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Improved Metabolic Profile After Switch to Darunavir/Ritonavir in HIV Positive Patients Previously on Protease Inhibitor Therapy

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Metabolic abnormalities associated with cumulative exposure to antiretroviral therapy have been linked to an increased risk of myocardial infarction in HIV positive individuals. The aim of this study was to evaluate whether the switch from lopinavir/ritonavir (LPV/r) or fosamprenavir/ritonavir (FPV/r) to darunavir/ritonavir (DRV/r) is able to improve the lipid profile. A total of 13 Caucasian subjects (7 from LPV/r and 6 from FPV/r) were enrolled in the study and received DRV/r at the dose of 800/100 mg, without change in their NRTI backbone. Viro-immunological parameters, triglycerides (TGs), total cholesterol (TCh), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, fasting glucose, HOMA-IR, indexes of hepatic and renal functionality, microalbuminuria and cystatin C were measured at baseline (T0), 3 months (T3), 6 months (T6), and 12 months (T12). The switch to DRV/r reduced levels of TCh, LDL, and TGs at T3. Similar improvements were confirmed further at T6 and at T12. A 14% increase in CD4+ count cells ($P < 0.05$) was observed. Serum cystatin C values showed a statistically significant decrease. After 12 months of switching to DRV/r from LPV/r or FPV/r, patients infected with HIV with TGs above 200 mg/dl, showed a 49% decrease in TGs, along with a 16% reduction of LDL and 19% reduction of TCh. Switching to DRV/r also improved immunological parameters, such as CD4+ cells count and cystatin C plasmatic levels, which may translate into a reduction of the cardiovascular risk. In conclusion, a switch to DRV/r should be considered in those HIV positive patients undergoing antiretroviral therapy, who also present abnormal lipid profiles. ***J. Med. Virol. 85:755–759, 2013.***

KEY WORDS: cholesterol; triglycerides; dyslipidemia; lopinavir; fosamprenavir

INTRODUCTION

Although life expectancy increased dramatically in HIV positive patients, other health conditions, such as hypertension, diabetes, and dyslipidemia, contribute to worsen the quality of life and increase the cardiovascular risk [Falasca et al., 2006, 2007; Audelin et al., 2008; Vecchiet et al., 2011]. Several medications are known induce adverse metabolic effects, such as dyslipidemia. The family of protease inhibitors (PIs) is known to be associated with dyslipidemia, and particularly hypertriglyceridemia, in 28–80% of patients. The prevalence of dyslipidemia is significantly higher in patients treated with antiretroviral regimens containing ritonavir than other regimens not containing ritonavir [Calza et al., 2004]. In addition, the PIs are not equally likely to impair the lipid profile. Regimens with lopinavir/ritonavir (LPV/r) and

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fosamprenavir/ritonavir (FPV/r), indeed, induce greater increment in the lipid parameters than saquinavir/ritonavir or atazanavir/ritonavir or darunavir/ritonavir (DRV/r) [Hill et al., 2009], with no differences between LPV/r and FPV/r on their impact on the lipid profile [Eron et al., 2006].

Several studies of switching regimens have previously been conducted to the scope of simplifying therapies and improving the lipid profiles. However, limited evidences are available on the switch to DRV/r.

This study aimed at comparing the effect of the switch from LPV/r, or FPV/r, to DRV/r on the lipid profile in virologically suppressed patients infected with HIV.

MATERIALS AND METHODS

This was a 12-month prospective, open label, single center study involving HIV-1 infected Caucasian male patients older than 18, who switched from LPV/r or FPV/r to DRV/r. The study enrolled outpatients attending the Clinic of Infectious Diseases at the SS Annunziata Hospital, "G. d'Annunzio" University of Chieti-Pescara, Italy, from January to April 2010.

Virologically suppressed HIV-1 infected patients (defined as HIV-RNA never above 400 cp/ml in the 12 months preceding the study enrolment) who were stable on LPV/r or FPV/r regimens for more than 12 months, and who had at least two consecutive triglycerides (TGs) serum levels above 200 mg/dl, unresponsive to dietary restrictions, were considered eligible.

Patients were enrolled if they were receiving three drugs (1 PI + 2 NRTI), with abacavir/lamivudine (ABC/3TC) or tenofovir/emcitrabine (TDF/FTC) as backbone.

Exclusion criteria were: current alcohol or drug abuse; use of megestrol acetate, ketoconazole, steroids, growth hormone, medroxyprogesterone acetate, testosterone, or any anabolic agent within 6 months from study enrolment; any acute infection in the 6 months preceding the study; acute hepatitis at the beginning of the study or advanced liver disease; kidney disease or serum creatinine level higher than twice the normal upper limit in the 6 months prior to the study. Patients were also excluded if they had TGs $\geq$1,000 mg/dl or if they used lipid-lowering drugs before the beginning of the study.

