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SCIENTIFIC LETTER

Effects of HMG-CoA Reductase Inhibition on Endothelial Function and Lipid Profile in HIV-infected Persons on Protease Inhibitor-containing Antiretroviral Combination Therapy: A Randomized Double-Blind Cross-Over Trial

D Hürlimann¹, R Chenevard¹, F Ruschitzka¹, M Flepp², F Enseleit¹, M Béchir¹, R Kobza¹, J Muntwyler¹, B Ledergerber², T F Lüscher¹, G Noll¹, R Weber²

¹Cardiovascular Center, Cardiology, University Hospital, Zurich, Switzerland

²Division of Infectious Diseases and Hospital Epidemiology, University Hospital, Zurich, Switzerland

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Address for correspondence

Rainer Weber, MD
Division of Infectious Diseases and Hospital Epidemiology
University Hospital
CH-8091 Zürich
Switzerland
Phone +41-1-255 11 11
FAX +41-1-255 32 91
Email:infweb@usz.unizh.ch

Introduction of antiretroviral combination therapy has profoundly altered both the course and prognosis of the disease in HIV-infected persons. Recent data, however, have raised concerns that antiretroviral combination therapy is associated with premature manifestation of coronary artery disease.[1] In particular, protease inhibitors have been linked to metabolic changes such as insulin resistance, abnormalities in lipid metabolism and lipodystrophy and increased coronary artery calcification. While previous studies have reached conflicting conclusions about the incidence of myocardial infarction, the most substantial database recently provided by Friis-Møller and co-workers demonstrated an increased incidence in HIV-infected persons on protease inhibitors or non-nucleosid reverse transcriptase inhibitor-containing therapy.[2]

One of the postulated mechanisms of proatherogenic effects of protease inhibitors is the promotion of atherosclerotic lesion formation by an increase in CD-36-dependent cholesteryl ester accumulation in macrophages. Additionally, hypercholesterolemia promotes a CD-36-dependent and endothelial nitric oxide synthase mediated endothelial dysfunction. Endothelial dysfunction is associated with future risk of adverse cardiovascular events.[3] Impaired endothelial function was previously shown in HIV-infected persons on protease inhibitor therapy.[4] The effect of statins (HMG-CoA reductase inhibitors) in antiretroviral combination therapy associated dyslipidemia remains still to be determined. As most statins are metabolized by the cytochrome P450 3A4 isoform and thus interfere with the metabolism of many antiretroviral drugs, resulting in increased toxicity, cytochrome P450-independent statins such as pravastatin may be advantageous.

Hence, the present study aimed to evaluate the effects of pravastatin on endothelial function and plasma lipid profile in persons on protease inhibitor-containing antiretroviral combination therapy.

METHODS

This was a randomized, cross-over, double-blind and placebo-controlled interventional trial investigating pravastatin 40mg daily and matching placebo for 8 weeks each. Laboratory, clinical and endothelial function parameters were assessed at baseline and after each treatment period. An additional ultrasound measurement was performed at 4 weeks. Inclusion criteria were HIV-infection, protease inhibitor-containing antiretroviral combination therapy for at least 4 months that was unchanged for 2 months. Exclusion criteria were cholesterol <5mmol/L, statins or ACE inhibitors, diabetes mellitus and acute coronary syndromes within the previous 4 weeks. Concomitant medication remained unchanged throughout the study course. Each patient gave written informed consent and the study was approved by the local ethics committee of the University Hospital of Zurich.

Brachial artery endothelium-dependent flow-mediated dilation (FMD), induced by inflation of a wrist cuff to suprasystolic pressure for 5 minutes, and endothelium-independent vasodilation (0.4mg glycerol trinitrate sublingually) were assessed by a high-resolution ultrasound vessel wall tracking device with a 10-MHz linear array transducer (ESAOTE AU-5, WTS-2, Pie Medical, Maastricht, The Netherlands). Vessel diameter was recorded every 15 seconds for 5 minutes.

All data is presented as medians and interquartile range as 25th to 75th percentile. For changes of FMD and lipid parameters comparing pravastatin to placebo Wilcoxon signed rank test was used. For comparison of baseline characteristics Mann-Whitney test was used. Statistical significance was accepted at $p < 0.05$. Results of linear univariable and multivariable regression analysis are expressed as regression co-efficients \pm SEM.

RESULTS

29 participants (median age 43 years, 79% male) were included for final analysis. Baseline patients' characteristics between the two treatment arms did not differ. HIV parameters were: previous clinical AIDS, 10 of 29 (34%) patients; median CD4 lymphocyte nadir and baseline count, 93×10^3 (range, 45-245) and 484 (328-633) cells/mL, respectively; median duration of

antiretroviral therapy, 4.8 (2.3-5.9) years; median baseline HIV-1 RNA below 50 copies/mL. During the study, no progression of HIV infection was observed.

