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Pravastatin in HIV-Infected Patients Treated with Protease Inhibitors: A Placebo-Controlled Randomized Study

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Purpose: The objectives of the study were to assess the effects of pravastatin on plasma HIV RNA, lipid parameters, and protease inhibitor (PI) concentrations in patients treated with PI-containing regimens and with total cholesterol (TC) ≥ 5.5 mmol/L. **Method:** A clinical trial including patients randomized to receive pravastatin or matching placebo for 12 weeks was implemented. **Results:** Twelve patients were included in the pravastatin group and 9 in the placebo group. At week 12 (W12), no patient had experienced virological failure. Between week 0 (W0) and W12, the median differences for TC were -1.4 mmol/L in the pravastatin group and $+0.2$ mmol/L in the placebo group ($p = .005$); for LDL, they were -1.0 mmol/L and $+0.3$ ($p = .007$), respectively. A significant decrease of the PI concentration (12 hours after administration) ratio W12 – W0/W0 was noticed in the pravastatin group (-0.2 [interquartile range, -0.3 to -0.1] as compared with the placebo group (0.1 [IQR, 0.0 to 0.3]) ($p = .03$). When the study was restricted to patients treated with lopinavir/ritonavir, a decrease from 3.8 μ g/mL at baseline to 2.9 μ g/mL at W12 was noticed in the pravastatin arm ($p = .04$) but not in the control arm ($p = 1.00$). No clinical adverse event reached a severity of grade 3. **Conclusion:** We observed in this study that the use of pravastatin in PI-treated patients was not associated with major change in the plasma HIV RNA on 12 weeks of follow-up. However, we found a trend of decrease of the trough PI concentration at W12, suggesting a possible drug-drug interaction of pravastatin on PI metabolism. **Key words:** HIV, pravastatin, protease inhibitors

Highly active antiretroviral therapy (HAART) including protease inhibitors (PIs) is associated with disturbances of plasma lipid levels. Metabolic effects of PI include an increase of plasma triglycerides (TG) and total cholesterol (TC) in 51% to 80% of patients according to the drug regimen.^{1,2} This increase of plasma lipids is associated with an increase of low-density lipoprotein (LDL-C) and of atherogenic ratios (TC/HDL-C and apolipoprotein B/apolipoprotein A1).^{3,4} In addition, recent studies have shown an increased risk of cardiovascular events in HIV-infected patients treated with combination antiretroviral therapies.^{5,6}

At the present time, the management of PI-associated dyslipidemia involves modifications of HAART combination and/or the use of lipid-lowering drugs, such as fibrates and statins. The use of fibrates in hypertriglyceridemia seems safe and useful.⁷⁻⁹ However, the use of statins in PI-

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associated hypercholesterolemia requires caution, according to hypothetic drug-drug interactions through the cytochrome enzymes. Previous study by Fichtenbaum et al. has shown that among statins, simvastatin and atorvastatin had a significantly larger area under the curve in the presence of ritonavir and saquinavir, whereas pravastatin had a decreased area under the curve in the same conditions.¹⁰ Thus, pravastatin, which is less reliant on CYP3A4 for its metabolism, may be the best choice in PI-associated hypercholesterolemia to prevent statin side effects. However, drug-drug interactions of statins on PI have been poorly studied, and one cannot exclude the possibility that statins could influence PI plasma levels and therefore could have impact on virological response.

To date, only one randomized placebo-controlled study has been conducted to assess the effects of pravastatin on lipids in HIV-infected patients treated with boosted PI, showing limited benefit on total cholesterol.¹¹ However, no formal study has been conducted to assess the impact of pravastatin on HIV RNA and PI concentration and to closely evaluate its tolerance.

PARTICIPANTS AND METHOD

Patients

Patients were eligible for enrollment in the study if they tested positive for anti-HIV antibodies, had been receiving stable antiretroviral therapy including at least one PI for ≥3 months, had a plasma HIV RNA level of <50 copies/mL for ≥3 months before randomization, a TC ≥5.5 mmol/L with LDL-C ≥ 3.4 mmol/L on fasting status after at least 12 hours and after 3 months of standardized dietary advice, and were able to provide written informed consent.

