Impatto sulla funzione renale di un regime contenente tenofovir in combinazione con inibitori delle integrasi.

Impact on renal function of a tenofovir-containing ART in combination with integrase inhibitors.

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Riassunto

In questo articolo presentiamo i dati preliminari di tenofovir disoproxil fumarato/emtricitabina (TDF/FTC) rispetto all'impatto renale di tenofovir alafenamide fumarato/emtricitabina (TAF / FTC), in una terapia antiretrovirale contenente un inibitore delle integrasi. Abbiamo retrospettivamente valutato una coorte di pazienti naïve HIV-positivi che iniziano FTC/TDF o FTC/TAF in associazione a dolutegravir (DTG) o raltegravir (RAL). La funzionalità renale, valutata mediante la formula Modification of Diet in Renal Disease (MDRD), è stata raccolta al basale, 6 mesi e 12 mesi di follow-up. Abbiamo eseguito un modello lineare a effetti misti per misure ripetute per valutare la variazione del tasso di filtrazione glomerulare stimato (eGFR) e la regressione lineare per valutare i predittori di cambiamenti nei valori MDRD. Abbiamo arruolato 112 pazienti con un'età mediana di 39 anni, 65 dei quali hanno iniziato una terapia antiretrovirale contenente DTG, mentre 47 hanno iniziato un regime contenente RAL. Valutando le variazioni MDRD, abbiamo trovato una variazione mediana di eGFR di -10 e -6 ml/min a 6 e 12 mesi, rispettivamente. Queste variazioni erano statisticamente significative (p = 0,009). Abbiamo riscontrato una diminuzione significativa di eGFR nei pazienti che hanno iniziato dolutegravir, indipendentemente dal backbone (TAF o TDF). In un'analisi multivariata, i predittori indipendenti del declino dell'eGFR sono stati identificati nel valore basale di MDRD, nell'età e all'inizio di terapia con dolutegravir.

I nostri dati preliminari non hanno mostrato un impatto importante di FTC/TDF sulla velocità di filtrazione glomerulare rispetto al profarmaco tenofovir alafenamide.

Abstract

In this paper, we present preliminary data of tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) vs tenofovir alafenamide fumarate/emtricitabine (TAF/FTC) renal impact on an integrase inhibitor-containing antiretroviral therapy (ARV). We evaluated a cohort of HIV-positive ART-naïve patients starting FTC/TDF or FTC/TAF plus either dolutegravir (DTG) or raltegravir (RAL) retrospectively. Renal function, using Modification of Diet in Renal Disease (MDRD) formula, was collected at baseline, 6 months and 12 months of follow-up. We performed a mixed-effects linear model for repeated measures to evaluate variation in estimated glomerular filtration rate (eGFR) and linear regression to evaluate the predictors of changes in MDRD values. We enrolled 112 patients with a median age of 39 years; among them, 65 patients started a DTG-based ARV, and 47 patients started a RAL-based regimen. Evaluating MDRD variations, we found a median variation of eGFR of -10 and -6 mL/min at 6 and 12 months, respectively. These variations were statistically significant (p=0.009). We found a significant decrease in eGFR in patients starting dolutegravir independently from the backbone (TAF or TDF). In a multivariate analysis, the independent predictors of eGFR decline were identified in MDRD baseline, age and starting cART with dolutegravir.

In conclusion, our preliminary data did not show a major impact of FTC/TDF on glomerular filtration rate when compared with the prodrug tenofovir alafenamide.

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Introduction

Emtricitabine (FTC) either associated with tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide fumarate (TAF) represents one of the most widely prescribed backbones of the combination antiretroviral therapy (cART) for the treatment of HIV. Despite its considerable safety profile and very low side or adverse effects, TDF is occasionally associated with increased risk of toxicities, including renal impairment (from mild to severe,

especially among people of African descent) [1]. The renal impact of tenofovir appears to be lowered when administered in its prodrug form alafenamide [2]. Aim of this paper is to present preliminary data of tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) vs tenofovir alafenamide fumarate/emtricitabine (TAF/FTC) renal impact on an integrase inhibitor (INI)containing antiretroviral therapy.

