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CYP2B6 516 G>T polymorphism and side effects of the central nervous system in HIV-positive individuals under Efavirenz treatment: Study of a sample from southern Brazil

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ABSTRACT

This study aimed to identify the 516 G>T polymorphism of the *CYP2B6* gene and evaluate its influence on central nervous system (CNS) side effect development in HIV-positive individuals undergoing Efavirenz (EFV) treatment in a population from southern Brazil. Additionally, we performed a survey on the clinical and epidemiological characteristics of our sample. In addition to medical records evaluation, whole blood of 89 individuals was analyzed for viral load, T lymphocyte count (CD4+ and CD8+), and the polymorphism. Considering the side effects of the CNS reported by individuals but without considering the genetic variables, no statistically significant association was noted between the adverse effects and the antiretroviral treatment (including or not EFV). In addition, no statistically significant difference was noted for the influence of genotype on the viral load or the number of T lymphocytes (CD4+ and CD8+) among individuals undergoing EFV treatment. This is the first study that investigated the impact of the 516 G>T polymorphism of the *CYP2B6* gene among HIV-positive individuals from southern Brazil. Its clinical significance indicates the need for prospective studies in this population.

Key words: HIV, Efavirenz, antiretroviral therapy, *CYP2B6*.

INTRODUCTION

Since its introduction in the 90s, highly active antiretroviral therapy (HAART) has provided enormous benefits for the quality and life expectancy of HIV-positive patients. Despite its benefits, HAART triggers numerous side effects associated with the chronic use of antiretroviral drugs, and particularly effects on the central nervous system (CNS). In Brazil, Efavirenz (EFV) is one of the non-nucleoside reverse transcriptase

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inhibitors (NNRTI) recommended as part of the first antiretroviral regimen of choice in HIV treatment (Brasil 2013). The side effects related to the use of EFV include abnormal dreams, anxiety, depression, dizziness, impaired concentration, lightheadedness, and reduction in sleep quality (Gaida et al. 2016). Different factors modulate the development of side effects, including the genetic variability of the patient.

Several drug-metabolizing genes have been described as key factors in drug absorption, treatment response, and side effects during HAART. Taking into consideration the development of new antiretroviral drugs and the diversity of responses related to HAART, individual genetic background has an important impact on the different responses to pharmacological treatment (Michaud et al. 2012). The knowledge of individual genetic variations on the response to treatment with antiretroviral drugs is essential for individualizing therapy (Pirmohamed and Back 2001). Furthermore, the impact of single nucleotide polymorphisms on EFV metabolism was observed by different authors (Sánchez Martín et al. 2013, Cusato et al. 2016).

EFV is principally metabolized by the cytochrome P450 2B6 (CYP2B6), resulting in 8-hydroxy-efavirenz, its main metabolite, which is associated with neurotoxicity (Apostolova et al. 2015). A transversion of G to T allele in exon 4 (516 G>T, rs3745274) of the *CYP2B6* gene contributes to reduced clearance of EFV and its increased concentration in plasma, causing side effects in the CNS and indicating decreased enzyme function *in vivo* (Kwara et al. 2008, Gounden et al. 2010, Rakhmanina and van den Anker 2010). In addition, an association is noted between the slow and intermediate metabolizer phenotypes and virological suppression (Frasco et al. 2012).

In this context, this study aimed to investigate the 516 G>T polymorphism of the *CYP2B6* gene and evaluate the impact of this genetic variation on the side effects of the CNS in HIV-positive patients under EFV treatment or other antiretroviral drugs in a southern Brazilian population. In addition, we performed a survey on the clinical and epidemiological characteristics of the studied individuals.

