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SHORT COMMUNICATION

Significant improvement in triglyceride levels after switching from ritonavir to cobicistat in suppressed HIV-1-infected subjects with dyslipidaemia

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Objectives

Cobicistat seems to have a low rate of adverse events compared with ritonavir.

Methods

This restrospective observational study to evaluated changes in lipid parameters and the percentage of subjects with dyslipidemia in virologically suppressed HIV-infected patients who were receiving a regimen containing darunavir/ritonavir and were then switched from ritonavir to cobicistat, carried out from December 2015 to May 2016, included 299 HIV-1-infected patients who were on stable antiretroviral treatment including darunavir/ritonavir (monotherapy, bitherapy or triple therapy for at least 6 months) and were then switched from ritonavir to cobicistat. Lipid parameters, as well as plasma HIV-1 RNA and CD4 cell counts, were recorded at baseline just before the switch, and 24 weeks after the switch. Patients were stratified according to the presence of hypercholesterolaemia [baseline total cholesterol > 200 mg/dL and/or low-density lipoprotein (LDL) cholesterol > 130 mg/dL] or hypertriglyceridaemia (baseline triglyceride levels > 200 mg/dL).

Results

Two hundred and ninety-nine patients were enrolled in the study. Fifty-two per cent of the total study population showed dyslipidaemia at baseline. All patients maintained HIV-1 RNA ≤ 50 HIV-1 RNA copies/mL at week 24. No statistically significant changes were seen in CD4 T-cell count from baseline to week 24 [654 (298) to 643 (313) cells/μL; $P = 0.173$]. When patients were stratified according to the presence of hypercholesterolaemia at baseline ($n = 124$), significant changes were observed in total cholesterol ($P < 0.001$), LDL cholesterol ($P = 0.047$), high-density lipoprotein (HDL) cholesterol ($P = 0.002$) and triglyceride levels ($P = 0.025$), and when they were stratified according to the presence of hypertriglyceridaemia at baseline ($n = 64$), changes from baseline to week 24 in triglyceride level were statistically significant [median (interquartile range) 352 (223, 389) mg/dL at baseline and 229 (131, 279) mg/dL at week 24; $P < 0.001$].

Conclusions

Cobicistat as a booster of darunavir in HIV-infected subjects had a beneficial effect on the lipid profile in patients with hypercholesterolaemia or hypertrigliceridaemia at baseline.

Keywords: darunavir/cobicistat, darunavir/ritonavir, lipid profile, suppressed HIV-1-infected subjects

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Introduction

The effectiveness of antiretroviral therapy (ART) continues to improve with the development of new antiretroviral drugs and regimens. The current goal in HIV management, however, is to improve adherence by minimizing toxicity and pill burden with new formulations, including fixed-dose combinations (FDCs).

Cobicistat-boosted darunavir is a boosted protease inhibitor in an FDC that has been recently approved for the treatment of HIV-1-infected patients [1, 2]. It contains

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darunavir, a known protease inhibitor with a good efficacy and safety profile [1, 3], and cobicistat, a relatively new nonantiretroviral cytochrome P450 3A inhibitor (booster/pharmacoenhancer) that can be used as an alternative to ritonavir, which is associated with adverse events and drug–drug interactions [2].

Studies in healthy volunteers have established bioequivalence between cobicistat and ritonavir as pharmacoenhancers for both atazanavir and darunavir [4–7]. In addition, a randomized phase III noninferiority clinical trial has demonstrated that the efficacy and safety of cobicistat are comparable to those of ritonavir as a pharmacoenhancer for darunavir through 48 weeks of treatment in antiretroviral-naïve HIV-1-infected patients [8]. Furthermore, a phase III, open-label, single-arm clinical trial has shown that darunavir/cobicistat has similar virological and immunological outcomes, safety and tolerability to published data for darunavir/ritonavir (800/100 mg once daily), supporting the use of darunavir/cobicistat (800/150 mg once daily) as an alternative pharmacoenhancer to ritonavir in mostly treatment-naïve HIV-infected patients without darunavir resistance-associated mutations [9].

