Enferm Infecc Microbiol Clin. 2016;34(1):29–32

Enfermedades Infecciosas y Microbiología Clínica

www.elsevier.es/eimc

Original article

Switching from tenofovir containing regimens to boosted protease inhibitor monotherapy: Impact on renal function

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ARTICLE INFO

Article history:
Received 29 May 2014
Accepted 28 January 2015
Available online 27 February 2015

Keywords:
Reversibility
Renal toxicity
Tenofovir
Monotherapy
HIV

ABSTRACT

Objective: To evaluate the effect on creatinine clearance (CG-CrCl, Cockcroft–Gault equation) of switching to boosted protease inhibitor (PI) monotherapy in patients receiving a triple drug antiretroviral regimen containing TDF.
Methods: All patients who had received a TDF-containing regimen for at least one year and had been switched to PI monotherapy were included. A rapid decrease in CG-CrCl during exposure to TDF was defined as a decrease in CG-CrCl at least five times higher than the expected due to age (0.4 ml/min/year by the years of exposure to TDF). In this subgroup of patients, we considered improvement if the last value of CG-CrCl on PI monotherapy was 10% higher than the last value of CG-CrCl before switching to PI monotherapy. A multivariate logistic regression was constructed to identify factors associated to renal improvement after switching to bPI monotherapy.
Results: 64 patients included. The median (IQR) annual change in CG-CrCl during PI monotherapy was significantly lower than the median (IQR) annual change while exposed to TDF [−0.9 (−4.7 to +2.8) ml/min vs. −4 (−8 to −1) ml/min, $p = 0.001$]. 44 patients experienced a rapid decline during TDF exposition. After switch to PI monotherapy, 15/44 (34%, 95% CI: 21–50%) had an improved CG-CrCl and 16/44 (36%, CI 23–52%) experienced a further decline in CG-CrCl. The only variable associated to CG-CrCl improvement was a more rapid CG-CrCl decline in the last year of exposure to TDF.
Conclusion: Switching to PI monotherapy partially reversed CG-CrCl decrease associated to TDF use, especially in patients with a more rapid decline while receiving TDF.

Simplificación a monoterapia con inhibidores de la proteasa potenciados desde regímenes con tenofovir: impacto en la función renal

Palabras clave:
Reversibilidad
Toxicidad renal
Tenofovir
Monoterapia
VIH

RESUMEN

Objetivo: Evaluar el efecto de la retirada de TDF en el aclaramiento de creatinina medido mediante la fórmula de Cockcroft-Gault (CG-ClCr) en pacientes que simplifican a monoterapia con un inhibidor de la proteasa (IP) potenciado.
Métodos: Se incluyeron todos los pacientes que habían recibido un regimen con TDF durante al menos un año y que posteriormente habían sido simplificados a monoterapia. Se definió como rápida disminución del CG-CrCl durante la exposición a TDF a una disminución del CG-CrCl de al menos 5 veces mayor de lo esperado para la edad (0.4 ml/min/año por los años de exposición al TDF). En este subgrupo de pacientes, se consideró mejoría si el último valor del CG-CrCl durante la exposición a monoterapia era un 10% más alto que el último valor de CG-CrCl antes de la simplificación. Se construyó una regresión logística multivariante para identificar los factores asociados a mejoría del CG-ClCr.
Resultados: Se incluyeron 64 pacientes. La mediana del cambio anual en el CG-CrCl durante la exposición a monoterapia fue significativamente inferior a la mediana del cambio anual durante la exposición a TDF

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http://dx.doi.org/10.1016/j.eimc.2015.01.013

(p = 0.001). 44 pacientes presentaron una rápida disminución del CG-CrCl durante la exposición a TDF. Después de la simplificación, 15/44 (34%, IC 95%: 21–50%) presentaron una mejoría del CG-CrCl y 16/44 (36%, IC 23–52%) continuaron con un empeoramiento en el CG-CrCl. La única variable asociada con mejoría fue haber presentado una disminución más rápida del CG-CrCl en el último año de exposición a TDF.
Conclusión: La simplificación a monoterapia revierte parcialmente la disminución del CG-CrCl asociada al TDF, especialmente en los pacientes que presentan una disminución más rápida durante la exposición a TDF.

Introduction

Tenofovir (TDF) is a nucleotide reverse transcriptase inhibitor, excreted through glomerular filtration and active tubular secretion.[1] In a recent meta-analysis, TDF-containing regimens were associated with a statistically significant loss of renal function of modest magnitude.[2]

The European AIDS Clinical Society Guidelines[3] recommend stopping TDF if there is a progressive decline in creatinine clearance (CG-CrCl) not explained by other causes. However it is not clear if CG-CrCl recovers completely after stopping TDF. The reversibility of TDF-related renal impairment has been evaluated in three retrospective studies.[4–6] In these studies, renal function improved after TDF discontinuation but renal impairment was not fully reversible.