MATERIALS AND METHODS

INDIVIDUALS, CLINICAL DATA, AND ETHICAL CONSIDERATIONS

Eighty-nine HIV-positive patients who initiated antiretroviral therapy (with or without EFV [600 mg once a day]) from 2013 to 2014 at the Municipal Center for Assistance to Serology (Centro Municipal de Atendimento à Sorologia - CEMAS) in the city of Santa Cruz do Sul (Rio Grande do Sul - RS, Brazil) were selected for the present study. Whole blood samples were collected for genetic analyses. Epidemiological and clinical data were obtained by consulting medical records.

Clinical data investigated in this study (viral load (VL), T CD4+ lymphocyte count, and T CD8+ lymphocyte count) were evaluated at three time points: (I) baseline (last measurement before treatment); (II) three months after starting treatment; and (III) six months after starting treatment. T CD4+ and T CD8+ lymphocyte counts were obtained by flow cytometry using the FACSCount system (Becton Dickinson, San Jose, CA, USA). HIV-1 viral load was assessed using the NASBA technique (Biomerieux, Marcy l'Etoile, France). All subjects enrolled in the study signed a consent form. This study was approved by the Research Ethics Committee of the University of Santa Cruz do Sul (UNISC, RS, Brazil) under protocol #639490.

CYP2B6 GENE: 516 G>T POLYMORPHISM GENOTYPING

DNA was obtained with the QIAamp DNA Blood Mini Kit (QIAGEN) using 500 μL of whole blood collected with EDTA (Ethylenediamine tetraacetic

acid). Genotyping of the 516 G>T polymorphism was performed by real-time PCR (RT-PCR) using EvaGreen (Solis BioDyne) according to the manufacturer's instructions. Briefly, 4 µL of 5X HOT FIREPol EvaGreen qPCR Mix Plus (Solis BioDyne), 0.33 µL of each forward and reverse primers (10 pmol/µL), 2.5 µL of DNA (10 ng/µL), and 12.84 µL of MilliQ water were used to obtain a final volume of 20 µL.

The primers used for amplification of the 223-bp fragment of the *CYP2B6* gene were as follows: wild w-5'GACCCCACCTTCCTCTTCTAG3', variable 5'GACCCCACCTTCCTCTTCTAT3', and common c-5'GGTCATCCTTTTCTCGTGTG3', as described by Haas et al. (2004). The PCR reactions were performed in a Step One Plus (Applied Biosystems). The following temperature and cycling conditions were used: initial denaturation of 95°C for 5 minutes followed by 40 denaturing cycles at 95°C for 15 seconds, annealing at 60°C for 20 seconds, and elongation at 72°C for 20 seconds. In all reactions, negative controls were used, and the reactions were performed in duplicate. For an internal control, each *CYP2B6* 516 G>T genotype sample was confirmed by sequencing using ABI 3500 Genetic Analyzer (Applied Biosystems).

STATISTICAL ANALYSIS

Data analysis was performed using the Statistical Package for Social Sciences software (SPSS 17.0). For each analysis, individuals who had missing data for certain characteristics were excluded from the test. Categorical and quantitative variables were analyzed by Chi-square and Mann-Whitney U tests, respectively. Asymmetric continuous distributions are described by the median and the 25th and 75th percentiles. Potential confounders evaluated included age, ethnicity, drug, and alcohol status. Covariates were entered in the logistic regression models if they were associated with the study factor and with the outcome at $p<0.20$. Logistic regression was performed to evaluate the strength of association between genetic markers and outcomes using odds ratio (OR) and respective 95% confidence interval (CI). Hardy-Weinberg equilibrium was calculated for the patient and control groups. For all instances, p-values <0.05 were considered to be significant.

RESULTS

Epidemiological and clinical characteristics of the subjects are presented in Table I. We observed a significant difference between the proportion of European-derived and African-derived individuals evaluated in our study ($p<0.001$). This result can be explained by the fact that the Brazilian population is genetically admixed. Additionally, the studied population belongs to a region historically colonized mainly by European-derived individuals, explaining the higher rate of individuals with this phenotypic characteristic reported in this study. Evaluating the clinical characteristics of the individuals, we highlight that the use of EFV has no effect on T CD4+ lymphocyte recovery, and the viral load was reduced compared with non-users of EFV (Table I).

