Significant Decrease in Plasma Levels of D-Dimer, Interleukin-8, and Interleukin-12 After a 12-Month Treatment with Rosuvastatin in HIV-Infected Patients Under Antiretroviral Therapy

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Abstract

Objectives: Statins have shown anti-inflammatory and immune-modulatory properties in both general and HIV-infected population, but their effect on plasma D-dimer levels is controversial and it has not been investigated to date in HIV-positive patients. The aim of our study was to assess the effect of rosuvastatin on D-dimer and other serum inflammation markers among these subjects.

Methods: Prospective, cohort study of HIV-1-infected adult patients receiving a stable combination antiretroviral therapy (cART), who started a lipid-lowering therapy with rosuvastatin (10 mg daily) and were followed up for at least 12 months. The primary endpoint was the change at month 12 in the median plasma concentration of D-dimer. The secondary endpoints included the variation in median plasma levels of these inflammatory biomarkers: interleukin-8 (IL-8), interleukin-10 (IL-10), and interleukin-12 (IL-12).

Results: Sixty-two patients were enrolled in the study, and the endpoints were available for 54 subjects. After 12 months, a significant decrease in median plasma concentration of D-dimer was observed (−21.4%; interquartile range [IQR], −35.5; −4.2; $p = .029$). With regard to the inflammatory biomarkers, a significant decrease in median levels of IL-8 (−24.6%; IQR, −30.8; −1.8; $p = .012$) and IL-12 (−18.7%; IQR, −25.8; +2.5; $p = .033$) was also observed. Rosuvastatin led to a significant reduction in serum lipid values and showed a good tolerability profile.

Conclusions: Our findings show that a 12-month treatment with rosuvastatin associated with an effective cART can significantly decrease the plasma levels of D-dimer, IL-8, and IL-12, and suggest a potential role for this statin to reduce activated coagulation and systemic inflammation among HIV-infected persons.

Keywords: HIV, immune activation, antiretroviral therapy, inflammation

Introduction

CHRONIC INFLAMMATION and systemic immune activation are known to play a crucial role in the progression of HIV disease and the occurrence of noninfectious HIV-associated comorbidities, such as cardiovascular diseases. Although both inflammation and immune activation are certainly reduced by the virological suppression associated with the combination antiretroviral therapy (cART), residual inflammation and/or immune activation persist in virologically suppressed HIV-infected patients and may lead to the increased morbidity/mortality observed in subjects with comorbidities.^{1–4}

The identification of therapeutic approaches able to significantly reduce the residual systemic inflammation in pa-

tients on cART is today a crucial challenge to define the optimal therapeutic strategy for the long-term management of the HIV disease.

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, are known to produce a potent lipid-lowering effect by inhibiting the synthesis of mevalonate, the precursor of sterols. At the same time, these agents have significant anti-inflammatory and immunomodulatory properties in the general population, independent of their lipid-lowering effects, and they can slow down the atherosclerotic disease progression, as demonstrated by several randomized and observational studies.^{5–8}

Recent experimental and clinical studies have shown that statins may also act on the coagulation cascade at several

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levels, leading to a decreased coagulation activity and thrombosis by inhibiting platelet activation, decreasing tissue plasminogen activator (tPA) and plasminogen activator inhibitor-I (PAI-I), increasing the activity of protein C anticoagulant pathway, and producing various effects on intracellular signaling molecules such as nuclear factor (NF)- κ B and Kruppel-like factor 2 (KLF2). However, the effect of statins on plasma D-dimer, the mostly used circulating marker of activated coagulation, is still controversial.^{9–11}

Some clinical studies have demonstrated anti-inflammatory and immunomodulatory properties of statins in HIV-infected people too, but data are limited and not always concordant.^{12,13} Moreover, data are still lacking about the statin effect on the coagulation markers in HIV-infected patients.

The aim of our observational, prospective study is to evaluate the effect of a 12-month treatment with rosuvastatin on plasma levels of D-dimer, IL-8, IL-10, and IL-12 in adult HIV-infected subjects under suppressive cART.