Patients were not eligible for inclusion if they had current AIDS event or infectious disease; tumoral, inflammatory, or muscle diseases; kidney or hepatic failure; psychiatric conditions; biological elevated muscular enzymes; chronic alcohol consumption; or if they were pregnant or displayed no evidence of use of effective contraception.

Study Design and Treatment Regimen

This 3-month study was a randomized, placebo-controlled, double-blind trial. Two groups of pa-

tients receiving PI-containing regimen and having an indication of statin therapy were randomized to receive pravastatin or placebo for 3 months. Patients were randomized centrally at the Central Data Center (INSERM U593) following a computer-generated random-number list to one of the two treatment groups. At the end of the study, treated patients could continue to receive pravastatin therapy, and patients included in the placebo group initiated this treatment. The study was approved by the ethics committee of the Bordeaux University Hospital. Pravastatin 40 mg or placebo was provided orally once a day, with dosing in the evening. During follow-up, specific adverse events of statins were graded in severity 1 to 4, in accordance with the grading usually used in therapeutic studies. Particularly, moderate myalgias (without repercussion on general status) were graded 2; severe myalgias (with repercussions on general status) were graded 3. Muscle enzymes (creatinine kinase) up to 5 times the normal range were graded 2, between 5 and 10 times the normal range graded 3, and above 10 times the normal range graded 4.

Follow-up

Clinical, laboratory, and virology were collected at a screening visit ≤14 days before randomization, on the day of randomization (baseline), and at week 4 (W4) and week 12 (W12) after randomization. Routine follow-up included complete physical examination, peripheral blood cell count including CD4+ cell count, HIV RNA, and biochemical profile including liver function tests and creatine kinase. Lipids were measured after at least 12 hours of fasting status. PI concentrations were measured in the morning around 12 hours after previous night intake and documented with the patient and around 2 hours after the morning PI intake and around 3 hours for lopinavir/ritonavir.

Laboratory Measurements

The plasma level of HIV RNA was determined with the branched DNA assay (Ultrasensitive Monitor HIV 3.0; Chiron Diagnostics, Emeryville, California, USA) with lower detection 50 copies/mL. CD4 and CD8 cell counts were measured using flow cytometry.

TC, HDL-C, apolipoprotein A1, apolipoprotein B, and triglycerides were performed on an auto-

mate LX 20 (Beckman, Paris, France). LDL-C was either calculated with Friedewald's formula for triglycerides under 4 mmol/L or performed on an automated Hitachi 911 (Roche, Paris, France) for triglycerides above 4 mmol/L.

A total of 124 blood samples were drawn for plasma PI measurements. After centrifugation, plasma was frozen at -80°C. Plasma PI concentration was measured using validated high-performance liquid chromatography (HPLC) method and mass-spectrometry detection after specific treatment of the samples.¹² Measurement of pravastatin used a reverse-phase HPLC with ultraviolet detection.¹³

Endpoints

The primary endpoint of the study was the difference of plasma HIV RNA level between baseline and W12. The other endpoints were the differences of CD4 cell counts, plasma lipids, and PI concentrations between baseline and W12 and clinical and laboratory toxicity of pravastatin at 3 months follow-up. At last, pravastatin concentration was performed at W4 and W12.

Statistical Analysis

With a sample size of 13 patients to be recruited in each group, the study had a power to show a difference of $\geq 0.5 \log_{10}$ in HIV RNA levels between the groups at W12 with a $0.5 \log_{10} SD$ (type I error: 5%, two-sided). In accordance with the intent-to-treat principle, all patients were kept in their initial arm of randomization for the analysis. After a total of 21 patients (81%) had been randomized, the Scientific Committee halted recruitment after consultation with the Data Safety and Monitoring Board. The reason for this premature stop was the lack of new patients fulfilling inclusion criteria in the center thanks to the new therapeutic strategies to manage PI-related dyslipidemia (therapeutic windows, switch for NNRTI, triple nucleoside-based regimen or atazanavir).