8 weeks of treatment with pravastatin significantly improved FMD *v* both baseline ($p=0.003$) and placebo ($p=0.03$) (figure 1 and 2, table 1). At 4 weeks, FMD was not different between pravastatin and placebo ($p=0.12$). A mild carry over effect was perceivable: FMD after 4 weeks of placebo in the group first receiving pravastatin was increased *v* baseline (2.6% *v* 1.6%, $p=0.01$), resembling the preceding 8 week pravastatin measure point (2.6%, $p=0.48$). In contrast, in patients who first received placebo, FMD was comparable to baseline (2.3% *v* 2.8%, $p=0.26$) after 4 weeks of placebo. GTN induced vasodilation was not influenced by either treatment. Values for plasma creatinine, creatinine kinase, AST, ALT and glucose were within normal limits at baseline and did not change during the study. Laboratory and clinical parameters are summarized in table 1.

Table 1: Comparison of parameters at baseline and after 8 weeks of placebo and pravastatin treatment, respectively*

	Baseline	Placebo	Pravastatin	p	p
	N=29	8 weeks	8 weeks	pravastatin/ baseline	pravastatin/ placebo
	N=29	N=29	N=29		
HIV surrogate markers					
CD4 cell count (10^3 cells/mL)	484 (328-633)	472 (320-646)	464 (354-650)	0.60	0.42
HIV-1 RNA (copies/mL)	8 (0-37)	0 (0-22)	0 (0-18)	0.57	0.33
Clinical parameters					
Body mass index (kg/m^2)	22.9 (21.4-25.1)	23.1 (21.3-25.1)	22.6(21.2-25.4)	0.53	0.93
Systolic blood pressure (mmHg)	120 (114-128)	118 (114-129)	119 (113-127)	0.33	0.99
Diastolic blood pressure (mmHg)	77 (71-83)	78 (73-83)	76 (71-84)	0.41	0.95
Heart rate (bpm)	76 (71-81)	75 (70-82)	75 (71-80)	0.85	0.47
Laboratory parameters					
Total cholesterol (mmol/L)	6.4 (6.0-7.4)	6.4 (5.3-7.2)	5.5 (4.8-6.3)	<u><0.0001</u>	<u>0.001</u>
HDL cholesterol (mmol/L)	1.2 (1.1-1.6)	1.2 (1.0-1.6)	1.3 (1.1-1.4)	0.90	0.38
LDL cholesterol (mmol/L)	3.7 (2.8-4.2)	3.9 (2.7-4.4)	3.0 (2.4-3.7)	<u>0.001</u>	<u>0.01</u>
Triglycerides (mmol/L)	3.0 (2.1-4.0)	2.7 (2.1-3.8)	2.3 (1.6-2.9)	<u>0.05</u>	<u>0.04</u>
Oxidized LDL (IU)	53 (45-66)	55 (43-70)	47 (38-57)	<u>0.0003</u>	<u>0.007</u>
hs CRP (mg/L)	2.2 (0.7-4.5)	2.1 (0.8-5.1)	2.1 (1.0-4.8)	0.50	0.29
Endothelial Function					
FMD (%)	2.0 (1.5-2.6)	2.5 (1.8-3.2)	3.2 (1.9-4.1)	<u>0.003</u>	<u>0.03</u>
GTN induced vasodilatation (%)	11.3 (10.0-14.4)	11.3 (9.6-16.3)	10.8 (7.0-15.7)	0.16	0.85
Vessel diameter (mm)	4.4 (4.1-4.8)	4.3 (3.8-4.6)	4.3 (3.9-4.8)	0.26	0.65

*Numbers represent medians (interquartile range) unless otherwise stated

Change of LDL cholesterol was found to be inversely related to percentage change of FMD ($r=0.36$, $p=0.014$). This relationship remained significant in a multivariable model additionally including treatment sequence and heart rate as independent variables ($r=0.53$, $p=0.003$).

DISCUSSION

This randomized, double-blind investigation demonstrates that statin therapy not only lowers total, LDL- as well as oxidized LDL cholesterol, but significantly improves endothelial function in HIV-infected persons on protease inhibitors-containing antiretroviral combination therapy.