Patients and Methods

A prospective cohort analysis of HIV-1-infected adult patients followed at our Clinic of Infectious Diseases, receiving a stable cART and starting a rosuvastatin treatment was performed. Inclusion criteria were as follows: adult patients receiving cART for at least 24 months, unchanged cART during the last 12 months, plasma HIV RNA <20 copies/ml for at least 6 months, current CD4⁺ T lymphocyte count ≥ 500 cells/mm³, and beginning a lipid-lowering therapy with rosuvastatin (10 mg daily) from January 1, 2013, through December 31, 2014.

Exclusion criteria were active opportunistic diseases or severe infectious diseases, acute or chronic hepatitis B virus (HBV) infection, acute or chronic hepatitis C virus (HCV) infection, acute or chronic inflammatory diseases, known cardiovascular diseases (coronary artery disease, peripheral vascular disease, or cerebrovascular disease), diabetes mellitus, alcohol or drug abuse, hypothyroidism, Cushing's syndrome, acute or chronic myopathy, acute or chronic kidney diseases, liver cirrhosis, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >80 U/L, creatinine >1.2 mg/dl, creatine phosphokinase (CPK) >150 U/L, pregnancy, or an underlying treatment with corticosteroids, androgens, estrogens, growth hormones, thiazide diuretics, beta-blockers, thyroid preparations, proton pump inhibitors, acid-reducing agents, statins, or other lipid-lowering drugs.

All enrolled subjects were followed up for 12 months. Patients were excluded from the final evaluation if they had any change in the current lipid-lowering treatment or in the current antiretroviral regimen during the 12-month follow-up, or if they had not a regular 12-month follow-up. The study was approved by the Ethics Committee of the S.Orsola-Malpighi Hospital in Bologna and all the enrolled patients provided a signed written consent before participating in the study.

The following demographic, clinical, and laboratory data were recorded at the start of therapy and at 3-month intervals during the 12-month follow-up: sex, age, race, body mass index (BMI), arterial pressure, clinical manifestations; serum levels of D-dimer, IL-8, IL-10, IL-12; plasma lipid levels (triglycerides, total cholesterol, LDL cholesterol, and HDL cholesterol), HIV RNA, CD4⁺ T lymphocyte count, glucose, complete liver and kidney function tests, CPK, aldolase, and

urinalysis. All the plasma samples were analyzed for HIV-RNA level using the automated COBAS AmpliPrep Instrument for specimen processing and the COBAS TaqMan Analyzer for amplification and detection (Roche Cobas AmpliPrep/Cobas TaqMan HIV-1 tests version 2.0; Roche Diagnostics, Mannheim, Germany). The limit of quantification, as defined by the manufacturer, was reduced to 20 copies/ml. Virologic failure was defined by a confirmed plasma HIV RNA ≥ 20 copies/ml and a virological blip as a plasma HIV RNA between 20 and 200 copies/ml followed by a plasma HIV RNA <20 copies/ml. D-dimer, IL-8, IL-10, and IL-12 concentrations were measured by a sandwich immunological assay by an EVIDENCE analyzer (Medical Systems, Genova, Italy).

Adherence to the current therapy was carefully checked on the outpatient visits by self-reported questionnaires.

The primary endpoint was the variation between baseline and month 12 in median plasma concentration of D-dimer. The secondary endpoints included the variation during the 12-month follow-up in median plasma levels of the inflammatory biomarkers (IL-8, IL-10, and IL-12), serum lipid values (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides), and incidence of adverse events.

The aim of the study was to evaluate whether the rosuvastatin treatment could lead to a $\geq 10\%$ decrease in the median concentration of D-dimer and inflammatory biomarkers between baseline and month 12. Assuming an SD of 20%, a power of 80%, a type I error of 0.05, and a two-tailed Wilcoxon paired test, 40 patients needed to be enrolled in the study. Variables were described by using proportions for categorical variables, median and interquartile range (IQR) for continuous variables. To compare the variations in continuous variables between baseline and month 12, the Wilcoxon paired test was used. All reported *p*-values are two tailed and *p*-values of <.05 were considered as statistically significant.

