Lipid Lowering Therapy with Fluvastatin and Pravastatin in Patients with HIV Infection and Antiretroviral Therapy: Comparison of Efficacy and Interaction with Indinavir

A. Benesic, M. Zilly, F. Kluge, B. Weißbrich, R. Winzer, H. Klinker, P. Langmann

Abstract

Background: Lipoprotein disorders in HIV-positive patients receiving highly active antiretroviral therapy (HAART) are becoming a major concern in HIV treatment, since there is growing evidence for an association between HAART-induced hyperlipidemia and increased cardiovascular risk. Yet relatively few data are available on the possible interactions of HAART and treatment with statins.

Patients and Methods: In this prospective study, 25 HIV-positive, treatment-experienced patients (five female, 20 male, all Caucasian) were treated with either fluvastatin or pravastatin. Total cholesterol, low density lipoprotein (LDL) and high density lipoprotein (HDL) levels, and serum triglycerides were determined at regular intervals, as well as therapeutic drug monitoring to assess possible drug interactions.

Results: In 13 pravastatin-treated patients, a decrease in total cholesterol levels (from 7.12 mmol/l to 6.29 mmol/l) after 12 weeks of therapy was seen. In 12 patients treated with fluvastatin, a permanent reduction of total cholesterol (from 6.46 mmol/l to 5.31 mmol/l) after 12 weeks was observed. The reduction of LDL levels was 30.2% in the fluvastatin group and 14.4% in the pravastatin group. In eight patients receiving an indinavir-containing HAART, indinavir plasma levels were not significantly influenced. No effect on triglycerides or HDL was observed.

Conclusion: Fluvastatin and pravastatin are efficient in lowering total and LDL cholesterol levels in HIV-positive patients receiving HAART. Furthermore, no influence on indinavir plasma levels could be observed. Therefore, both compounds seem to be a viable treatment option in HAART-induced hypercholesterolemia.

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Introduction

Among the rising awareness of long-term side effects of HIV treatment, a wide range of abnormalities of lipid metabolism has recently been described in HIV-infected patients receiving highly active antiretroviral therapy (HAART) [1–8]. These changes in lipid metabolism are sometimes correlated with an increased cardiovascular risk [1–3]. If diet and lifestyle changes do not effectively lower elevated cholesterol and triglyceride levels, statins are considered the first-line therapy for protease inhibitor (PI)-related hypercholesterolemia [2, 3]. Among these substances, fluvastatin and pravastatin are the two most commonly used in HIV-infected patients receiving HAART. Fluvastatin is metabolized by cytochrom P450 (CYP) 2C9 and pravastatin is not significantly metabolized by the CYP enzyme system [9]. Therefore, they are unlikely to interfere with antiretroviral therapy by influencing the plasma levels of antiretroviral drugs through metabolic interactions concerning the CYP enzyme system. Multiple mechanisms of drug interactions are a challenge in HIV therapy [10–13]. On the one hand, reduced absorption or enhanced metabolization (e.g. by enzyme induction) could reduce plasma levels leading to a loss in the effectiveness of HIV treatment. On the other hand, increased plasma levels of HIV drugs could occur via inhibition of metabolic pathways, decreased protein-binding etc., which could increase toxicity and the frequency of side effects. HAART could also reduce the effectiveness or enhance toxicity of lipid lowering drugs. The aim of this study was to compare the effectiveness of cholesterol synthesizing enzyme(CSE)-inhibitor therapy with fluvastatin and pravastatin in HIV-infected patients and their possible interactions with HAART, especially the plasma level of the protease inhibitor indinavir.

A. Benesic, *(corresponding author)*
Division of Infectious Diseases, Dept. of Internal Medicine, University of Würzburg, Josef-Schneider-Str. 2, D-97080 Würzburg, Germany; Phone: (+49/931) 201-36174, Fax: -36485,
e-mail: benesic_a@klinik.uni-wuerzburg.de
A. Benesic, M. Zilly, F. Kluge, R. Winzer, H. Klinker, P. Langmann
Medical Policlinic, University of Würzburg, Division of Infectious Diseases, Würzburg, Germany
B. Weißbrich
Dept. of Virology, University of Würzburg, Würzburg, Germany

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Table 1
Characterization of the patient population.