An elective switch from LPV/r (400/100 mg twice a day) or FPV/r (700/100 mg twice a day) to DRV/r (800/100 mg once a day) was proposed for reasons related to therapy simplification and lipid alterations.

Patients were evaluated at baseline (T0) at 3 months (T3), 6 months (T6), and 12 months (T12) of follow-up. At each visit patients underwent a routine physical examination and the following testing: HIV-RNA level and CD4+ cell count; kidney and liver function; glucose levels; insulin resistance determined by the homeostasis model assessment index (HOMA-IR); total cholesterol (TCh), high-density lipoprotein cholesterol (HDL), low-density lipoprotein (LDL), TGs levels; microalbuminuria; serum cystatin C. Routine laboratory tests were performed at the Division of Clinical Pathology in the same hospital. The study was approved by our local ethical committee and conducted in accordance with the Declaration of Helsinki. All subjects gave their written informed consent to the study participation.

STATISTICAL ANALYSIS

Sample Size and Statistical Analysis

This study was designed to detect that DRV therapy reduced TGs values. Assuming a difference of at least 90 mg/dl in the TGs values, using a *t*-test for paired data at a level of 0.05 with 80% power and the standard deviation of differences of 100 mg/dl, at least 12 patients were required.

The quantitative variables were summarized as mean $\pm$ standard deviation (SD) in the tables and as a mean $\pm$ standard error in the figures. The qualitative variables were summarized as frequency and percentage.

Four different one-way analyses of variance (ANOVA) for repeated measures were used to evaluate the variation of TCh, TGs, LDL, and Cystatin C during the follow-up. In all models the contrast analysis, a priori specified, was conducted to evaluate the significance of difference between different follow-up control value. The same analysis was conducted on other parameters such as CD4+ cells count and CD8 cell count.

All statistical tests were evaluated at an alpha level of 0.05. Statistical analysis was performed using SPSS® Advanced Statistical 11.0 software (SPSS, Inc., Chicago, IL).

RESULTS

A total of 13 Caucasian subjects (7 from LPV/r and 6 from FPV/r) were enrolled in the study and received DRV/r at the dose of 800/100 mg. The NRTI backbone was TDF/FTC in eight and ABC/3TC in five subjects. Patients were followed longitudinally for 12 months. All patients completed the follow-up period. The main characteristics of patients at baseline are summarized in Table I. None of the patients showed substantial changes of the liver and kidney function indices throughout the study.

Significant reduction of the levels of TCh ($P = 0.050$), LDL ($P = 0.005$) and TGs ($P < 0.001$) were observed during the study. The contrast analysis showed a statistically significant reduction at T3 of TCh (200.1 ± 31.9 mg/dl vs. 244.7 ± 51.3 mg/dl, $P < 0.001$), LDL (114.1 ± 30.7 mg/dl vs. 139.3 ± 43.4 mg/dl, $P < 0.01$), TGs (202.4 ± 60.7 mg/dl vs. 383.7 ± 70.2 mg/dl, $P < 0.001$). Such reductions were confirmed at T6 and at T12 (TCh at T12 was 198.2 ± 40.9 mg/dl, $P < 0.001$; LDL at T12 was

TABLE I. Mean and Standard Deviation of Principal Characteristics of Patients

Variable	
Age (years)	43.3 ± 7.9
Sex (M/F), n	11/2
Total cholesterol (mg/dl)	244.7 ± 51.3
HDL cholesterol (mg/dl)	41.9 ± 12.0
LDL cholesterol (mg/dl)	139.3 ± 43.4
Triglycerides (mg/dl)	383.7 ± 213.3
Glucose (mg/dl)	96.3 ± 22.7
Insulin (μU/ml)	16.5 ± 13.4
HOMA-IR	2.2 ± 1.6
Microalbuminuria (mg/L)	6.4 ± 6.7
Cystatin-C (mg/L)	0.8 ± 0.2
CD4 (cells/μl)	558.6 ± 357.3
CD8 (cells/μl)	933.1 ± 428.3
CD4/CD8 ratio	0.7 ± 0.5

117.4 ± 38.9 mg/dl, $P < 0.05$; and TGs at T12 were 187.1 ± 70.8 mg/dl, $P < 0.001$). Additionally, no changes in the HDL cholesterol level were observed, while the ratios of TCh/HDL and HDL/LDL improved (TCh/HDL at T0 6.2 ± 2.0 vs. T12 4.9 ± 1.5, $P < 0.01$ HDL/LDL at T0 0.36 ± 0.25 vs. T12 0.42 ± 0.25, $P < 0.05$). Interestingly all the patients showed improvement of the lipid parameters. The improvement of lipid parameters is depicted in Figure 1.