Results

Sixty-two patients were enrolled into the study and 55 subjects completed the study. Reasons for discontinuation were adverse events for four subjects (diarrhea in two cases and nausea in two cases) and virological failure with change in current cART for three subjects. All primary and secondary endpoints were available for only 54 patients who completed the study, because of missing data in one case.

Median age of the 62 enrolled patients was 46.4 years (IQR, 40.3; 55.6), 48 (77.4%) patients were men, and 57 (91.9%) were white. Median current CD4⁺ lymphocyte count was 552 cells/mm³ (IQR, 366; 749), median duration of current cART was 35 months (IQR, 26; 47), and median duration of plasma HIV RNA <20 copies/ml was 32 months (IQR, 25; 49). Patients with total cholesterol >200 mg/dl were 49 (79%) and those with triglycerides >200 mg/dl were 41 (66.1%). Ongoing cART included tenofovir/emtricitabine in 37 cases (59.7%), abacavir/lamivudine in 25 cases (40.3%), a ritonavir-boosted protease inhibitor (PI/r) in 35 cases (56.5%), and efavirenz in 27 cases (43.5%).

Demographic, clinical, and laboratory characteristics of the 54 patients who completed the study and were evaluated are summarized in Table 1.

Table 2 shows changes during the 12-month rosuvastatin treatment in median plasma concentrations of D-dimer, IL-8,

TABLE 1. DEMOGRAPHIC, CLINICAL, AND LABORATORY CHARACTERISTICS OF PATIENTS WHO COMPLETED THE STUDY AND WERE ANALYZED

Total number	54
Males, no. (%)	45 (83.3)
White subjects, no. (%)	51 (94.4)
Age (years), median (IQR)	46.8 (40.6–55.9)
HIV transmission risk category, no. (%)	
IDU	3 (5.5)
MSM	28 (51.8)
Heterosexual	23 (42.6)
Nadir CD4 ⁺ lymphocyte count (cells/mm ³), median (IQR)	223 (149–315)
Current CD4 ⁺ lymphocyte count (cells/mm ³), median (IQR)	564 (388–767)
Duration of HIV infection (years), median (IQR)	9.7 (4.8–14.7)
Duration of current cART (months), median (IQR)	37 (25–49)
Cumulative exposure to cART (years), median (IQR)	7.6 (5.5–13.7)
Duration of plasma HIV RNA <20 copies/ml with current cART (months), median (IQR)	34 (23–46)
BMI (Kg/m ²), median (IQR)	23.2 (21.9–24.8)
Cigarette smokers, no. (%)	31 (57.4)
Patients with arterial hypertension, no. (%)	9 (16.7)
Glucose (mg/dl), median (IQR)	82 (61–107)
Insulin (ng/mol), median (IQR)	0.51 (0.32–0.84)
Total cholesterol (mg/dl), median (IQR)	239 (186–262)
LDL cholesterol (mg/dl), median (IQR)	141 (119–172)
HDL cholesterol (mg/dl), median (IQR)	49 (35–64)
Triglycerides (mg/dl), median (IQR)	256 (211–295)
Patients with total cholesterol >200 mg/dl, no. (%)	47 (87)
Patients with triglycerides >200 mg/dl, no. (%)	38 (70.4)
Current cART, no (%)	
Tenofovir/emtricitabine	32 (59.2)
Abacavir/lamivudine	22 (40.7)
Efavirenz	24 (44.4)
Darunavir/ritonavir	18 (33.3)
Atazanavir/ritonavir	12 (22.3)

IQR, interquartile range; IDU, injection drug users; MSM, men who have sex with men; cART, combination antiretroviral therapy; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

IL-10, and IL-12 in the whole study population. A statistically significant decrease in median plasma concentration of D-dimer in comparison with the baseline value was reported after both 6 months (–20.2%) and 12 months (–21.4%). With regard to the inflammation markers, a significant reduction in median plasma levels both at month 6 and at month 12 was observed for IL-8 (–21.7% and –24.6%, respectively) and IL-12 (–23.4% and –18.7%, respectively). On the contrary, median concentration of IL-10 decreased but not significantly during the 12-month follow-up.