		Fluvastatin group	Pravastatin group	Total
Sex	female, no.	3	2	5
	male, no.	9	11	20
Age (years)		41.0 ± 6.7	41.4 ± 10.2	40.4 ± 8.5
Years since HIV primary diagnosis		10.1 ± 5.1	8.1 ± 4.6	9.0 ± 4.9
No. of therapeutic lines		3.3 ± 2.7	3.8 ± 2.3	3.6 ± 2.5
Mean CD4 (cells/µl)		549/µl	530/µl	558/µl
Viral load (copies/ml) undetectable, no.		6	7	13
	< 500	4	5	8
	≤ 1,000	2	2	4
	> 1,000	0	0	0
Presently smokes, no.		6	6	12
Arterial hypertension, no.		1	1	2
Diabetes mellitusv, no.		1	2	3
Cardiovascular events[a], no.		1	0	1

[a] one patient had an acute myocardial infarction prior to statin therapy

Table 2
Characteristics of HAART in the treatment groups (start of treatment).

	Fluvastatin group (n)	Pravastatin group (n)	Total (n)
NRTI only	5	2	7
NRTI backbone + NNRTI	2	4	6
NRTI backbone + PI	5	7	12
Changes in HAART during treatment period	5	4	9

NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor

Patients and Methods

Patients

In this prospective, non-randomized, open-label study, 25 patients receiving antiretroviral therapy were treated with fluvastatin (n = 12) or pravastatin (n = 13). Patient characteristics are outlined in table 1; details of their antiretroviral therapy are shown in table 2. Inclusion criteria were: documented HIV infection, ongoing antiretroviral therapy for longer than 2 years, and hypercholesterolemia refractory to changes in lifestyle and diet. Exclusion criteria were use of comedication interfering with the CYP-450 system as well as a lack of therapy adherence.

Data Collection

Levels of total cholesterol, low density lipoprotein (LDL) and high density lipoprotein (HDL) and serum triglycerides were determined in a fasting state, with regular measurements during the 72-week observation period. Subsequent analysis of cholesterol and triglycerides was performed by enzymatic and colorimetric assays (ChodPap [cholesterol oxidase-phenol aminophenazone peroxidase reaction] and GPO-PAP [glycerol-phosphate oxidase phenol amonophenazone reaction]. HDL was measured enzymatically (direct HDL) and LDL was calculated by the Friedewald formula. In addition, non-specific parameters for potential toxic effects were determined (liver enzymes, lactate-dehydrogenase [LDH], creatine-kinase [CK], creatinine, blood urea nitrogen [BUN]). Normal values were: total cholesterol 3.4-5.7mmol/l, LDL cholesterol ≤ 3.9 mmol/l, HDL cholesterol > 0.9 mmol/l, triglycerides 0.8-19 mmol/l.

Determination of Plasma Indinavir Levels

Plasma indinavir (IDV) levels were determined as described by *Langmann* et al. [14]. A high performance liquid chromatographic (HPLC) method for the determination of IDV in human plasma was used. Quantitative recovery following liquid-liquid extraction with diethyl ether from 500 µl of human plasma was achieved.

The HPLC system consisted of a Beckman System Gold (Beckman Instruments, Munich, Germany), a 126 solvent pump module, and a 502 e autoinjector. A 167 programmable detector module and Beckman System Gold software were employed for peak determination and peak identification/integration, respectively.

The sample preparation was performed with 500 µl of patient plasma, an equal volume of carbonate buffer (0.1M sodium carbonate-sodium bicarbonate pH 9.4) and 100 µl of an internal standard (A-86093) added to a 15 ml glass tube. The sample was vortexed for 10 sec and extracted twice with 3 ml diethyl ether for 5 min, followed by centrifugation at 3,000 g (4 °C). Subsequently, the organic layers were transferred into a glass centrifuge tube and evaporated to dryness with a gentle stream of nitrogen at 37 °C.

The residue was reconstituted in 300 µl 67mM potassium-dihydrogen-phosphate-methanol (1:1 v/v) and washed for 5 min with 1.5 ml n-hexane. The aqueous layer was transferred to autosampler vials with glass micro inserts for HPLC analysis. A 100 µl aliquot was injected into the chromatograph.

