Rosuvastatin versus pravastatin in dyslipidemic HIV-1-infected patients receiving protease inhibitors: a randomized trial

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Background: HIV infection and its treatment with protease inhibitors, especially when boosted with ritonavir, can cause lipid disorders. Statins, with the exception of fluvastatin, pravastatin and rosuvastatin, interact with protease inhibitor metabolism via CYP450. Pravastatin is recommended for patients with protease inhibitor-associated dyslipidemia. Rosuvastatin is the statin most effective on low-density lipoprotein cholesterol (LDL-c) in non-HIV patients.

Methods: HIV-1-infected patients treated with boosted protease inhibitor were randomized to receive either rosuvastatin 10 mg/day or pravastatin 40 mg/day for dyslipidemia (LDL-c >4.1 mmol/l and triglycerides <8.8 mmol/l). The percentage change in LDL-c, triglyceride and high-density lipoprotein-cholesterol levels, measured in a central laboratory, was determined after 45 days of statin treatment.

Results: Eighty-eight patients were randomized and 83 took the study drugs, 41 rosuvastatin and 42 pravastatin. The median duration of prior antiretroviral treatment was 9 years. At baseline, the median LDL-c level was 4.93 mmol/l, the triglyceride level 2.29 mmol/l, and the high-density lipoprotein-cholesterol level 1.27 mmol/l. The median percentage changes in the rosuvastatin and pravastatin arms were −37 and −19% for LDL-c ($P < 0.001$), respectively, and −19 and −7% for triglycerides ($P = 0.035$), respectively. The change in the high-density lipoprotein-cholesterol level was not significantly different between the two arms. None of the four severe adverse events was attributed to the statins; in particular, there were no renal, hepatic or muscular events.

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Conclusion: Rosuvastatin 10 mg/day was more effective than pravastatin 40 mg/day on LDL-c and triglyceride levels in HIV-1-infected patients receiving a boosted protease inhibitor.

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Keywords: boosted protease inhibitor, dyslipidemia, pravastatin, rosuvastatin

Introduction

Dyslipidemia is a frequent side effect of combined antiretroviral therapy (cART), especially when boosted protease inhibitors are used. The lipid disorders usually consist of mixed hyperlipidemia, but isolated hypercholesterolemia and isolated hypertriglyceridemia can also occur. The management of protease inhibitor-associated dyslipidemia is controversial. A low-fat diet is recommended but is not always adequate. Three fibrates (gemfibrozil, bezafibrate, and fenofibrate) have been tested in this setting, reducing triglyceride levels by 41–58% on average [1,2]. Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are the most effective drugs for hypercholesterolemia and mixed dyslipidemia. Most statins are metabolized by CYP3A4 or are substrates of transporters (OATP-C) or both, whereas protease inhibitors potentially inhibit CYP3A4 or transporters or both [3,4]. Ritonavir is the most powerful CYP3A4 inhibitor. The use of statins in cART-treated patients is complicated by statin–protease inhibitor interactions, especially with ritonavir. Fluvastatin, pravastatin, and rosuvastatin are not metabolized by CYP3A4. Although pravastatin is the most widely prescribed statin in the context of HIV infection in France [5], rosuvastatin is the statin with the most potent effect on the LDL-cholesterol (LDL-c) level in the non HIV-1-infected population.

The primary objective of this randomized trial was to compare the efficacy of rosuvastatin and pravastatin, after 45 days treatment, on plasma lipid levels in HIV-1-infected patients taking a cART regimen containing at least one protease inhibitor boosted with ritonavir and whose LDL-c level exceeded 4.1 mmol/l.