Among the subjects who used EFV (n=50), the frequencies of reported side effects were as follows: headache (n=15, 30%), dizziness (n=10, 20%), insomnia (n=9, 18%), somnolence (n=4, 8%), and difficulty concentrating (n=3, 6%). The absence of side effects was reported by 18% (n=9) of individuals from this first group. The frequencies of side effects among subjects who did not use EFV (n=37) were as follows: headache (n=11, 29.7%), dizziness (n=10, 27.1%), difficulty concentrating (n=2, 5.4%), insomnia (n=2, 5.4%), and somnolence (n=1, 2.7%). The absence of side effects was reported by 29.7% (n=11) of individuals from this second group. Considering all side effects of the CNS and without considering the genetic variables, no significant difference in the presence or absence of these effects was noted regardless of the use of EFV ($p=0.199$).

TABLE I
Epidemiological and clinical characteristics of the individuals evaluated in the study.

Characteristics		EFV used	EFV not used	*p*-value
Sex n (%)	Female	28 (54.9)	25 (65.8)	0.301[a]
	Male	23 (45.1)	13 (3412)	
Age (median, IQR)		36 (32-44)	34.5 (28-45)	0.219[b]
Drug use (yes) n (%)		8 (15.7)	4 (10.5)	0.546[c]
Alcohol consumption (yes) n (%)		5 (9.8)	1 (2.6)	0.233[c]
Ethnicity n (%)	European-derived	46 (90.2)	21 (55.3)	<0.001[a]
	African-derived	5 (9.8)	17 (44.7)	
T CD4+ Lymphocytes [mm^3/mL] Baseline (median, IQR)		350 (215-506)	347 (202-499)	0.749[b]
T CD4+ Lymphocytes [mm^3/mL] 3 months after starting treatment (median, IQR)		351 (172-505)	319 (248-666)	0.301[b]
T CD4+ Lymphocytes [mm^3/mL] 6 months after starting treatment (median, IQR)		445 (239-610)	388(216-497)	0.384[b]
T CD8+ Lymphocytes [mm^3/mL] Baseline (median, IQR)		945 (659-1379)	876 (636-1167)	0.468[b]
T CD8+ Lymphocytes [mm^3/mL] 3 months after starting treatment (median, IQR)		755 (501-1168)	913 (638-1219)	0.152[b]
T CD8+ Lymphocytes [mm^3/mL] 6 months after starting treatment (median, IQR)		839 (587-1308)	895 (674-1190)	0.876[b]
Viral Load $\log_{10}$ (copies/mL) Baseline (median, IQR)		3.45 (0.5-4.36)	3.42 (1.65-4.48)	0.844[b]
Viral Load $\log_{10}$ (copies/mL) 3 months after starting (median, IQR)		0.5 (0.5-3.77)	2.43 (0.5-3.51)	0.305[b]
Viral Load $\log_{10}$ (copies/mL) 6 months after starting treatment (median, IQR)		0.5 (0.5-1.74)	0.5 (0.5-3.27)	0.415[b]

[a]Pearson Chi-square test; [b]Mann-Whitney test; [c]Fisher's Exact test; EFV = Efavirenz; IQR = Interquartile range.

Table II presents the results of the main comparisons between genetic and non-genetic variables. The influence of the genotype on viral load, T CD4+ lymphocyte count, and T CD8+ lymphocyte count (baseline, three and six months after treatment) among individuals who was enrolled in EFV treatment was also evaluated. However, none of these analyses revealed a statistically significant result, even when adjusted for covariates (p>0.05). In addition, we also grouped T allele carriers (GT+TT) and compared them with non-carriers of the allele. However, no significant difference was noted regarding the variables tested (p>0.05).