Limited data are available on the use of darunavir/cobicistat in treatment-experienced participants [8, 10, 12]. Fisher *et al.* [11] studied the effects of switching to either darunavir/cobicistat- or atazanavir/cobicistat-containing regimes in 73 participants with a creatinine clearance of 50–89 mL/min. The study demonstrated similar efficacy, tolerability and renal profile to those found in other studies [10]. A study by Tashima *et al.* involving 18 treatment-experienced and 295 treatment-naïve participants found no difference between the two groups, supporting the use of darunavir/cobicistat in treatment-experienced participants [8, 9].

Although *in vitro* studies suggest that cobicistat may result in a lower incidence of undesired lipid-associated disorders than ritonavir [12, 13], phase III studies have not properly addressed these issues, and data are therefore limited [8, 9, 14, 15].

We evaluated changes in lipid parameters and the percentage of subjects with dyslipidaemia in virologically suppressed HIV-infected patients who were receiving a regimen containing darunavir/ritonavir and were then switched from ritonavir to cobicistat (without any other change), both in the overall group and in the subgroups of subjects with hypercholesterolaemia and hypertrygliceridaemia before the switch.

Methods

This retrospective observational study included all HIV-1-infected patients receiving care in our unit from December 2015 to May 2016, who were on stable ART including darunavir/ritonavir (monotherapy, bitherapy or triple therapy for at least 6 months) and were then switched from ritonavir to cobicistat.

Patients who withdrew from the study, or changed or added other antiretroviral drugs at the time of the switch were excluded from our analysis, as well as patients for whom there was incomplete lipid profile data at baseline (i.e. immediately prior to the switch) and 24 weeks after the switch.

Demographic and HIV-related data (sex, age, time since HIV diagnosis, risk factor, clinical stage, cumulative exposure to ART, current CD4 cell count and viral load, use of lipid-lowering agents, etc.) were obtained from the patients' records.

Lipid parameters [total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides], always assessed after at least 10 h of fasting, were recorded just before the switch from ritonavir to cobicistat (the baseline point) and then 24 weeks after the switch, as well as plasma HIV-1 RNA and CD4 cell counts.

Patients were considered to have hypercholesterolaemia if they were taking lipid-lowering drugs or if their total cholesterol level was > 200 mg/dL and/or their LDL cholesterol level was > 130 mg/dL (criteria for HIV-infected patients according to the European Guidelines on cardiovascular disease prevention in clinical practice) and hypertriglyceridaemia if triglyceride levels were > 200 mg/dL (according to the reference values of the local laboratory).

The trial protocol was reviewed and approved by the appropriate institutional ethics committees and health authorities and fulfilled the stipulations of the Declaration of Helsinki and Good Clinical Practice (GCP) (PI-16-140, protocol FLS-DA-2016-01).

Statistical analysis

Demographic and clinical parameters are expressed as the mean and standard deviation (SD) or as the median and interquartile range (IQR); qualitative variables are expressed as frequencies and percentages. Normally distributed continuous variables were compared using the *t*-test; nonnormally distributed variables were compared using the Mann–Whitney test. The dependent *t*-test for paired samples or the Wilcoxon signed rank test was performed to assess the significance of changes observed over time; proportions were compared using the McNemar test.

Univariate P values < 0.05 were considered significant. The statistical analysis was performed using SPSS 15.0.0 (SPSS Inc., Chicago, IL, USA).

Results

Two hundred and ninety-nine patients were enrolled in the study. Epidemiological, clinical, and HIV-related characteristics are summarized in Table 1. Overall, the median (IQR) age was 49 (42, 54) years and 85% of patients were male. The median (IQR) time since diagnosis of HIV infection was 16 (7, 23) years; the median (IQR) times on ART and on protease inhibitors were 12 (6, 20) years and 7.5 (4, 14) years, respectively.

At baseline, 49.5% of patients were being treated with darunavir/ritonavir monotherapy, 9% with darunavir/ritonavir bitherapy and 41.5% with triple therapy including two nucleoside reverse transcriptase inhibitors (see Table 1). Fifty-two per cent of the total study population showed dyslipidaemia at baseline (hypercholesterolaemia and/or hypertriglyceridaemia); of these, 52% were on monotherapy, 61% on bitherapy and 70% on triple therapy.

All patients maintained HIV-1 RNA $\leq$ 50 HIV-1 RNA copies/mL at week 24. For the whole population, no statistically significant changes were seen in mean CD4 T-cell count from baseline to week 24 [mean (SD)] 654 (298) cells/mm3 at baseline and 643 (313) cells/mm3 at week 24, p = 0.173.