Methods

Study design

This study (VIHstatine ANRS 126; ClinicalTrials.gov identifier NCT00117494) was a randomized, multicenter, open-label trial involving dyslipidemic HIV-1-infected patients and comparing rosuvastatin 10 mg per day and pravastatin 40 mg per day given for 45 days. This was the officially recommended rosuvastatin dose when the study was designed, while the pravastatin dose was the highest authorized dose that, in pilot studies, was well tolerated [6–8]. The primary endpoint was the change in the LDL-c level relative to baseline. The patients were centrally randomized, with blocks of size 6, using the SAS PLAN procedure. The Pitié-Salpêtrière Hospital institutional review board approved the protocol, and all the patients gave their written informed consent.

Patients

Patients were eligible for enrolment in this study if they had tested positive for anti-HIV-1 antibodies, had been receiving a stable cART regimen comprising a ritonavir-boosted protease inhibitor for at least 2 months (with no planned treatment modification for the following 2 months), and had a plasma HIV-1 RNA level of 10 000 copies/ml or less at randomization. Required fasting lipid status included LDL-c levels more than 4.1 mmol/l and triglyceridemia (triglyceride) less than 8.8 mmol/l. Transaminase levels had to be no more than three times the upper limit of normal [ULN $\leq$ 5 times in case of hepatitis C virus (HCV) or hepatitis B virus (HBV) infection, without cirrhosis], and the creatine phosphokinase level five times of ULN or less. Patients were not eligible if they had documented coronary heart disease, a muscle disorder, a previous muscular adverse reaction to a statin or fibrate, impaired hepatic function (prothrombin <70%) or renal function (creatinine clearance <30 ml/min), proteinuria exceeding ++, alcohol consumption over 40 g per day, an ongoing opportunistic infection, pregnancy or statin or fibrate exposure less than 2 months before the first dose of study treatment.

Monitoring

The patients had a physical examination and lipid assays at the screening visit (within 2 weeks before baseline), baseline (D0), D15, and D45. Adverse events were recorded at each visit during the study treatment. The CD4 cell count and plasma HIV-1 RNA level were determined at the screening visit, and HIV-1 RNA was also determined at D45. Lipid parameters [fasting serum levels of total cholesterol, high-density lipoprotein cholesterol (HDL-c), LDL-c and triglycerides] were determined locally at the screening visit and in a central laboratory on D0 and D45 (LDL-c was directly measured on D0 and D45).

Sampling

Venous blood was collected in Vacutainer tubes with gel (Becton-Dickinson, Plymouth, UK) after a 12-h fast.

Serum lipid levels were determined in a reference laboratory using standard enzymatic methods. Triglycerides were measured with the PAP 1000 enzymatic method (BioMérieux, Marcy-l'étoile, France) [9]. Total cholesterol, direct LDL-c, and direct HDL-c were determined as recommended by ARCOL (Comité Français de coordination des recherches sur l'athérosclérose et le cholestérol) with automated enzymatic methods (Konelab Thermo Fisher Scientifics, Cergy-Pontoise, France) [10–12]. If the triglyceride level exceeded 2.28 mmol/l, free glycerol was measured independently by using the Randox colorimetric method (Randox Laboratories Ltd, Crumlin, United Kingdom). All lipid parameters were determined with a Konelab 30i analyzer (Thermo Electron Corporation, Waltham, Massachusetts, USA).

Protease inhibitor trough plasma concentrations were determined with a high-performance liquid chromatographic method (HPLC) as previously described [13] on D0 and D15 (at steady state), 12 ± 2 h after the last drug intake (except for atazanavir, which was determined 24 ± 4 h after the last drug intake). Pravastatin plasma concentrations were measured centrally in a unique laboratory by using an HPLC method [14]. Rosuvastatin plasma concentrations were measured by Covance Laboratories, Inc. (Madison, Wisconsin, USA), as previously described [15].

Statistical considerations

We calculated that 39 patients per arm would be required to detect a between-group difference of 1 mmol/l in the change in LDL-c between baseline and D45, with a standard deviation of 1.25 mmol/l, a power of 90%, a type I error of 0.05, and a two-tailed nonparametric test. To account for the dilution effect associated with nonassessable patients, it was planned to enroll 43 patients per arm.