Materials and methods

A cohort of HIV-positive ART-naïve patients starting a regimen consisting of emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) or emtricitabine/tenofovir alafenamide (FTC/TAF) plus dolutegravir (DTG) or raltegravir (RAL), was retrospectively evaluated. We excluded the boosted INI elvitegravir in order to prevent an eventual role of cobicistat on the kidney function. Patients with HCV (positive for HCV antibody) or HBV infection (HBsAg positive) were excluded. We evaluated the epidemiologic and demographic data and renal function using MDRD formula for estimated glomerular filtration rate (eGFR) at baseline, 6 months and 12 months of follow-up (+/- 1 month). We performed a mixed effects linear model for repeated measures to evaluate variation in eGFR and linear regression to evaluate the predictors of changes in MDRD values.

Results

We enrolled 112 patients with a median age of 39 years (Interquartile Range [IQR] 33-46): 86 (76.8%) were males; the principal risk factor for HIV infection was sexual intercourses (77 pa-tients, 68.8%, of which 45 [40.2%] MSM and 32 [28.6%] heterosexual). HIV diagnosis was con-comitant with an AIDS event in 35 (31.3%) patients. Median CD4+ cells count and HIV-RNA at baseline were 232 (IQR 88-430) cells/µL and 5.05 (IQR 4.49-5.49) log10 copies/mL, respectively. Among the studied population, 65 (58.1%) patients started a DTG-based ARV (48 with FTC/TDF and 17 with FTC/TAF), and 47 (41.9%) patients started a RAL-based regimen (39 with FTC/TDF and 8 with FTC/TAF). Overall, median eGFR at baseline was 100 (IQR 82-118) mL/min, although the population on DTG showed a higher median filtration rate value at baseline (106.3 ml/min) when compared to the RAL counterpart (85.1 ml/min) (p=0.003). Full patients' characteristics are shown in **Table 1**.

Variables	Overall (n=112)	FTC/TDF+RAL (n=39)	FTC/TDF+DTG (n=48)	FTC/TAF+RAL (n=8)	FTC/TAF+DTG (n=17)
Age (years), Median (IQR)	39 (33-46)	41 (36-48)	39 (32-45)	37 (33-56)	36 (33-46)
Male, n (%)	86 (76.8)	27 (69.2)	38 (79.2)	7 (87.5)	14 (82.4)
Risk factor for HIV infection, n (%):					
Heterosexual	32 (28.6)	16 (41)	10 (20.8)	2 (25)	4 (23.5)
MSM	45 (40.2)	14 (35.9)	23 (47.9)	2 (25)	6 (35.3)
IDU	7 (6.3)	4 (10.3)	3 (6.3)	0	0
Others	28 (25.0)	5 (12.8)	12 (25)	4 (50)	7 (41.2)
CDC stage C, n (%)	35 (31.3)	13 (33.3)	15 (31.3)	3 (37.5)	4 (23.5)
Nadir of CD4+ (cell/µL), Median (IQR)	232 (88-430)	253 (121-350)	175 (62-473)	460 (460-460)	550 (40-680)
Zenith HIV-RNA (log copies/mL), Median (IQR)	5.05 (4.49-5.49)	5.16 (4.52-5.57)	4.91 (4.43-5.49)	5.28 (5.17-5.42)	5.25 (3.18-6.11)
Serum creatinine (mg/dL), Median (IQR)	0.82 (0.72-0.96)	0.90 (0.71-1.05)	0.78 (0.71-0.91)	0.81 (0.76-1.00)	0.80 (0.72-0.92)
eGFR (mL/min), Median (IQR)	99.7 (82.1-118.4)	85.1 (74.1-113.5)	109.1 (89.8-122.7)	91.5 (75.2-116.1)	103.3 (92.9-114.8)

Table 1. Baseline characteristics of patients included in the study, overall and by antiretroviral regimen.

Evaluating MDRD variations, we found a median variation of eGFR of -10 (IQR -22, 3) and -6 (IQR -28, 8) mL/min at 6 and 12 months, respectively. These variations were statistically significant (p=0.009). When stratified for backbone (FTC/TDF vs FTC/TAF), those on TAF had a median difference of -10.3 ml/min and + 4.0 ml/min at 6 and 12 months respectively, while their TDF counterpart showed -8.9 ml/min at 6 months and - 7.0 ml/min at 12 months.