Changes in coagulation and inflammation markers were also analyzed according to the current cART. When considering the subgroups of patients taking tenofovir/emtricitabine (32 subjects) or abacavir/lamivudine (22 subjects), we found

TABLE 2. BASELINE VALUES AND CHANGES AFTER 6 AND 12 MONTHS IN PLASMA D-DIMER AND INFLAMMATION MARKERS

	Baseline (N = 62)	Month 6 (N = 57)	Percentage change at month 6	p-value (vs. BL)	Month 12 (N = 54)	Percentage change at month 12	p-value (vs. BL)
D-Dimer (ng/ml), median (IQR)	345 (166; 445)	275 (149; 381)	–20.2% (–31.3; –3.1)	.018	268 (167; 379)	–21.4% (–35.5; –4.2)	.029
IL-8 (pg/ml), median (IQR)	18.4 (10.2; 24.6)	14.3 (7.8; 19.5)	–21.7% (–27.8; +2.5)	.041	13.6 (6.4; 20.2)	–24.6% (–30.8; –1.8)	.012
IL-10 (pg/ml), median (IQR)	21.3 (12.6; 33.4)	18.6 (9.5; 26.4)	–12.6% (–20.4; +6.5)	.089	17.8 (8.6; 27.2)	–16.2% (–24.5; +5.9)	.068
IL-12 (pg/ml), median (IQR)	15.6 (7.5; 27.9)	11.9 (4.7; 22.4)	–23.4% (–30.2; –3.1)	.002	12.7 (4.6; 18.7)	–18.7% (–25.8; +2.5)	.033

Values in *bold* are statistically significant.

BL, baseline; IQR, interquartile range; IL-8, interleukin-8; IL-10, interleukin-10; IL-12, interleukin-12.

that changes in D-dimer, IL-8, and IL-12 were significant between baseline and month 12 for each subgroup, without significant difference between these two subgroups (Table 3). In the same way, changes between baseline and month 12 in D-dimer, IL-8, and IL-12 were significant in both subgroups of patients taking a PI/r (30 subjects) or efavirenz (24 subjects), without significant difference between these two subgroups (Table 4). On the contrary, changes from baseline to month 12 in serum concentration of IL-10 were not significant in all these four subgroups (Tables 3 and 4).

After 12 months of treatment, rosuvastatin led to a statistically significant reduction in median levels of total cholesterol, LDL cholesterol, and triglycerides versus respective baseline values. The observed changes in median lipid concentrations were -23.2% (IQR, -30.3 ; -9.8 ; $p < .001$) for total cholesterol, -25.4% (IQR, -32.1 ; -10.6 ; $p = .021$) for LDL cholesterol, and -19.2% (IQR, -27.8 ; -5.6 ; $p = .027$) for triglycerides. The change in median HDL cholesterol was not significant (-4.2% ; IQR, -9.4 ; $+3.3$; $p = .766$).

Changes in median levels of glucose and insulin were not significant. Median glucose concentration (IQR) at baseline and after 12 months was 82 (61–107) and 84 (63–106) mg/dl, respectively ($p = .388$); median insulin concentration (IQR) at baseline and after 12 months was 0.51 (0.32–0.84) and 0.58 (0.41–0.89) ng/mol, respectively ($p = .078$).

When considering immunological and virological parameters, mean CD4⁺ lymphocyte count and percentage of patients with undetectable plasma HIV viral load did not significantly change during the hypolipidemic treatment, showing neither appreciable interaction between antiretroviral drugs and rosuvastatin nor significant immunological effects of the lipid-lowering agents. Change in median CD4⁺ lymphocyte count during the 12-month follow-up was $+41$ cells/mm³ (IQR, -12 ; $+79$; $p = .578$) and all the 54 evaluated patients had plasma HIV RNA <20 copies/ml at month 12. A virological failure was observed in 3 out of the 62 enrolled patients (4.8%), leading to a change in current cART, but genotype testing did not show any resistance mutations for the antiretroviral drugs. The adherence level to cART was $<95\%$ in all these three patients. A viral blip was observed in five subjects (8.1%), but no viral blips were reported in patients with virological failure.