Metabolic changes

Considering the total study population, no statistically significant differences were seen in total, HDL or LDL cholesterol from baseline to week 24 after switching from ritonavir to cobicistat. Only changes in triglyceride levels were statistically significant from median (IQR) 167 (93, 187) mg/dL at baseline to 124 (87, 175) mg/dL at week 24; $P = 0.018$) (Table 2).

When the analysis included only those patients with hypercholesterolaemia at baseline ($n = 124$), changes from baseline to week 24 were statistically significant for total cholesterol [median (IQR) 231 (209, 243) at baseline and 212 (189, 239) at week 24; $P < 0.001$], LDL cholesterol [median (IQR) 144 (131, 161) and 131 (113, 152), respectively; $P = 0.047$], HDL cholesterol [median (IQR) 45 (40, 54) and 52 (44, 59), respectively; $P = 0.002$] and triglyceride levels [median (IQR) 157 (109, 209) and 131 (101, 202), respectively; $P = 0.025$] (Table 2).

When only patients with hypertriglyceridaemia at baseline were considered ($n = 64$), statistically significant differences in triglyceride levels were seen from baseline to week 24 [median (IQR) 352 (223, 389) mg/dL and 229 (31; 279) mg/dL, respectively; $P < 0.001$] (Table 2).

Table 1 Clinical and epidemiological characteristic of the study population ($n = 299$)

Age (years) [median (IQR)]	49 (42, 54)
Gender (male) (%)	85
HCV coinfection (%)	6
HBV coinfection (%)	2
Time since diagnosis of HIV infection (years) [median (IQR)]	16 (7, 23)
HIV infection > 5 years (%)	87
Cumulative exposure to antiretrovirals (years) [median (IQR)]	12 (6, 20)
Cumulative exposure to protease inhibitors (years) [median (IQR)]	7.5 (4, 14)
Current CD4 count (cells/μL) [median (IQR)]	646 (448, 847)
CD4 count < 200 cells/μL (%)	5.4
HIV RNA $\leq$ 50 copies/mL (%)	100
Antiretroviral treatment (%)	
DRV/r monotherapy	49.5
DRV/r bitherapy	9
DRV/r triple therapy	41.5
Truvada/TDF	26

HCV, hepatitis C virus; HBV, hepatitis B virus; DRV/r, darunavir/ritonavir; TDF, tenofovir; IQR, interquartile range.

Discussion

The degree of antiretroviral-related dyslipidaemia seen in HIV-1-infected patients varies according to their

Table 2 Changes in lipid parameters

Lipid parameter	Baseline	Week 24 after change	*P*-value
Total population ($n = 299$)			
Use of lipid-lowering agents (%)	12	12	–
TC (mg/dL) [median (IQR)]	190 (162, 216)	184 (154, 211)	0.085
LDL-c (mg/dL) [median (IQR)]	111 (92, 136)	109 (84, 132)	0.530
HDL-c (mg/dL) [median (IQR)]	44 (38, 54)	45 (38, 54)	0.440
TG (mg/dL) [median (IQR)]	167 (93, 187)	124 (87, 175)	**0.018**
Subjects with TC $\geq$ 200 mg/dL, LDL-c $\geq$ 130 mg/dL and/or TG $\geq$ 200 mg/dL (%)	52	45	0.112
Subjects with hypercholesterolaemia at baseline (TC > 200 mg/dL and/or LDL-c > 130 mg/dL) ($n = 124$)			
TC (mg/dL) [median (IQR)]	231 (209, 243)	212 (189, 239)	**0.001**
LDL-c (mg/dL) [median (IQR)]	144 (131, 161)	131 (113, 152)	**0.047**
HDL-c (mg/dL) [median (IQR)]	45 (40, 54)	52 (44, 59)	**0.002**
TG (mg/dL) [median (IQR)]	157 (109, 209)	131 (101, 202)	**0.025**
Subjects with TG > 200 mg/dL at baseline ($n = 64$)			
TC (mg/dL) [median (IQR)]	207 (182, 232)	191 (158, 215)	0.067
LDL-c (mg/dL) [median (IQR)]	109 (84, 121)	105 (83, 127)	0.299
HDL-c (mg/dL) [median (IQR)]	40 (36, 45)	40 (36, 48))	0.381
TG (mg/dL) [median (IQR)]	352 (223, 389)	229 (131, 279)	**< 0.001**

IQR, interquartile range; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; TG, triglycerides.
Significant *P*-values are shown in bold.

treatment regimen, and protease inhibitors are usually more potent inducers of this association probably being atributable to the use of ritonavir [16,17].

