF was discontinued in patients who developed renal impairment while taking this drug. We collected the number of patients whose renal function values returned to normal and the time to complete recovery, the number of patients whose renal function improved without achieving normal values, and the number of cases of irreversibility.

The secondary objective was to identify factors that predisposed to complete recovery.

2.3. Measurements and Definitions. Renal impairment was defined as at least 1 of the following 3 criteria: (i) estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 in 2 consecutive measurements (calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD EPI] equation) [5], (ii) a ≥2-fold increase in serum creatinine above baseline values, and (iii) at least 2 determinations with altered urine protein/creatinine ratio and urine albumin/creatinine ratio, low levels of serum phosphate, and presence of glycosuria without hyperglycemia or hematuria. All the abnormalities in the patients selected were detected in at least two consecutive determinations for a period of 3 months or more previous to the baseline visit. Subjects with extra renal causes of glycosuria and hypophosphatemia were excluded from the study.

The normal local reference values were as follows: eGFR ≥90 mL/min/1.73 m^2; creatinine ≤106 μmol/L; urine albumin/creatinine ratio ≤30 mg/g; urine protein/creatinine ratio ≤200 mg/g; serum phosphate 0.87–1.50 mmol/L; and negative glycosuria and qualitative hematuria.

Renal outcome after discontinuation of TDF was classified as normalization, improvement, or irreversible damage, as described elsewhere [4]. Briefly, the return to the baseline normal values in all renal parameters was considered normalization. An improvement in altered renal parameters but without achieving normal values was defined as improvement. Finally, renal damage was considered irreversible when the patient did not present any improvement in any of the altered parameters observed at discontinuation of TDF. Time to normalization was considered the first time at which patients returned to normal range values for all renal parameters after interruption of TDF. Time to improvement was considered the first time at which patients achieved consistently better values in any renal parameter.

Demographic data, comorbidities, and HIV-related data were also collected from the patient's clinical history. Virological, immunological, and renal data were collected immediately before discontinuation of TDF and every 3 months thereafter until 72 weeks after discontinuation. All determinations were performed under fasting conditions.

2.4. Statistical Analyses. The mean (SD), median (IQR), and frequency (%) were used to describe patients' characteristics, as appropriate.

A descriptive data analysis was performed in order to identify time to normalization or time to maximum improvement.

A subanalysis using Kaplan-Meier survival analysis was performed in order to detect the first time for each patient where all the altered values return to normality.

Univariant and multivariant Cox regression models were performed and included the following variables: gender, age, hepatitis coinfection, time since diagnosis of HIV, viral load, CD4 T-cell count at the beginning and end of the TDF-containing regimen, nadir CD4 T-cell count, months on antiretroviral treatment, months on protease inhibitors and TDF, type of change in antiretroviral therapy, diabetes mellitus, and arterial hypertension.

All analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, Illinois, USA) and the R software package (version 3.2.1). A p value of less than 0.05 was considered statistically significant.

3. Results

The study population comprised 60 patients. One patient was excluded owing to missing data. Most patients were male (41, 69.5%), median (IQR) age was 53 (44; 58) years, and median time on TDF-containing regimens was 55.4 (28; 87.7) months. Most of the patients were receiving protease inhibitor- (PI-) based regimens (67%). A total of 19 patients (32%) were coinfected with hepatitis, 14 (24%) had arterial hypertension, and 8 (13.6%) had diabetes mellitus (supplementary web table in Supplementary Material available online at http://dx.doi.org/10.1155/2016/4380845).

The most frequent renal abnormality before discontinuation of TDF was altered proteinuria/creatinine ratio (37%), which was mild in most cases (69.5%); 5 patients (6.7%) presented occasional proteinuria >1 g, and only 2 patients (3%) had sustained proteinuria >1 g.

After interruption of TDF, a significant improvement was observed in creatinine and eGFR values. The number of patients with an eGFR <60 mL/min/1.73 m^2 decreased significantly. A trend toward improvement was observed in the percentage of patients with an abnormal urine protein/creatinine ratio. The results are summarized in Table 1.