Other parameters, which could produce some effects on the inflammation biomarkers, did not present significant variations during the entire follow-up period. The median BMI (IQR) changed from 23.2 (21.9–24.8) kg/m² at baseline to 23.1 (21.7–24.9) kg/m² at month 12 ($p = .702$). Similarly, the number of cigarette smokers changed from 31 (57.4%) to 30 (55.5%; $p = .887$).

Serious toxicity associated with discontinuing statin therapy occurred in 4 out of the 62 enrolled patients (6.4%) and was represented by diarrhea in 2 cases and nausea in 2 cases. Toxicity not associated with statin discontinuation occurred in 13 patients (20.9%) and was represented by gastrointestinal symptoms (nausea and diarrhea) in 8 subjects (12.9%), myalgias in 5 (8.1%), headache in 4 (6.4%), and mild elevation in the creatine kinase (CK) concentration (always below 300 U/L) in 4 (6.4%).

Discussion

Several clinical studies have proved the anti-inflammatory effects of statins and their ability to reduce the serum

TABLE 3. BASELINE VALUES AND CHANGES AFTER 12 MONTHS IN PLASMA D-DIMER AND INFLAMMATION MARKERS IN PATIENTS TREATED WITH A CART, INCLUDING TENOFOVIR/EMTRICITABINE OR ABACAVIR/LAMIVUDINE

	Group A (TDF/FTC)				Group B (ABC/3TC)			
	Baseline (N = 37)	Month 12 (N = 32)	Percentage change at month 12	p-value (vs. BL)	Baseline (N = 25)	Month 12 (N = 22)	Percentage change at month 12	p-value (vs. BL)
D-Dimer (ng/ml), median (IQR)	339 (157; 431)	271 (144; 367)	-22.5% (-32.6 ; -5.4)	.004	352 (166; 418)	277 (158; 342)	-20.4% (-35.5 ; -4.2)	.037
IL-8 (pg/ml), median (IQR)	17.9 (9.5; 23.6)	14.1 (8.4; 19.2)	-26.5% (-28.6 ; $+0.9$)	.028	18.3 (10.4; 25.6)	13.3 (5.9; 21.5)	-25.2% (-32.1 ; -3.8)	.006
IL-10 (pg/ml), median (IQR)	23.2 (14.6; 35.2)	18.1 (8.5; 29.2)	-14.8% (-19.9 ; $+7.1$)	.265	21.8 (12.6; 33.7)	16.7 (7.9; 25.8)	-17.3% (-22.7 ; $+6.8$)	.322
IL-12 (pg/ml), median (IQR)	14.3 (7.1; 24.6)	11.1 (5.2; 20.4)	-22.5% (-32.1 ; -4.6)	<.001	16.4 (5.5; 27.1)	13.1 (4.6; 18.7)	-20.2% (-27.3 ; $+0.7$)	.018

p-value*, referring to group A versus group B value at month 12.

Values in **bold** are statistically significant.

TDF/FTC, tenofovir/emtricitabine; ABC/3TC, abacavir/lamivudine.

TABLE 4. BASELINE VALUES AND CHANGES AFTER 12 MONTHS IN PLASMA D-DIMER AND INFLAMMATION MARKERS IN PATIENTS TREATED WITH A cART, INCLUDING A RITONAVIR-BOOSTED PROTEASE INHIBITOR OR EFVIRENZ

	Group A (PI/r)				Group B (EFV)			
	Baseline (N=35)	Month 12 (N=30)	Percentage change at month 12	p-value (vs. BL)	Baseline (N=27)	Month 12 (N=24)	Percentage change at month 12	p-value (vs. BL)
D-Dimer (ng/ml), median (IQR)	341 (178; 446)	263 (159; 382)	-22.8% (-34.7; -7.2)	<.001	352 (189; 447)	285 (178; 361)	-19.3% (-31.6; -1.9)	.041
IL-8 (pg/ml), median (IQR)	19.3 (8.7; 26.2)	15.1 (6.2; 20.2)	-21.9% (-27.8; -2.2)	.008	18.4 (11.5; 28.7)	14.2 (5.1; 19.6)	-22.6% (-30.4; -5.2)	.027
IL-10 (pg/ml), median (IQR)	24.1 (12.3; 37.9)	20.1 (10.2; 32.6)	-16.2% (-20.5; +5.1)	.061	20.6 (10.1; 30.8)	16.9 (8.5; 27.2)	-15.2% (-19.2; +5.8)	.209
IL-12 (pg/ml), median (IQR)	16.7 (8.9; 27.8)	11.4 (5.2; 20.4)	-27.9% (-38.2; -9.4)	<.001	14.2 (6.6; 25.2)	10.1 (4.2; 19.4)	-29.1% (-36.8; -8.2)	<.001