Variables were summarized by using proportions for categorical variables: the median and interquartile range (IQR) for age, time since HIV diagnosis, the CD4 cell count, and the time on cART; and the mean and standard deviation (SD) for continuous variables used as endpoints. The primary endpoint (LDL-c) and secondary lipid endpoints (total cholesterol, HDL-c, and triglycerides) were analyzed with an intent-to-treat approach (ITT), with the last observation carried forward, and also on available data. Changes from baseline were compared between the groups by using the nonparametric Mann–Whitney test. Two-way analysis of variance was used to test simultaneously for the randomized treatment effect and the protease inhibitor effect. Fisher's exact test was used to compare the proportions of patients with LDL-c levels less than 4.1 mmol/l in the two groups. All analyses were performed with the SPSS software package version 15.0 for Windows (SPSS, Inc., Illinois, Chicago, USA).

Results

Patient disposition

Between October 2005 and January 2007, 129 patients were screened and 88 patients were enrolled in 21 centers in France. As shown in Fig. 1, 83 patients initiated the study treatment and are included in the analyses. Lipid parameters could not be determined on D45 in three patients in the pravastatin arm, and the last-observation-carried-forward technique was used to include them in

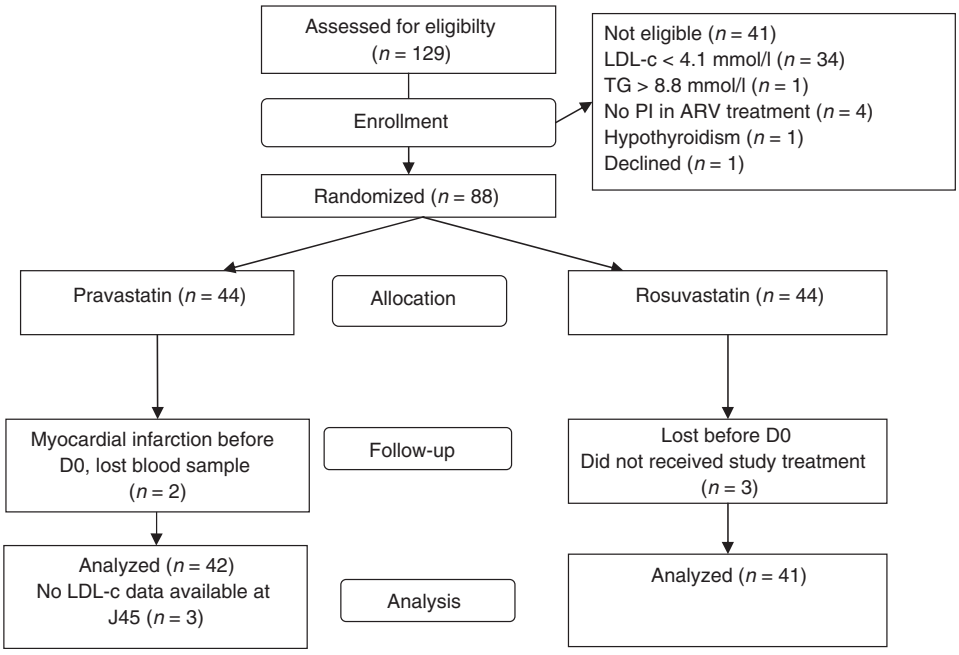

Fig. 1. Flow chart of the study. ARV, antiretroviral; LDL, low-density lipoprotein; PI, protease inhibitor; TG, triglycerides.

Table 1. Baseline characteristics of the patients.