DISCUSSION

The choice of antiretroviral drugs generally depends on (I) convenience, (II) safety, and (III) potency (Jiménez-Nácher et al. 2008). Physician's preference and patient characteristics also influence this choice (Elzi et al. 2012). Furthermore, the population characteristics may be taken into consideration for the prescription of EFV. Non-Caucasian patients may be more prone to EFV-induced toxicity (Burger et al. 2005). The impact of the non-adherence to EFV-containing regimens on virologic failure is stronger in black than in white individuals (Schackman et al. 2007). Moreover, the results from a cohort of HIV-infected South Africans indicated that EFV is associated with low bone mineral density in this population (Dave et al. 2015). These cited results could support the use of EFV in Caucasians, but not in non-Caucasians. In addition, regional protocols developed to guide HAART direct the prescription of EFV and other antiretrovirals for different populations. Among

TABLE II
Influence of *CYP2B6* 516 G>T genotypes on the presence or absence of CNS side effects in EFV patients.

Analysis performed	Genotype and T allele (In all subjects studied, n=87)	Clinical parameters		Statistical data		
		Presence of CNS side effects, n (%)	Absence of CNS side effects, n (%)	OR*	CI (95%)	*p*-value
Association between CNS side effects and the polymorphism	GG	11 (16.4)	1 (5.0)	1	-	-
	GT	45 (67.2)	15 (75.0)	0.27	(0.03 - 2.29)	0.232
	TT	11 (16.4)	4 (20.0)	0.25	(0.024 - 2.60)	0.247
	T allele (GT + TT)	56 (83.6)	19 (85.0)	0.27	(0.032 - 2.21)	0.222
Frequency of genotypes and T alleles between individuals using or not using EFV	**Genotype and T allele** (In all subjects studied, n=89)	**Use of EFV, n (%)**	**No use of EFV, n (%)**	**OR***	**CI (95%)**	***p*-value**
	GG	6 (11.8)	7 (18.4)	1	-	-
	GT	38 (74.5)	23 (60.5)	1.93	(0.58-6.44)	0.287
	TT	7 (13.7)	8 (21.1)	1.02	(0.23-4.53)	0.978
	T allele (GT + TT)	45 (88.2)	31 (81.6)	1.70	(0.52 - 5.53)	0.383
Association between the use of EFV, side effects and genotype	**Genotype and T allele** (In individuals using EFV, n=50)	**Presence of CNS side effects, n (%)**	**Absence of CNS side effects, n (%)**	***p*-value***		
	GG	6 (14.6)	-	-		
	GT	30 (73.2)	7 (77.8)	0.412		
	TT	5 (12.2)	2 (22.2)	-		
	T allele (GT + TT)	35 (85.4)	9 (100)	0.576		

CI = confidence interval; CNS = central nervous system; EFV = Efavirenz; OR = Crude odds ratio, *Fisher's Exact Test.

various factors, these protocols take into account the best-performing antiretrovirals for the large portion of the population. Similar to Brazil, the use of EFV is part of the regimens for initial therapy against HIV in European populations (Brasil 2013, EACS 2014).

The introduction of antiretroviral therapy associated with the prevention and control of HIV infection has resulted in important changes in the AIDS epidemic pattern (UNAIDS 2015). In Brazil, the rate of AIDS detection among men remains higher compared with women (Brasil 2015). In the present study, our sample was principally composed of women. The collection site was a public health service. In general, women have better health monitoring and knowledge about their health status than men. These factors may help explain the higher number of women involved in our study. The average age of the studied subjects is consistent with the current Brazilian HIV epidemic, where the infection rate is higher among individuals aged 25 to 39 years. Although the number of AIDS cases among drug users is decreasing in Brazil (Brasil 2015), drug users accounted for approximately 13% of our sample.