p-value*, referring to group A versus group B value at month 12.
Values in *bold* are statistically significant.
PI/r, ritonavir-boosted protease inhibitor; EFV, efavirenz.

concentration of some inflammatory biomarkers among HIV-infected patients.

A randomized, double-blind trial investigated the effect of a 45-day course of pravastatin (40 mg daily) or rosuvastatin (10 mg daily) on the high-sensitive C-reactive protein (hsCRP) concentration in 58 dyslipidemic HIV-positive patients. All the enrolled patients were treated with a PI/r-based cART and had a baseline hsCRP <10 mg/L. At the end of follow-up, statins led to a significant decrease in the median hsCRP level (-20% overall), without correlation with changes in lipid parameters. No significant reductions were reported in median levels of other biomarkers, such as soluble tumor necrosis factor- α receptor-1 and -2 (TNFR-1 and -2), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1).¹⁴

In a previous retrospective analysis of 151 HIV-infected patients receiving a stable cART including one PI/r and affected by hypercholesterolemia, we have assessed the anti-inflammatory effect of treatment with rosuvastatin (10 mg daily), atorvastatin (10 mg daily), or pravastatin (40 mg daily). After 12 months, all statins led to a similar and significant decrease in serum concentration of hsCRP (-23% overall) and tumor necrosis factor- α (TNF- α) (-28% overall), without correlation between inflammation markers and lipid parameters.¹⁵

We have also evaluated the effects of rosuvastatin plus cART on several biomarkers (hsCRP, IL-6, IL-8, and TNF- α) in a prospective, observational study, including 86 antiretroviral-naïve HIV-infected patients starting tenofovir/emtricitabine/efavirenz. After 12 months, patients with hypercholesterolemia and treated with cART plus rosuvastatin (10 mg daily) had a significantly greater decrease in serum levels of hsCRP and TNF- α than those with normal cholesterol levels and taking cART only. Changes in hsCRP were -35.1% versus -8.2%, and changes in TNF- α were -22.4% versus -5.4%, respectively.¹⁶

In a randomized controlled trial, 50 HIV-positive persons with mixed dyslipidemia were treated for 3 months with high-dose rosuvastatin (40 mg daily) or 10 mg/day rosuvastatin plus 2 g/day of omega-3 polyunsaturated fatty acids (PUFAs) to assess changes in plasma levels of vascular endothelial growth factor (VEGF) and IL-8. Both rosuvastatin monotherapy and rosuvastatin plus PUFAs reduced significantly the IL-8 levels, while only high-dose rosuvastatin reduced significantly the VEGF values.¹⁷

The SATURN randomized, placebo-controlled trial evaluated the effects of rosuvastatin (10 mg daily) on the inflammation and immune activation markers in 147 HIV-infected patients under cART, with normal LDL cholesterol, but with evidence of either heightened T cell activation or level of high-sensitivity C-reactive protein (hsCRP) $\geq$ 2 mg/L. After 48 weeks, rosuvastatin led to a significant reduction in soluble CD14 (sCD14), lipoprotein-associated phospholipase A2, and interferon gamma-inducible protein-10 (IP-10) concentrations compared to placebo.¹⁸

Data about the immunomodulatory effects of statins are more limited and conflicting, in part.