	Pravastatin ($n = 42$)	Rosuvastatin ($n = 41$)
Male patients [*n* (%)]	33 (79)	31 (76)
Age [years, median (IQR)]	49 (42–53)	47 (42–56)
Transmission group [*n* (%)]		
Men who have sex with men	22 (52)	20 (49)
Heterosexuals	18 (43)	15 (37)
Unknown/others	2 (4)	6 (14)
Ethnic origin [*n* (%)]		
Caucasian	36 (86)	37 (90)
Sub-Saharan African	5 (12)	4 (10)
Other	1 (2)	0 (0)
Time since HIV diagnosis [years, median (IQR)]	10 (4–13)	9 (5–11)
CD4 cells [cells/μl, median (IQR)]	436 (314–662)	521 (314–827)
Plasma HIV RNA $\leq$ 400 copies/ml [*n*/*N* (%)]	38/41 (93)	37/40 (92)
Prior AIDS events [*n* (%)]	12 (29)	8 (20)
Number of previous ARVs [median (IQR)]	7 (6–9)	7 (5–9)
Time on cART (years) [median (IQR)]	10 (5–13)	9 (5–12)
Protease inhibitors [*n* (%)]		
LPV/r	14 (33)	11 (27)
fAPV/r	11 (26)	8 (20)
ATV/r	8 (19)	15 (37)
Others (TPV/r; IDV/r; SQV/r)	9 (21)	7 (17)
Cardiovascular risk factors[a] [*n* (%)]		
0	24 (63)	22 (55)
1	7 (18)	13 (33)
2	6 (16)	5 (13)
3	1 (3)	0 (0)
Total cholesterol [mmol/l, mean (SD)]		
Screening	7.40 (0.85)	7.58 (1.14)
Baseline	7.12 (0.98)	7.28 (1.21)
LDL cholesterol [mmol/l, mean (SD)]		
Screening	5.05 (0.69)	5.14 (0.90)
Baseline	4.86 (0.90)	5.02 (1.11)
HDL cholesterol [mmol/l, mean (SD)]		
Screening	1.26 (0.35)	1.31 (0.32)
Baseline	1.34 (0.37)	1.39 (0.39)
Triglycerides [mmol/l, mean (SD)]		
Screening	2.48 (1.13)	2.74 (1.41)
Baseline	2.58 (1.64)	2.65 (1.30)

ARV, antiretroviral; ATV/r, atazanavir/ritonavir; fAPV/r, fosamprenavir/ritonavir; HDL, high-density lipoprotein; IDV/r, indinavir/ritonavir; IQR, interquartile range; LDL, low-density lipoprotein; LPV/r, lopinavir/ritonavir; SQV/r, saquinavir/ritonavir; TPV/r, tipranavir/ritonavir.
[a]An addition of male patients with age more than 50 years or female patients with age more than 60 years, current or past smoker since less than 3 years, HDL-c less than 1 mmol/l, high blood pressure, diabetes mellitus, family history of cardiovascular diseases. HDL-c levels above 1.5 mmol/l, implicates a subtraction of one risk factor.

the ITT analysis, while they were excluded from the analysis on available data.

Characteristics of the patients

The baseline characteristics were well balanced between the two arms (Table 1). Three-quarters (77%) of the patients were men, and the median age was 47 years [(IQR 42–54]. The baseline median CD4 cell count was 482×10^6/l (IQR 314–678), and the plasma HIV-1 RNA level exceeded 400 copies/ml in seven patients (7%) (maximum 5238 copies/ml).

At the screening visit (day 15), the LDL-c level was above 4.1 mmol/l (1.6 g/l) in all the patients, in keeping with the inclusion criteria. At baseline (D0), the median LDL-c, HDL-c, triglyceride, and total cholesterolemia levels were 4.93 mmol/l [IQR 4.52–5.55], 1.27 mmol/l [IQR 1.05–1.50], 2.29 mmol/l [IQR 1.81–3.25], and 7.48 mmol/l [IQR 6.80–8.04], respectively, and were well balanced between the two arms. The LDL-c level was below 4.1 mmol/l in 22% of patients overall (26% in the pravastatin arm and 17% in the rosuvastatin arm).