An increase of the CD4 cell count (558.0 ± 357.3 cell/mmc at T0 vs. 639.0 ± 413.7 cell/mmc, $P < 0.05$) was observed, with an increase rate of 15% at 12 months. Plasma HIV-RNA ranging between 20 and 400 cp/ml was observed in 23% of patients at baseline (2 from FPV/r and 1 from LPV/r). At the end of study 12 patients had HIV-RNA <20 cp/ml and one patient showed HIV-RNA ranging between 20 and 100 cp/ml.

The ANOVA showed a significant decrease of serum cystatin C values during the follow-up period ($P < 0.001$). The contrast analysis showed a significant decrease at T3 compared to T0 values (0.77 ± 0.12 mg/dl vs. 0.84 ± 0.16 mg/dl, $P < 0.01$), confirmed at T12 (0.73 ± 0.14 mg/dl, $P < 0.001$). This reduction was independent from the lipid parameters changes.

Other not significant changes observed included a decrease of HOMA-IR (22% T0 vs. T12) and microalbuminuria (15% T0 vs. T12).

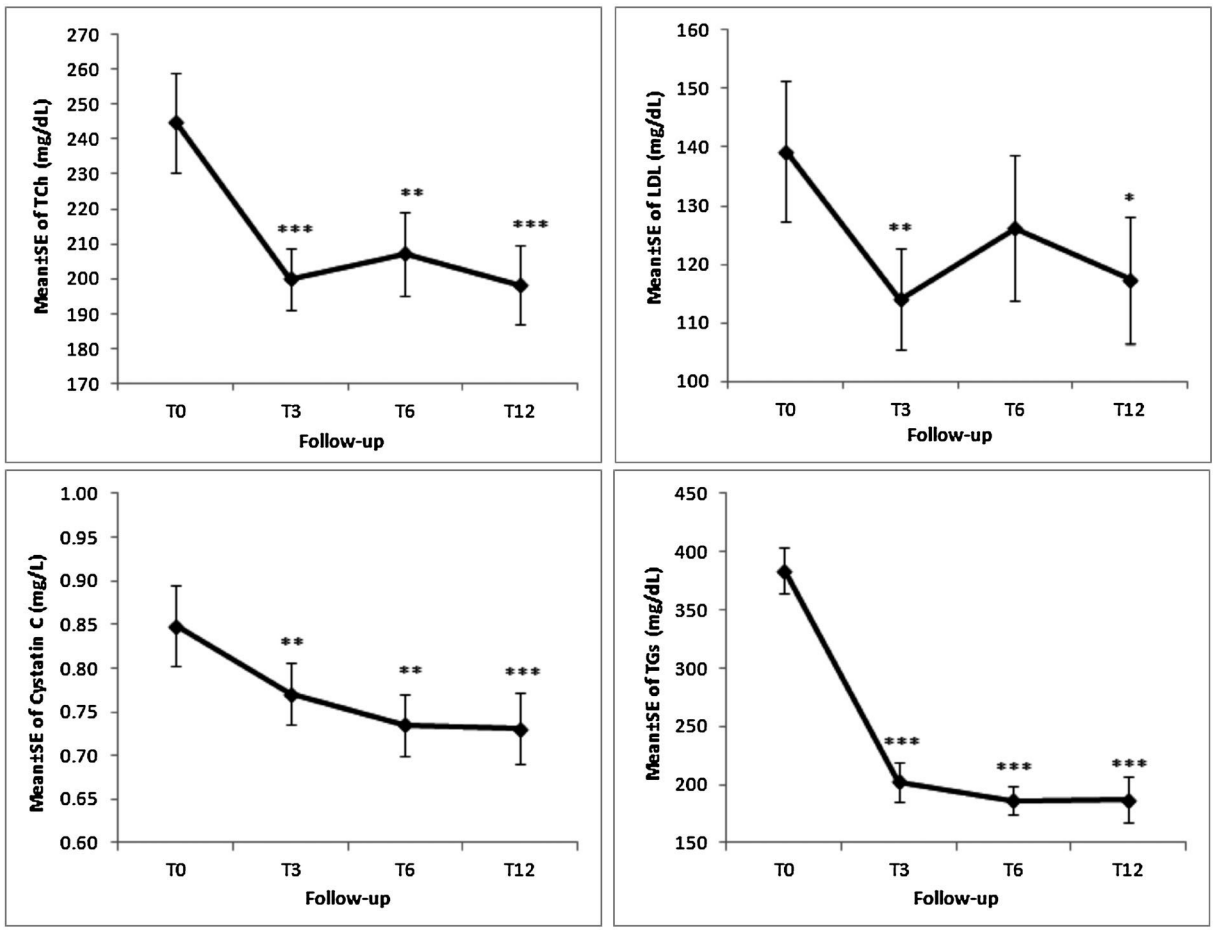

Fig. 1. Lipid profile of patients: total cholesterol (TCh), LDL cholesterol (LDL), cystatin C, and triglycerides (TGs), and at baseline (T0), 3 months (T3), 6 months (T6), and 12 months of follow-up. $^{***}P < 0.001$, $^{**}P < 0.01$, and $^{*}P < 0.05$ contrast analysis versus baseline follow-up control.