Boosted protease inhibitor (PI) monotherapy has demonstrated to be effective in maintaining long-term viral suppression in the majority of patients. PI monotherapy avoids the long-term toxicity associated with nucleoside/nucleotide analogs.[7] Therefore, switching to PI monotherapy might be an option in patients with a progressive TDF-associated renal decline. None of the published studies has systematically evaluated the reversibility of TDF-associated renal impairment in patients switching away from a TDF-containing regimen to PI monotherapy. The aim of our study was to evaluate the effect on CG-CrCl of switching to PI monotherapy in patients receiving a TDF-containing regimen.

Methods

We performed a retrospective cohort study of all patients attending our HIV Unit who had received a TDF-containing regimen for at least one year and had been switched to PI monotherapy. During this period all creatinine determinations were done with a modified Jaffe method. We excluded patients with less than two annual determinations of creatinine during TDF therapy or during PI monotherapy, patients without a serum creatinine measurement within 3 months prior to starting TDF and/or those whose follow-up after the switch to PI monotherapy was less than 5 months. This limit was chosen because five months was the median time to maximum improvement in renal function after TDF cessation in Wever's study.[5]

Our renal function measurement was the estimated creatinine clearance calculated by the Cockcroft–Gault equation (CG-CrCl). CG-CrCl was recorded at 6 months intervals from the last value before starting TDF to the last available value while the patient was still receiving PI monotherapy.

A rapid decrease in CG-CrCl during exposure to TDF was defined arbitrarily as a decrease in CG-CrCl at least five times higher than the one expected due to age. We calculated the expected CG-CrCl decline multiplying 0.4 ml/min/year by the years of exposure to TDF. Estimating CG-CrCl loss related to age was based on the results of an observational study in healthy Caucasian volunteers.[8] Renal function outcomes after switching to PI monotherapy in patients with a rapid decrease in the CG-CrCl during exposure to TDF was analyzed separately. We defined the categorical variable *improvement* of CG-CrCl in this subgroup of patients if the last value of CG-CrCl during exposure to PI monotherapy was 10% higher than the last value of CG-CrCl before switching to PI monotherapy. The study was approved by the Ethics Committee for Clinical Research of La Paz Hospital.

Statistical methods

Patient characteristics were described using median (IQR) for continuous variables and frequency (%) for categorical variables. A logistic regression model with a predictive approach was constructed to identify factors associated to renal *improvement* (with dichotomous outcome) after switching to PI monotherapy in the group of patients with a significant decrease in the CG-CrCl during treatment with TDF. We analyzed the following variables: age, sex, hypertension, diabetes, hepatitis C, months on TDF, months on PI in triple therapy, use of didanosine, dose of ritonavir (100 or 200 mg.) on PI monotherapy, CD4 count, CG-CrCl at starting TDF, CG-CrCl at switch to PI monotherapy and change of CG-CrCl in the last year of TDF. Variables with a p value of <0.1 in the univariate analysis were retained in the multivariate analysis. Data were analyzed using SPSS version 18.0, *p*-values <0.05 were considered significant.

Results

We included 64 patients (Table 1). Forty-six patients switched to lopinavir/ritonavir monotherapy, 17 to darunavir/ritonavir monotherapy and one to atazanavir/ritonavir monotherapy. Most patients continued on the same PI after the switch to PI monotherapy. Four patients on lopinavir/ritonavir in triple therapy switched to darunavir/ritonavir monotherapy. The median time on PI monotherapy was 30 (19.9–38.6) months.

During exposure to TDF the median annual CG-CrCl change was −4 (−8 to −1) ml/min and the incidence rate of a decrease of CG-CrCl of at least 25% was 11 (95% CI: 7–15) per 100 patients-years. After switch to PI monotherapy, the median annual CG-CrCl change was −0.9 (−4.7 to +2.8) ml/min. The annual change in CG-CrCl during PI monotherapy was significantly lower than the annual change while exposed to TDF ($p = 0.001$).

Patients with rapid CG-CrCl decline during TDF exposure

During exposure to TDF, 44 patients (68.8%) experienced a rapid decline of CG-CrCl. In this group of patients, the median CG-CrCl declined from 109 (95–121) ml/min to 81 (69–95) ml/min, for a median of exposition to TDF of 42 (31.5–72.3) months. There were no relevant differences between the characteristics before starting TDF of the subgroup of patients with rapid CG-CrCl decline and the total sample (data no shown).

In patients with a rapid CG-CrCl decline while exposed to TDF the median annual CG-CrCl change was −7 (−11 to −4) ml/min. After switch to PI monotherapy, the median annual change of CG-CrCl was significantly lower: −0.4 (−3 to +4) ml/min ($p < 0.001$).