Kaplan-Meier results showed that all patients returned to normal values in all the altered parameters at any time of the follow-up with the exception of two subjects (96.6%; see Figure 1). Median (IQR) time to normal values was 12 (4; 24) weeks. From the 2 patients whose values did not return to normal, one had abnormal eGFR at baseline that improved but without reaching normal values (from 66 to 80 mL/min/1.73 m^2), while proteinuria returned to normal values (from 220 mg/gr to 160 mg/gr at the final visit). The other subject only showed a slight improvement in proteinuria/creatinine ratio (from 320 to 240 mg/gr). Nevertheless, not all the patients maintained the total normalization during the follow-up and, at the final visit, 35 patients had normality in all the parameters (59.3%); improvement but without complete recovery was detected in 13 patients (22%); and, finally, 11 subjects did not show improvement (18.7%).

The univariate analysis revealed an inverse correlation between age and renal recovery (hazard ratio [HR] = 0.973; p = 0.046) and a trend toward a positive correlation between patients who discontinued TDF only (without changing their

Table 1: Changes in laboratory values.

	Baseline	End of follow-up	p value
Creatinine, median (IQR), μmol/L	84.9 (73.8; 97.5)	78 (69.9; 91)	**0.013**
Abnormal creatinine values, n (%)	10 (16.9)	3 (5.1%)	0.125
eGFR (CKD EPI), median, (IQR), mL/min/1.73 m^2	87.7 (67; 99)	89.9 (73.6; 99.3)	**0.017**
eGFR (CKP EPI), n (%) <60 mL/min/1.73 m^2	9 (15.3%)	1 (1.7%)	**0.031**
eGFR (CKP EPI), n (%) ≥90 mL/min/1.73 m^2	25 (42.4%)	23 (39%)	0.549
Serum phosphate levels, mmol/L, median (IQR)	1.02 (0.9; 1.13)	1.00 (0.9.; 1.5)	0.632
Abnormal phosphate levels, n (%)	12 (23%)	9 (21%)	0.319
Urine albumin/creatinine ratio (mg/g)	18.4 (3; 56)	8.7 (1.7; 38)	0.446
Abnormal urine albumin/creatinine ratio, n (%)	11 (18.6%)	8 (13.6%)	1
Urine protein/creatinine ratio (mg/g)	180.5 (95; 322)	85 (69; 198)	0.118
Abnormal urine protein/creatinine ratio, n (%)	22 (37%)	8 (13.6%)	0.057
Urine hemoglobin	19 (32.2%)	11 (18.6%)	0.068
Glycosuria, n (%)	4 (6.8%)	0	0.18

TDF: tenofovir disoproxil fumarate; IQR: interquartile range; eGFR: estimated glomerular filtration rate; CKD EPI: Chronic Kidney Disease Epidemiology Collaboration; n: number of patients.

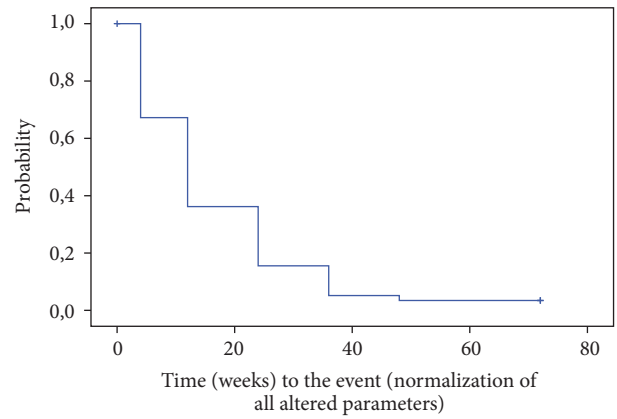

Figure 1: Kaplan-Meier survival analysis. First time to achieve total normalization in all parameters (weeks). Median: 12, IQR (4; 24).

other drugs) (HR = 1.57, $p = 0.10$) and those who switched TDF to abacavir (HR = 0.652, $p = 0.12$). When these 3 factors were included in the multiple Cox model, the inverse correlation with recovery was only maintained for age (HR = 0.972, $p = 0.032$).

The characteristics of the patients whose renal values recovered fully and rapidly (<6 months after the change in treatment) were compared with those whose values recovered later and/or incompletely. The associated factors were age (median [IQR]: 49.5 [43; 58] years in early normalization versus 55 [50; 62] in >6 months to normalization [$p = 0.034$; OR = 0.937; 95% CI, 0.883; 0.995]) and time on HIV infection (151.4 [81.3; 212.1] months versus 199.3 [151.6; 264.3] months [$p = 0.049$; OR = 0.994; 95% CI, 0.988; 1.00]). The differences for other variables, such as time on antiretroviral treatment, time on TDF, and comorbidities, did not reach statistical significance.