There were no adverse events or drop-outs during the study period and all study visits occurred at the predefined time points. All patients reported being satisfied switching to a once daily drug regimen.

DISCUSSION

The main finding of this study is that 12 months after the switch from LPV/r or FPV/r to DRV/r patients infected with HIV with TGs above 200 mg/dl showed reduction of TGs; secondarily, a significant reduction of LDL and TCh levels was also observed. Furthermore, switching to DRV/r improved immunological parameters, such as CD4+ cell count, and improved cystatin C plasmatic levels, which may translate into a reduction of the cardiovascular risk.

Various simplification strategies have been proposed to improve the quality of life and the drug-related toxicity, particularly the one affecting the metabolic parameters [Martinez et al., 2003; Rubio et al., 2010]. Switching the PIs to DRV/r in virologically controlled patients, considering also the higher efficacy of DRV/r, reduces the likelihood of virological rebound and treatment discontinuation while sparing patients from the exposure to a new drug class [De Meyer et al., 2008]. In this study the switch to 800/100 mg DRV/r once a day was welcomed by the patients, who reported to prefer the single dose once a day administration.

These findings on the efficacy, safety, and beneficial effect on the lipid profile of DRV/r are consistent with other clinical trials [Ortiz et al., 2008]. Nonetheless, limited data are available on the switch to DRV/r from a stable PI based regimen. The current study showed that, even when administered as switch therapy, DRV/r keeps its efficacy and significantly reduced TGs, LDL, and TCh serum levels. Improvements of lipid plasmatic levels are sustained over time. At 12 months, the values of TGs, LDL, and TCh decreased of 49%, 16%, and 19%, respectively. These effects may be explained by the reduced booster dose of ritonavir (200–100 mg) and by a smaller impact of DRV on the lipid parameters as compared to regimens containing LPV or FPV, as previously demonstrated [Hill et al., 2009].

The switch also affected glucose metabolism. Although fasting glucose levels were not significantly altered throughout the study, a non-statistically significant 22% decrease of insulin resistance levels, was observed at T12.

The backbone used did not seem to influence the response.

Several trials have shown the non-inferiority of DRV/r versus LPV/r in improving immunological parameters [Clotet et al., 2007; Ortiz et al., 2008]. Confirming the data from the POWER study, a significant improvement in the CD4+ cell count was also observed (increase rate of 15%, +81 cells/mmc, at T12).

A further interesting finding of this study is the significant reduction of cystatin C serum levels at T12, ranging between 15% at 12 months. Cystatin C is a novel marker of inflammation, atherosclerotic disease and cardiovascular risk, as well as renal complications in the general population [Arpegard et al., 2008]. Data on cystatin C in patients infected with HIV are limited [Falasca et al., 2010; Neuhaus et al., 2010]. As cystatin C is likely to be an inflammatory marker, this reduction might be related to a possible reduced inflammatory status and decreased cardiovascular risk determined by the switch. Cystatin C reduction did not correlate with the lipid parameter improvement.

Finally, a noticeable trend of decrease of microalbuminuria (15% at T12) was found in patients without renal impairment or decreased glomerular filtrate. Although not significant, this finding is of interest as microalbuminuria has been found to be an independent risk factor for cardiovascular disease and mortality in persons infected with HIV [Baekken et al., 2008]. However the high standard deviation and the small sample size do not allow to understand whether this was a resulting from the switch.

Important limitations of this study need to be addressed. First, the sample size is small and the study is uncontrolled. Second, the Caucasian race of patients limits the generalization of the results to other ethnic groups. These issues warrant further studies.

CONCLUSION

In conclusion, this is the first study designed specifically to investigate the effects on lipid parameters of the active switch to DRV/r. The main findings are that switching to DRV/r from LPV/r or FPV/r was well tolerated and effective in improving TGs, TCh, and LDL levels in patients infected with HIV. Switching to DRV/r improved the CD4 cell count and viral control, confirming the potency of DRV/r, leading to decreased cystatin C serum levels, which is an independent marker of atherosclerotic disease or cardiovascular risk.

This study showed that switching to DRV/r represents an interesting strategy for improving the metabolic profile and CD4+ cell count in patients on LPV/r or FPV/r with metabolic disturbances, maintaining patients on a PI based regimen and thus sparing them from the exposure to a new class of medications.

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