Protease inhibitor therapy was well balanced between the two arms and mainly consisted of lopinavir (30%), atazanavir (28%), and fosamprenavir (23%), with slightly more patients receiving boosted atazanavir in the rosuvastatin arm as compared with the pravastatin arm ($P = 0.09$). The median time since cART initiation was 9 years [5,13]. A wide variety of nucleoside/nucleotide reverse transcriptase inhibitors or nonnucleoside reverse transcriptase inhibitors or both were being taken concomitantly (28 different regimens) with no difference between arms. Only six patients in the pravastatin arm and six patients in the rosuvastatin arm were receiving zidovudine, whereas only two patients in the rosuvastatin arm were receiving stavudine.

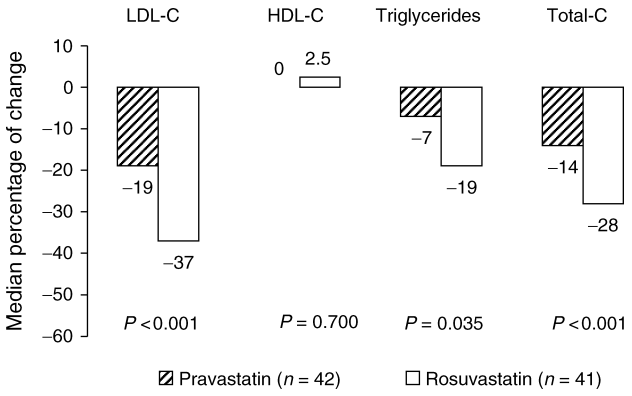

Fig. 2. Median percentage changes in low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and total cholesterol levels. HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Changes in lipid parameters

After 45 days of statin therapy, the change in the LDL-c level was -0.92 ± 0.79 mmol/l with pravastatin and -1.69 ± 0.87 mmol/l with rosuvastatin ($P < 0.001$), corresponding to respective median reductions of 19% (30–6%) and 37% (42–23%) ($P < 0.001$) (Fig. 2). On D45, the LDL-c was below 4.1 mmol/l in 60 and 88% of patients ($P = 0.006$). The change in HDL-c levels between baseline and D45 did not differ between the arms ($+0.05 \pm 0.23$ mmol/l with pravastatin and $+0.01 \pm 0.19$ mmol/l with rosuvastatin; $P = 0.750$). The change in triglyceride levels was less marked with pravastatin than with rosuvastatin (-0.20 ± 0.95 mmol/l and -0.67 ± 1.02 mmol/l; $P = 0.019$), corresponding to respective median reductions of 7 and 19% ($P = 0.035$) (Fig. 2).

The differences in the treatment effects on LDL-c and triglycerides were not influenced by the protease inhibitors received (P values for the interactions, 0.990 and 0.799, respectively).

Protease inhibitor and statin concentrations

Statin therapy did not significantly modify trough plasma concentrations of atazanavir, amprenavir, or lopinavir. Changes in protease inhibitor trough plasma concentrations before and after initiation of the statin were not significantly different between the pravastatin arm and the rosuvastatin arm ($P = 0.687$ for atazanavir, $P = 0.622$ for amprenavir, and $P = 0.364$ for lopinavir).

The median plasma rosuvastatin concentration, determined in 30 of the 41 patients concerned, was 1.05 ng/ml [IQR 0.72–1.66] 24 h after the last drug intake and was not influenced by the nature of the protease inhibitor ($P = 0.631$). The median pravastatin trough concentration, determined in 29 of the 42 patients concerned, was 6 ng/ml [IQR 2–13] and was not influenced either by the nature of the protease inhibitor ($P = 0.845$).

Adverse events

Changes in creatininemia, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine phosphokinase, and proteinuria between D0 and D45 were not significantly different between the arms. Tenofovir, taken by 14 patients in the rosuvastatin arm and by 12 patients in the pravastatin arm, did not influence the frequency of proteinuria either at baseline or during statin therapy. Four adverse events were reported during the study, one in the pravastatin arm (tuberculosis) and three in the rosuvastatin arm (programmed colonoscopy, cataract surgery, and urinary tract infection). None was considered linked to the study drugs by the investigators. In particular, there were no renal, hepatic, or muscular events. Overall 92% had a plasma-HIV-1 RNA less than 400 copies/ml at day 45, as at baseline.