The adherence rate for antiretroviral therapy in the first six months of treatment is generally low and has been directly related to individual factors and patient socio-cultural context. Moreover, the increased time between diagnosis of the HIV infection and AIDS manifestation in addition to the side effects caused by the treatment are important indicators of poor treatment adherence (Silva et al. 2015). These are some of the factors that may explain the minimal difference in the average number of T CD4+ lymphocytes and viral load

since the start of the treatment (baseline) and after three and six months of treatment in our study. However, we must note that information about patient adherence to antiretroviral therapy was not available in this study. No significant difference was noted among viral load, number of T CD4+ lymphocytes, and number of T CD8+ lymphocytes among individuals who used HAART with or without EFV. Our data indicated no difference in the clinical response associated with a specific drug among the subjects studied.

Interestingly, a non-statistically significant association was observed between allele and genotype frequencies compared with CNS side effects related to HAART. In addition, no differences were observed in the distribution of genotype and T allele carrier frequencies of individuals who used EFV compared with those who did not. Furthermore, no association among side effects, use of EFV and specific genetic characteristics were observed. We note that the sample size of this study was very small, and this limitation may have influenced these results.

In contrast to our results, it is reported that the use of EFV is associated with a number of side effects, mainly in the CNS. The use of EFV may result in increased neurocognitive effects compared with other antiretroviral drugs (Ma et al. 2016). EFV has a long half-life and is primarily metabolized by cytochrome P450 (CYP) 2B6. Furthermore, polymorphisms in the *CYP2B6* gene are associated with an increased risk of side effects related to EFV treatment (Gounden et al. 2010, Sánchez Martín et al. 2013). Moreover, it was reported that the difference in the expression and function of the *CYP2B6* gene cause great variability in the response to EFV. The *CYP2B6* 516 G>T polymorphism is one of the most important factors responsible for increased plasma concentrations of the drug and the neuropsychiatric effects associated with EFV (Kwara et al. 2008, Gounden et al. 2010).

The *CYP2B6* 516 G>T polymorphism is the variant most associated with side effects of the CNS. This allele occurs at frequencies of 15% to greater than 60% in different populations (Zanger and Klein 2013). The frequency with which the mutant allele appeared in the individuals studied in this work is similar to that reported in other studies evaluating individuals of various ethnic backgrounds. In contrast to our data, an association between the *CYP2B6* TT genotype and increased plasma exposure to EFV was noted. Additionally, the *CYP2B6* G516T genotype was associated with side effects of the CNS (in week 1 of a twenty-four-week cohort) (Haas et al. 2004). These results support the significant impact of *CYP2B6* genotypes on the clearance of the EFV.

As previously mentioned, in addition to the lack of differences among viral load, number of T CD4+ lymphocytes, and number of T CD8+ lymphocytes among individuals using or not using EFV, we also did not observe an influence of the 516 G>T genotypes on these three variables among individuals undergoing EFV treatment. Regarding the clinical response, this result differs from data presented by Frasco et al. (2012), who observed an association between the slow and intermediate metabolizer phenotypes with virological suppression. This finding underscores the concept that individuals with a slow metabolizer phenotype are more likely to achieve undetectable viral loads. EFV administration is currently recommended at a fixed dose of 600 mg once daily. However, an improvement in side effects is noted when the administration of EFV is adjusted according to the plasma concentration of the drug and the individual's genotype. This information reinforces the importance of genotyping the *CYP2B6* gene in the development of a personalized therapy (Martiny and Miteva 2013).

This study presents new data regarding this polymorphism among individuals from southern Brazil. Moreover, it is important to highlight

the originality of this work given that it presents new data on the pharmacogenetics of EFV in the studied population. Despite the novelty, our study has a small sample size. This limitation may have contributed to the lack of associations between the *CYP2B6* 516 G>T polymorphism and CNS side effects. However, the clinical significance of this polymorphism indicates the need for prospective studies in the population we evaluated. In addition, our results justify a new study involving a larger number of individuals and the investigation of other polymorphisms that influence the plasma concentration of EFV, aiming to support our results with more robustness and enable greater clinical and epidemiological exploitation of the findings presented here.

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