HIV infection has become a chronic disease, requiring long-term management strategies and greater attention to disease prevention issues. As such statins are expected to become a cornerstone of coronary artery disease prevention since emerging evidence suggests that HIV-infected persons on antiretroviral combination therapy, particularly on protease inhibitor-containing regimens, are at increased risk for cardiovascular morbidity and mortality by mechanism that are not fully understood yet.[1][2] Our study provides evidence that statins improve a clinically relevant cardiovascular surrogate endpoint and further corroborate and extend findings of a recent study by Stein showing a trend towards improvement of FMD in HIV patients. While significant beneficial effects of statins on vascular endothelial function have previously been demonstrated in a range of patient populations with hypercholesterolemia, the present study extends these results to HIV-positive individuals. The decrease in total cholesterol and LDL in the present study was considerably less than reported from large lipid-lowering studies using identical doses of pravastatin in hypercholesterolemic subjects. The relatively modest effects on plasma lipids in the present and previous studies in HIV patients may in part be explained by pharmacokinetic interactions. Indeed, in combination with protease inhibitors plasma concentration of simvastatin increased 30-fold, while pravastatin levels were found to decline by 50%.[5]

In conclusion, notwithstanding the results of the present study demonstrate that statin therapy beneficially impacts on a clinically relevant surrogate marker of cardiovascular disease, the definitive answer as to the net effect of statins on cardiovascular events in HIV patients can only be provided by large scale prospective randomized clinical trials.

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Figure 1:

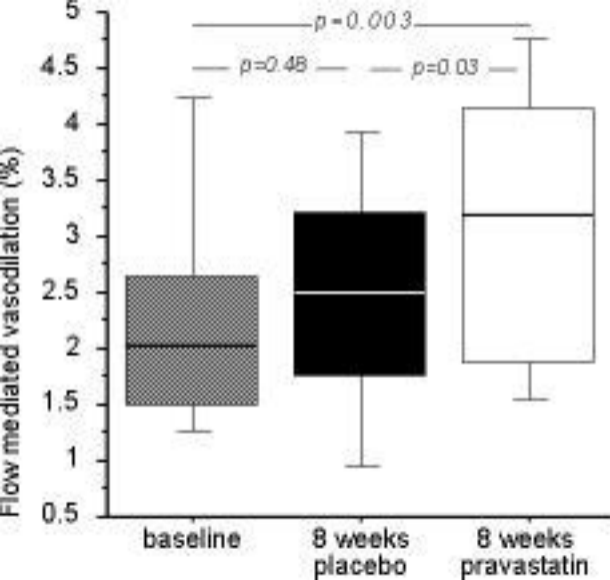
8 weeks of treatment with pravastatin resulted in a significant improvement of FMD (3.2% (1.9-4.1)) *v* both baseline (2.0% (1.5-2.6), $p=0.003$) and placebo (2.5% (1.8-3.2), $p=0.03$).

Figure 2:

Individual changes in FMD from baseline resulted in a significant improvement after 8 weeks of pravastatin (1.2%, $p=0.003$) but not after 4 weeks (0.3%, $p=0.2$). Placebo did not alter FMD at 8 weeks (0.5%, $p=0.48$) while FMD after 4 weeks of placebo was slightly increased *v* baseline (0.6%, $p=0.01$), which is largely attributable to a carry-over effect in the cross-over design. At 4 weeks, change of FMD did not vary between pravastatin and placebo ($p=0.12$).

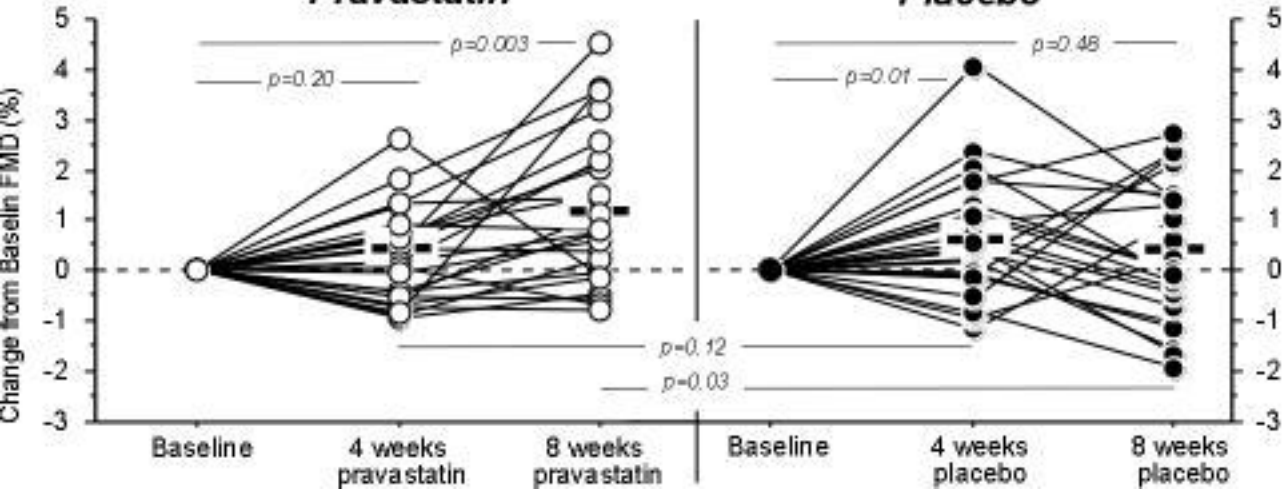
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Pravastatin

Placebo





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