HIV RNA, CD4 count, lipids, and plasma PI concentrations were compared at each follow-up visit using a Wilcoxon test. The evolution of the overall PI concentration between W0, W4, and W12 was assessed. The variation of the ratios W4 - W0/W0 and W12 - W0/W0 was studied. The differences in the values between baseline and W12 were compared to zero by the sign test or Wilcoxon signed

rank test when appropriate. Correlation coefficients between PI concentrations and pravastatin concentrations were calculated by Spearman rank correlation. Analyses were performed with SAS software, version 8.00 (SAS Institute, Inc., Cary, North Carolina, USA). A difference was considered significant when p was $< .05$.

According to the large number of patients treated with lopinavir/ritonavir, a subanalysis was conducted on these specific subgroup of patients to assess the evolution of lopinavir concentration.

RESULTS

Characteristics of the Patients at Baseline and Follow-up

There were 32 patients screened from March 2003 to December 2003. Eleven patients withdrew between screening and baseline because of TC and/or LDL-C in normal range on fasting status ($n = 8$), HIV RNA above 50 copies/mL ($n = 1$), increased creatine kinase ($n = 1$), and diagnosis of AIDS-related non-Hodgkin lymphoma ($n = 1$), and they were not included in the analysis. Twenty-one patients were included in the final analysis: 12 were assigned to the pravastatin group and 9 to the placebo group. PIs received at the time of inception of pravastatin or placebo were lopinavir/ritonavir ($n = 16$), indinavir/ritonavir ($n = 2$), saquinavir/ritonavir ($n = 1$), saquinavir ($n = 1$), and nelfinavir ($n = 1$). The characteristics of the two groups at baseline were similar with regard to clinical and laboratory characteristics (Table 1). PI and thymidine analogue exposures were not significantly different between the two groups ($p = .55$ for PI exposure; $p = .97$ for stavudine exposure; and $p = .24$ for zidovudine exposure).

One patient in the pravastatin arm prematurely discontinued the study because of seizure and hospitalization not imputed to study treatment. No patient was lost to follow-up until W12. We did not notice any change in antiretroviral therapies during the 3 months of follow-up.

Evolution of HIV RNA Level and CD4+ Cell Count up to Week 12 (Table 2)

There was no significant modification in the plasma level of HIV RNA after 12 weeks of treatment as compared with baseline value in either

Table 1. Baseline characteristics of patients ($n = 21$)

Characteristics	Pravastatin group ($n = 12$)	Placebo group ($n = 9$)
Clinical parameters		
Age, median (IQR)	42 (39–47)	41 (38–50)
Male sex (%)	92	78
Transmission category (%)	8	0
Injection drug use	58	67
Men who have sex with men	33	22
Heterosexual sex	0	11
Unknown	42	11
HIV clinical stage C	71 (62–79)	67 (64–73)
Weight, median kg (IQR)		
Antiretroviral treatment received (%)^a		
2 NRTIs + 1 PI	75	56
2 NRTIs + 2 PIs	17	11
1 NRTI + 1 NNRTI + 1 PI	0	22
1 NRTI + TNF + 1 PI	0	11
2 NRTI + TNF + 1 PI	8	0
Antiretroviral exposure, median months (IQR)		
PI exposure	21 (12–35)	52 (13–69)
d4T exposure	0 (0–16)	0 (0–29)
AZT exposure	10 (4–19)	38 (10–64)
Laboratory parameters, unit (IQR)		
CD4+ cell count, median/mm ³	465 (330–525)	484 (429–653)
HIV RNA, median log ₁₀ /mL	1.7	1.7
Total cholesterol, median mmol/L	6.1 (5.8–6.3)	6.4 (6.1–7.7)
HDL-cholesterol, median mmol/L	0.9 (0.8–1.1)	1.0 (0.8–1.1)
LDL-cholesterol, median mmol/L	4.1 (3.7–4.6)	3.9 (3.7–4.8)
Triglycerides, median mmol/L	2.0 (1.1–3.3)	3.2 (2.1–4.4)
Apolipoprotein A1, median g/L	1.3 (1.2–1.4)	1.3 (1.1–1.8)
Apolipoprotein B, median g/L	1.3 (1.1–1.4)	1.4 (1.2–1.5)
Total cholesterol/HDL	6.6 (5.5–8.1)	6.7 (5.8–8.0)
Apo B/Apo A1	1.0 (0.7–1.1)	0.9 (0.8–1.1)