A randomized, double-blind, placebo-controlled study investigated the effect of high-dose atorvastatin (80 mg daily) on HIV RNA and cellular markers of immune activation in 24 HIV-infected subjects not receiving cART. After 8 weeks of therapy, atorvastatin did not affect plasma HIV RNA but significantly decreased the proportion of activated T

lymphocytes, such as CD4⁺ HLA-DR⁺, CD8⁺ HLA-DR⁺, and CD8⁺ HLA-DR⁺ CD38⁺ T cells.¹⁹

In the SATURN trial, a 24-week treatment with rosuvastatin led to a significant decrease in serum markers of monocyte activation, such as sCD14 and tissue factor-positive patrolling monocytes, but no changes in levels of T cell activation were observed.²⁰ In a randomized, placebo-controlled study including 28 treatment-naïve HIV-infected men, rosuvastatin (20 mg daily) for 8 weeks produced a small but significant increase in the CD4/CD8 T lymphocyte ratio, but did not influence other markers of T cell activation.²¹

The IMEA 043-CESAR study is a pilot prospective study investigating changes in the proportion of activated T lymphocytes in 43 HIV-infected subjects under suppressive cART, with CD4 count <500 cells/mm³ and treated with rosuvastatin (20 mg daily) for 12 weeks. At the end of statin treatment, the proportion of CD8⁺ T lymphocytes coexpressing CD38 and HLA-DR did not change significantly, but the proportion of CD38⁺ CD8 T cells significantly decreased and this reduction remained significant 12 weeks after the statin interruption. Particularly, the proportion of activated CD8 T lymphocytes significantly decreased only in the subgroup of subjects with high baseline CD8 T cell activation. No significant variations in the plasma levels of hsCRP, IL-6, CD14, and D-dimers between baseline and week 12 were reported.²²

In our observational analysis, a 12-month treatment with rosuvastatin at 10 mg daily was effective to significantly reduce plasma levels of D-dimer and of two inflammatory markers (IL-8 and IL-12) in 54 HIV-infected patients under suppressive cART. This is the second study investigating the effect of statins on the D-dimer among HIV-positive persons, after the study by Weiss *et al.*²² but is the first study showing a significant decrease in the D-dimer level associated with statin therapy in HIV-positive people.

IL-8 is a chemokine produced by macrophages and endothelial cells, which induces chemotaxis in neutrophils and angiogenesis. IL-12 is an interleukin produced by macrophages and dendritic cells, which is involved in the differentiation of naïve T cells into Th1 cells. These chemokines are key mediators associated with systemic inflammation and with endothelial dysfunction,²³ but no data about these markers in HIV-infected patients on statin therapy were published to date. So, in the present study, we have evaluated changes in D-dimer, IL-8, IL-10, and IL-12 to analyze the effect of statin treatment on these coagulation and inflammation markers, while its effect on hsCRP, IL-6, and TNF-alpha was already evaluated in our previous reports.^{15,16}

Moreover, the observed changes in serum levels of D-dimer and biomarkers, even if statistically significant, are quite small, so their clinical significance is still unknown, in particular, in patients with a low cardiovascular disease risk. However, the capability of rosuvastatin in decreasing plasma levels of these biomarkers seems to confirm the potential role of these lipid-lowering drugs as anti-inflammatory agents among HIV-infected subjects.

Although some authors have reported an increased risk of insulin resistance and diabetes mellitus in association with statins among HIV-infected patients,^{24,25} in the present study, rosuvastatin treatment did not alter serum levels of both glucose and insulin, in conformity with our previous analyses.²⁶

Obviously, there are several limitations to our study, including the observational, noncontrolled design and the small

number of enrolled patients. Moreover, the short observation period may have limited the accuracy of the analysis. Many patients with high cardiovascular disease risk (known cardiovascular disease or currently treated with beta-blockers or thiazidic diuretics) were excluded from the study, so the final analysis did not include a group of subjects who could take great advantage from the statin effects. Finally, the concomitant antiretroviral therapy is not the same, and this difference could certainly influence the anti-inflammatory effects of statin.

In conclusion, the anti-inflammatory properties of statins in HIV-positive patients are emerging with growing evidence, but larger randomized studies are certainly needed to better define their potential role as anti-inflammatory agents in this population.

Author Disclosure Statement

The authors have no conflicts of interest to declare.
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