Discussion

The present study shows that rosuvastatin is more effective than pravastatin on both LDL-c and triglyceride levels in HIV-1-infected patients with dyslipidemia receiving ritonavir-boosted protease inhibitor.

Although this was an open-label study, the statin treatments were randomized, there were few missing data, and the patients were receiving a wide range of boosted protease inhibitor-containing cART regimens (excepting the most recently marketed drug darunavir), and the efficacy of rosuvastatin compared with that of pravastatin was not different according to the boosted protease inhibitor received. In addition, the lipid parameters were determined in a central laboratory blinded to the treatment arm. Follow-up was short (45 days) but similar to that of the registration trials and sufficient to detect a difference in efficacy [16]. The 10 mg/day rosuvastatin dose regimen was the only one authorized in Europe when the trial was designed in 2005. An initial dose of 5 mg/day has been recommended since 2006. However, no serious adverse effects occurred in our study.

Previously, the only available data in this setting came from small noncontrolled studies of rosuvastatin, in which the mean or median fall in LDL-c ranged from 22 to 33% [17,18]. In a more recent study, in which 10% of enrolled patients were excluded from the analysis, Calza [19] found a similar reduction in LDL-c but not in triglycerides, possibly owing to differences in the methods, the study design, the drug dosage, or the length of follow-up.

In the Mercury 1 study, involving HIV-seronegative patients, Stender *et al.* [20] observed a mean percentage

change in LDL-c of $-29.9 \pm 1.0\%$ in the pravastastin arm (40 mg/day) and $-46.7 \pm 1.0\%$ in the rosuvastatin arm (10 mg/day) after 8 weeks of therapy. The mean difference in efficacy between the statins (mean percentage change in LDL-c of 16.8%) was similar to that observed in our study (15.4%). However, the mean percentage changes were 13% lower in our study conducted in HIV-1-infected patients (mean percentage change: $17.4 \pm 2.4\%$ in the pravastatin arm versus $32.8 \pm 2.4\%$ in the rosuvastatin arm) for pravastatin and rosuvastatin ($P < 0.01$) as previously observed [16]. In addition, we observed no significant impact of either drug on HDL-c, whereas Stender *et al.* [20] observed a 9% increase in HIV-seronegative patients. This could suggest a difference in the mechanisms of hyperlipidemia in HIV-1-infected and uninfected patients. However, though smaller than for a non-HIV-1-infected patient, the clinical benefit of such LDL-c reduction is still important. As an example, let us consider a 45-year-old male smoker, without hypertension or diabetes, and a total cholesterolemia of 7 mmol/l with a normal HDL-c value. His 10-year risk of coronary artery disease would change from 26.6 to 19.7% using the Framingham equation when treated with rosuvastatin.

Trough plasma rosuvastatin concentrations were similar to those reported by van der Lee [18] and were not affected by the nature of the boosted protease inhibitor, including lopinavir. Likewise, the trough plasma pravastatin concentration did not depend on the protease inhibitor received. Trough plasma concentrations of pravastatin and rosuvastatin were both within the expected range with respect to the dose regimens, and no adverse effects were observed, including rhabdomyolysis and liver damage. This tends to rule out inhibitory/inducing effects on CYP450 enzymes, thus confirming results obtained *in vitro* [21].

Conclusion

Rosuvastatin is more effective than pravastatin on dyslipidemic HIV-1-infected patients treated with cART containing ritonavir-boosted protease inhibitors, in particular, with its effects on triglycerides. Long-term studies are now needed to evaluate the possible impact of rosuvastatin on cardiovascular events in this setting and also in normolipidemic HIV-1-infected patients.

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