Note: IQR = interquartile range; NRTI = nucleoside reverse transcriptase inhibitors; NNRTI = non-nucleoside reverse transcriptase inhibitors; PI = protease inhibitors; TNF = tenofovir; d4T = stavudine; AZT = zidovudine; HDL = high-density lipoprotein.

^aPI received: lopinavir/ritonavir ($n = 16$), indinavir/ritonavir ($n = 2$), saquinavir/ritonavir ($n = 1$), saquinavir ($n = 1$), and nefatinavir ($n = 1$).

group. Two patients in the pravastatin group had an increased HIV RNA to 1.80 and 2.16 log₁₀ copies/mL at W4, but all patients in the pravastatin group and the placebo group had an HIV RNA below 1.7 log₁₀ copies/mL at W12. Then, the median difference (W12 minus baseline) was zero in both groups ($p = 1.00$). The median difference of CD4+ cell count/mm³ was -4 (interquartile range [IQR], -48 to 47) in the pravastatin group and +50 (IQR, -9 to 223) in the placebo group ($p = .29$).

Evolution of Plasma Lipid Levels Up to Week 12

Of the 12 treated patients, the median difference (W12 - W0) of TC was -1.4 mmol/L ($p = .02$) as compared with the placebo group +0.2 mmol/L ($p = .18$; $p = .005$ for the difference between the two groups). LDL-C decreased significantly in the pravastatin group (-1.0 mmol/L; $p = .01$) and remained stable in the placebo group (0.3; $p = .51$; $p = .007$ for the difference between the two groups). Eight of the 11 patients treated with pravastatin reached the level

of 5.5 mmol/L for TC and 3.4 mmol/L for LDL-C at W12 and only one of the placebo group. Levels of HDL-C, triglycerides, and apolipoprotein A1 were not modified in any of both groups during follow-up. Atherogenic ratio TC/HDL-C decreased in the pravastatin group but not in the placebo group ($p = .001$).

Protease Inhibitor Concentrations

The evolution of the overall PI concentration between W0 and W12 showed a significant decrease of the ratio W12 - W0/W0 at trough in the pravastatin group (-0.2) ($p = .03$) as compared with the placebo group (+0.1) ($p = .51$; $p = .03$ for the difference between the two groups) (Table 2). Eight of 12 patients (67%) had a decrease of PI concentration at W4 and 7 of 11 (64%) at W12 in the pravastatin group. On the opposite, in the placebo group three of the nine patients had a decrease at W4, and only two were under their baseline dosage at W12. When this analysis was restricted to lopinavir-treated patients ($n = 16$), we noticed a significant decrease of the lopinavir concentration between W0 and W12 at trough (-0.9 µg/mL, $p = .04$), and this difference was at the limit of significance when compared with the evolution in the placebo group (+0.3 µg/

mL between W0 and W12; $p = 1.00$; $p = .09$ for the difference between the two groups) (Table 3). Overall PI concentrations and lopinavir concentration around 3 hours after the morning intake were not modified during follow-up (Tables 2 and 3).

Pravastatin Concentration

At W4 and W12, median pravastatin plasma concentrations measured 12 hours after the last intake (evening administration) were 13.5 ng/mL (range, 7.6–14.8) and 13.7 ng/mL (range, 6.8–16.2), respectively. The two patients with the lower pravastatin concentrations (below 8 ng/mL) at W4 and W12 were also treated with nelfinavir on one hand and with amprenavir/ritonavir on the other. We noticed a significant positive correlation between the plasma level of PIs just before the morning intake and pravastatin at W12 ($R = 0.73$, $p = .02$).