Ritonavir is a protease inhibitor, initially approved for treatment of HIV infection at high doses as a component of an antiretroviral regimen. Similar to other protease inhibitors, high doses of ritonavir have a very short plasma half-life and significant metabolic side effects. However, in lower doses (100–200 mg per day), this agent has been found to be an excellent booster for other protease inhibitors. Nonetheless, even when only administered as a booster, ritonavir may induce some side effects such as gastrointestinal intolerance and dyslipidaemia.

Tomaka *et al.* [17] showed that, after 7 days of coadministration of low-dose ritonavir with darunavir or atazanavir in HIV-negative health volunteers, the mean triglyceride concentration increased by approximately 30 mg/dL in both groups and resulted in minor and similar changes in lipid parameters.

A meta-analysis that evaluated the efficacy and safety of unboosted atazanavir compared with another ritonavir-boosted protease inhibitor demonstrated that unboosted atazanavir caused a significant reduction in total cholesterol, LDL cholesterol and triglycerides, without sacrificing virological efficacy [18]. Similar results were report by Santos *et al.* [19].

Estévez *et al.* [20] evaluated the pharmacokinetics, safety and tolerability of 300 mg of atazanavir boosted with 100 or 50 mg of ritonavir, both once daily, and demonstrated that, although the atazanavir exposure was equivalent when boosted with either 100 mg or 50 mg of ritonavir, the lipid profile was better under the lower 50 mg booster dose.

Given the adverse events reported for ritonavir, cobicistat has emerged as an alternative booster/pharmacoenhancer of protease inhibitors or other antiretroviral drugs for treatment of adults with HIV-1 infection [1, 2, 4]. However, to date, few data have been published about the effect of cobicistat on the lipid profile [12, 13]. Although *in vitro* studies suggest that cobicistat may result in a lower incidence of undesired drug–drug interactions and lipid-associated disorders than ritonavir, not all phase III studies have fully addressed these issues [8, 9, 14, 15].

One *in vitro* study suggests that cobicistat may have a lower potential toxicity with respect to lipid metabolism compared with ritonavir. The results showed that cobicistat affected adipocyte function less than ritonavir, the half maximal effective concentration (EC50) was >30 vs. 16 μM, respectively, for lipid accumulation in human adipocytes. Furthermore, in an insulin-stimulated glucose uptake assay, ritonavir showed a more pronounced mean inhibitory effect in mouse adipocytes compared with cobicistat [13].

In the present study, more than 50% of the total study population presented with dyslipidaemia at baseline. After the switch from ritonavir to cobicistat (in the whole study population), the percentage of patients on bitherapy or triple therapy showing dyslipidaemia decreased significantly. A significant improvement in all lipid parameters, including HDL cholesterol, was seen 24 weeks after the switch in those subjects with hypercholesterolaemia at baseline, and triglyceride levels improved mainly in patients who presented with hypertriglyceridaemia at baseline, while both virological efficacy and inmunological status were maintained after the change in treatment.

These results indicate that replacement of ritonavir with cobicistat could decrease the percentage of subjects with dyslipidaemia associated with ART and consequently the cardiovascular risk.

The retrospective design of the study did not allow us to exclude the possibility that changes during the study period in physical activity, diet, alcohol consumption, etc. may have had an impact on lipid parameters, and did not allow us to take account of potential changes in lipid-lowering drugs. However, this exploratory analysis provides, for the first time, descriptive results demonstrating the beneficial impact on the lipid profile that cobicistat seems to have when it is use as a booster/pharmacoenhancer of darunavir in HIV-infected subjects. In addition, this new co-formulation makes the compound easier to take, thus improving adherence.

Author contributions

PE, AB, JP, BC and EN participated in the study design, patient selection, data analysis, and critical review of the manuscript. AO participated in the statistical analysis.

Conflicts of interest

None of the authors has a financial or other conflict of interest to declare in relation to the present work.

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