4. Discussion

This is one of the few prospective studies that focus specifically on assessing progression of renal abnormalities, including urinary markers, after withdrawal of TDF. Consistent with data from retrospective [3, 4] and cross-sectional studies [6], our findings show that proteinuria is the most common TDF-related renal abnormality. However, in contrast, we found that renal abnormalities resolved fully in most of the patients.

Although median proteinuria values before interruption of TDF were above normal levels, abnormalities were mild in most patients (in fact, only 2 patients had a sustained urine protein/creatinine ratio >1 g/g). This finding could explain why interrupting TDF did not lead to a statistically significant improvement in proteinuria values, although values returned to normal in most of the patients after the interruption.

The main TDF-related toxicity is a proximal tubular dysfunction, while altered GFR and advanced renal disease seem to be infrequent [7]. Several mechanisms could play a role in the toxicity of the drug. Tenofovir is excreted from the tubular cell by a combination of glomerular filtration and active tubular secretion; the drug entry to the cell through the basolateral membrane involves organic anion transporters (OATs) mainly OAT1. Subsequently, its secretion to the tubular lumen is an active process mediated by protein transporters that included multidrug-resistance protein 2 (MRP2) [8]. Since the toxicity seems to be related to the intracellular concentration of the drug [9], by inhibition of mitochondrial DNA replication in proximal tubular cells and cellular apoptosis [10, 11], the concomitant use of PIs blocks this step and increases the intracellular concentration of TDF [12] and could relate to an increase in TDF-related nephrotoxicity.

Finally, a high plasma TDF concentration has been also correlated with an increase in nephrotoxicity [13, 14], and this fact occurs more frequently with the concomitant use of boosted PIs [15].

Although most of our patients were under PIs containing strategies, a considerable proportion of our subjects return to normal values, supporting the hypothesis of a functional alteration, but not necessarily structural defects in tubular cells [16]. Nevertheless, in some cases, the subjects did not

maintain the complete recovery through the follow-up. This fact could be related to the multifactorial nature of these alterations, or to some intercurrent process.

A previous retrospective study of 183 patients performed in our unit [4] showed that laboratory values returned to normal in almost 60% of patients, although in the remaining cases values partially improved or did not improve after interruption of TDF. When we assessed the same markers in this prospective study, similar results were shown in our patients. Guidelines published in recent years recommend routine monitoring of urine and renal values among patients receiving TDF-based therapy [17] so that nephrotoxicity can be detected quickly and the drug discontinued early to enable fast and complete recovery in a large proportion of subjects under TDF-containing strategies.

We found that renal values reversed early in younger people and in those infected for a shorter time. However, even though the median age of our patients was 53 years and the frequency of hypertension or diabetes was relatively high (24% and 14%, resp.), renal recovery was complete in most of them. In addition, more than two-thirds were concomitantly receiving a ritonavir-boosted PI, which is known to increase the risk of toxicity.

Our data confirm that TDF-induced renal damage resolves in a considerable proportion of patients, even in middle-aged patients who had received TDF for as long as 88 months (more than 7 years). Early detection of renal impairment in clinical practice is essential for a complete and rapid recovery.

A new prodrug of tenofovir, tenofovir alafenamide, (TAF) will be soon available. TAF seems to have a better renal profile than TDF [18]. However, it is still unclear whether this benefit will be maintained in the case of concomitant use of other antiretroviral agents that affect renal laboratory values, such as PIs, or in the long term (data available with TAF until 96 weeks) [19]. While waiting for this new agent to become available, detailed knowledge of TDF-related nephrotoxicity and its reversibility will help us to better select the most adequate antiretroviral agent for each patient and prevent permanent renal damage.

Our study is limited by the small number of patients included. However, we report the real prevalence of TDF-related renal toxicity in our clinical practice over 18 months. Even with this limitation, our results are robust and add to data from retrospective studies.

In conclusion, we highlight the low percentage of patients taking TDF who experienced irreversible nephrotoxicity and the importance of monitoring urine markers in these patients. Appropriate monitoring and early detection of renal abnormalities can ensure complete recovery of kidney impairment very quickly after the interruption of TDF in most of the subjects. Our findings show that TDF-related nephrotoxicity could be reversible, even in middle-aged individuals who have been receiving TDF for almost 2 years.

Competing Interests

The authors report no competing interests.

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