Adverse events

A total of 12 clinical adverse events in seven patients in the pravastatin group and five events in three patients in the placebo group were recorded. Myalgias (grade 2) were recorded in three patients of the pravastatin group (including one with a two-

Table 2. Median differences (W12 minus W0) of laboratories parameters and comparison between pravastatin and placebo group.

Parameters	Pravastatin group		Placebo group		p^{**}
	Median (IQR)	p^*	Median (IQR)	p^*	
HIV RNA (\log_{10} copies/mL)	-0 (0 to 0)		0 (0 to 0)		1.00
CD4+ cell count/mm ³	-4 (-48 to 47)	1.00	50 (-9 to 223)	.51	.29
Total cholesterol, mmol/L	-1.4 (-1.7 to -0.9)	.02	0.2 (0.1 to 0.2)	.18	.005
LDL-cholesterol, mmol/L	-1.0 (-1.5 to -0.6)	.01	0.3 (-0.3 to 0.4)	.51	.007
HDL-cholesterol, mmol/L	0.09 (0.04 to 0.09)	.18	-0.01 (-0.07 to 0.11)	1.00	.40
Triglycerides, mmol/L	-0.04 (-0.2 to 0.2)	1.00	-0.1 (-0.6 to 0.2)	1.00	.70
Apolipoprotein A1, g/L	0.10 (-0.01 to 0.22)	.11	0.04 (-0.24 to 0.08)	.73	.23
Apolipoprotein B, g/L	-0.34 (-0.43 to -0.12)	.02	0.02 (-0.20 to 0.18)	1.00	.01
Total cholesterol/HDL	-1.71 (-2.80 to -0.74)	.004	0.15 (-0.04 to 0.47)	.45	.001
Apo B/ApoA1	-0.18 (-0.39 to -0.12)	.002	0.07 (-0.03 to 0.09)	.73	.001
PI concentration at trough (ratio of variation: W12 - W0/W0)	-0.2 (-0.3 to -0.1)	.03	0.1 (-0.02 to 0.3)	.51	.03
PI concentration 3 hours after intake (ratio of variation: W12 - W0/W0)	0.03 (-0.1 to 0.1)	.85	0.03 (-0.02 to 0.06)	1.00	.96

Note: IQR = interquartile range; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PI = protease inhibitor.

*Sign or Wilcoxon signed rank test. **Wilcoxon test

Table 3. Evolution of lopinavir concentration in placebo and pravastatin between week 0 and week 12

Lopinavir concentration	Week 0			Week 12			Median evolution W12 - W0		
	Pravastatin Median (IQR)	Placebo Median (IQR)	p	Pravastatin Median (IQR)	Placebo Median (IQR)	p	Pravastatin Median (IQR)	Placebo Median (IQR)	p
At trough (just before the morning administration), µg/mL	3.8 (3.5–4.9)	4.0 (2.7–5.0)	.92	2.9 (2.5–3.8)	4.0 (3.1–4.7)	.10	-0.9 (-1.3 to -0.4)	.04 (-1.2 to 1.0)	1.00
Around C _{max} (3 hours after the morning administration), µg/mL	7.5 (5.1–12.7)	7.1 (5.4–11.1)	.60	8.8 (8.0–9.7)	8.2 (7.6–9.5)	.07	-0.02 (-1.4 to 1.1)	.81 (-1.0 to 0.6)	1.00

fold increase of creatine phosphokinase [CPK] and in one patient of the placebo group, digestive symptoms in four and three, depressive symptoms in one and zero, headache in one and zero, and others in three and one, respectively. One patient in the pravastatin group prematurely discontinued the study because of seizure and hospitalization not related to study treatment, and another patient in the pravastatin group temporarily stopped his treatment because of diarrhea between W4 and W12. We noticed no significant change of aspartate aminotransferase, alanine aminotransferase, bilirubin, glucose, CPK, and myoglobin during follow-up in both groups. Two patients of the pravastatin group had a two-fold increase of CPK and myoglobin at W4 (adverse event grade 1), and one patient of the placebo group had a two-fold increase of CPK at W4. All these abnormalities were normalized at W8.