The median variation of MDRD of patients starting raltegravir was + 1.5 at 6 months and + 4.2 at 12 months (p= 0.373). Those who started a DTG-containing cART regimen instead showed a median difference of -17.0 ml/min and -20.3 ml/min at 6 and 12 months respectively (p <0.01). (**Figure 1**).

In a multivariate analysis, the independent predictors of eGFR decline were identified in MDRD value at baseline (per 10 ml/min more, -5.8, 95% CI -8.3; -3.2, p <0.004), age (per 1 year more, -1.1 ml/min 95% CI -1.7; -0.5, p <0.001) and starting cART with dolutegravir (-20.6 ml/min, 95% CI -33.9; -7.2, p=0.004) after adjusting for sex, backbone, zenith HIV-RNA value and nadir CD4+ cell count.

Discussion

Preliminary data from our study show no statistically significant differences between the TAF and TDF group in eGFR when associated with unboosted INIs. Our data are in accordance with a previous metaanalysis from Hill et. al [4], reporting similar rate of renal adverse events between TAF-based and TDF-based regimens with unboosted INIs. Our experience, meanwhile, contrasts with TAF registration trials, where eGFR improved in association with the use of TAF [2]; it is to be noted that the study did not exclude patients with cobicistat, a possible explanation for the difference in the results.

Regarding the apparent worsening of renal function in patients on DTG, it is likely that the decrease in the glomerular filtration rate, found in our population at 48 weeks of follow-up, could be attributed to an intrinsic characteristic of dolutegravir. In fact, the drug inhibits the organic cation transporter 2 (OCT2), reducing the excretion at the tubular level of creatinine [5]. On the contrary, raltegravir has not such effect and long term observational studies have shown an overall good tolerability profile and a low rate of renal adverse events [6].

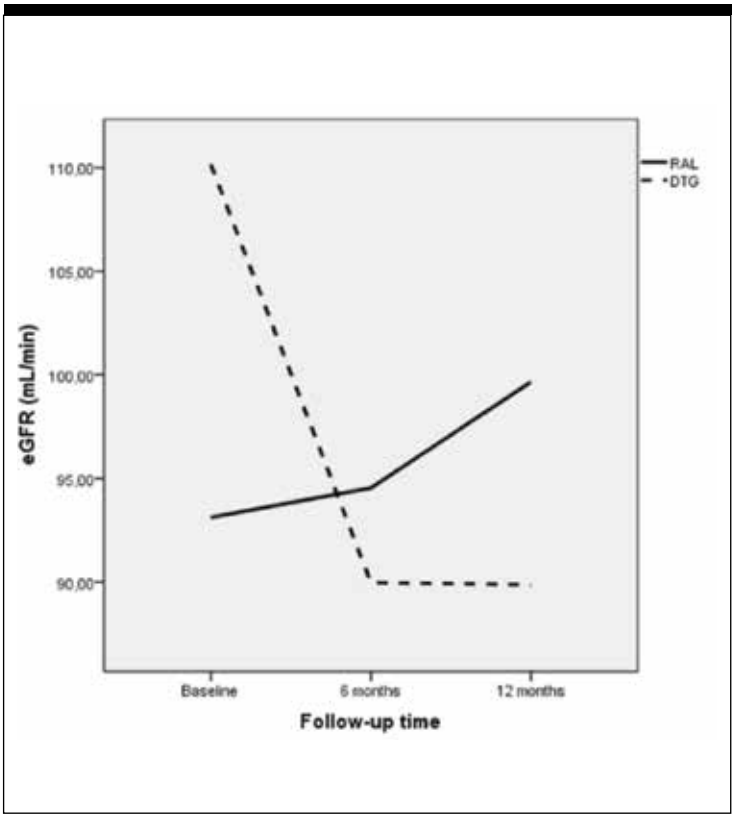

Figure 1. Variation in eGFR stratified for anchor drug.

Limitations of this study are the short follow up that we were able to achieve and the low number of patients involved. Further data are necessary to validate such statements.

In conclusion, our preliminary data did not show a major impact of TDF/FTC on glomerular filtration rate, when compared with the prodrug tenofovir alafenamide.

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