DISCUSSION

This randomized study suggests that the use of pravastatin in PI-treated patients does not induce major change in the plasma HIV RNA on 12 weeks of follow-up. However, we found a trend of decrease of the trough PI concentration at W12 suggesting a possible drug-drug interaction of pravastatin on PI metabolism. Three previous studies evaluated PI pharmacokinetics in healthy volunteers and HIV-infected patients treated with PI showing no

impact of pravastatin on PI trough and postdose exposure.^{10,14,15} Nevertheless, the PIs used were different as most of our patients were treated with boosted PIs, mainly lopinavir/ritonavir, that were poorly evaluated in these previous studies, and similar results were observed when our analyses were restricted to patients treated with lopinavir/ritonavir. The clinical implication of this interaction may be minimal. However, plasma trough concentrations of PI are associated with their efficacy in pharmacokinetics studies, and a significant decrease of plasma trough concentration is generally associated with an increased risk of virological failure, especially in treatment-experienced patients.¹⁶ Our results at W12 did not show any virological failure thanks to the high lopinavir plasma concentration observed in our study. However, in heavily pretreated patients, such a decrease particularly below 3.5 µg/L could lead to virological failure.¹⁶

Pravastatin is usually recommended in the context of hypercholesterolemia-associated PI because it is eliminated by metabolic routes other than cytochrome P450, also implicated in the metabolism of PI. However, if pravastatin is less subject to interaction with cytochromes, drug-drug interactions have been previously reported with cyclosporine, warfarin, and fibrates, suggesting that pravastatin could interact with other therapies through ways other than CYP3A4. At the present time, this is still unclear. The mechanism underlying the interactions between pravastatin and PIs may be due

to a competition at the cytochrome level and the transports protein P-glycoprotein level and may also be related to the genetic polymorphism.¹⁷ The combination of statins (pravastatin, simvastatin, lovastatin, fluvastatin) with warfarin leads to an increased plasma concentration of anticoagulant and to excessive anticoagulation,^{18–21} probably through a displacement of anticoagulant from binding sites. Simvastatin and atorvastatin have also been found to increase plasma digoxin concentrations.^{22,23} Recently, simvastatin has been found to significantly reduce the plasma diltiazem concentration through an unclear mechanism.²⁴

Our study does have limitations. It is a single-center study with a small number of patients included and a lack of power. Twelve weeks of follow-up may not have been enough time to confidently interpret the main objective of the study, namely HIV-RNA at W12, and the comparison of the PI plasma levels was not the main objective of our study. However, this study was randomized and placebo-controlled, and the results regarding the changes of PI concentration are clearly different between the two arms, suggesting a possible new drug-drug interaction for pravastatin on PIs, even if other confounding factors cannot be excluded.

The use of pravastatin 40 mg in PI-treated patients was safe as we noticed no severe side effects during the 3 months of follow-up, similar to other cohort and therapeutic studies.^{15,25,26} However, more than half of pravastatin-treated patients complained of at least one side effect of the treatment; it is difficult to systematically incriminate pravastatin in these troubles because of the lack of specificity of these side effects, which can be also mediated by antiretrovirals. The biological tolerance of pravastatin was also good with no significant modification of the muscular (CPK) and hepatic enzymes during follow-up. The decrease of TC (23%) and of LDL-C (24%) with pravastatin 40 mg was in the same magnitude as observed in other controlled studies in HIV and non-HIV-infected people and is associated with reductions in concentrations of atherogenic lipoproteins.^{25–27} However, 8 of 11 patients recovered a normal LDL-C value at W12, and as previously described pravastatin had no influence on the evolution of HDL-C. These results are much better than those of Mallon et al., but their patients had a higher plasma level of cholesterol at baseline suggesting that these patients could be exposed to a greater perturbation of cholesterol homeostasis.

However, baseline values of cholesterol were considered before diet advice, explaining in part the higher baseline cholesterol level of this study.¹¹

We have shown in this study that the use of pravastatin in PI-treated patients is not associated with virological failure and is safe over a 3-month follow-up period. However, due to a possible drug-drug interaction, the assessment of plasma PI trough concentrations should be evaluated, especially in PI-experienced patients requiring therapy with statins.

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