The assay was performed with a linear gradient starting at 67mM potassium-dihydrogen-phosphate-acetonitrile 65:35 (v/v) to 40:60 (v/v) as a mobile phase, a Phenomenex C18 column and UV detection at 258 nm. Linear standard curves were obtained for concentrations ranging from 75 to 20,000 ng/ml for IDV. The calculated intra- and inter-day coefficients of variation were below 6%. The detection limit of IDV in plasma was determined at 2 ng/ml and the lower limit of quantitation was reached at a concentration of 75 ng/ml for IDV [13].

A determination of IDV plasma concentrations in dosages of IDV 1.6 g/d (n = 2 samples) in combination with low-dose ritonavir and of IDV 2.4 g/d (n = 6) samples was performed 2–4 h after oral ingestion. The range of IDV plasma levels was expressed as mean ± standard deviation (SD).

Statistics

All data were presented as mean ± SD. Student's t-test was used for statistical analysis. Values were considered statistically significant if $p < 0.05$.

Role of the Funding Source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Therapy with Fluvastatin: Effects on Cholesterol and Triglyceride Levels

In order to reduce elevated levels of total and LDL cholesterol in HIV-infected patients under HAART, 12 patients were treated with the CSE-inhibitor fluvastatin (20 mg/d, n = 2 or 40 mg/d, n = 10). Characteristics of the antiretroviral combination therapy are given in table 2. Of the 12 patients at baseline, five patients had to change their antiretroviral therapy during the observation period (Table 2), including two patients receiving IDV. Total cholesterol (Figure 1) was decreased significantly from 6.5 ± 0.7 mmol/l (n = 12) at baseline to 5.3 ± 0.8 mmol/l (n = 12) after 12 weeks of treatment (p = 0.003). The treatment resulted in a total reduction of cholesterol by 19% (Table 3). Furthermore, the fluvastatin therapy maintained normalization of total cholesterol levels in the five patients who could be followed until week 72. Fluvastatin therapy also effectively lowered the LDL fraction of total cholesterol. LDL cholesterol was 4.2 ± 0.8 mmol/l at baseline (n = 11) and decreased to 3.2 ± 0.7 mmol/l (n = 12) in week 12 ($p < 0.05$). LDL cholesterol levels were well below the upper limit of 3.9 mmol/l during treatment with fluvastatin. Four of 12 patients could be followed for 72 weeks. In the observed group of patients, HDL cholesterol was not significantly influenced by fluvastatin and ranged between 1.0–1.2 mmol/l at baseline and throughout the therapy.

There was no significant effect of fluvastatin on the elevated levels of triglycerides. Triglyceride levels remained constantly elevated (baseline: 5.9 ± 2.7 mmol/l; n = 11; week 12: 5.8 ± 1.8 mmol/l; n = 12; p = 0.1).

No elevation of liver enzymes or serious side effects potentially related to the intake of fluvastatin occurred during the 72-week study period.

Effects on Plasma Levels of Indinavir

In the group of 12 patients receiving fluvastatin in order to treat hypercholesterolemia, four received the protease-IDV (3 × 800 mg) as component in their antiretroviral therapy, in combination with nucleoside-analogues (AZT/3TC/IDV: n = 2; d4T/3TC/IDV: n = 1; d4T/ddI/IDV: n = 1). Figure 2a shows the effect of fluvastatin on indinavir plasma levels. Of the four patients receiving IDV, two could be followed until the 72nd week. Two had to interrupt IDV therapy due to nephrotoxicity and virologic failure. After initiation of lipid lowering therapy with fluvastatin, there were no significant changes in IDV plasma levels detectable (baseline: 5.672 ± 5.109 ng/ml [n = 4], week 12: 2.908 ± 3.137 ng/ml [n = 4], week 24: 4.981 ± 4.551 ng/ml [n = 3], week 36: 7.895 ng/ml [n = 2], week 48: 9.749 ng/ml [n = 2], week 60: 6.191 ng/ml [n = 2], week 72: 3.078 ng/ml [n = 2]).

Therapy with Pravastatin: Effects on Cholesterol and Triglyceride Levels

Pravastatin (10 mg/d, n = 11 or 20mg/d, n = 2) was used to treat hypercholesterolemia in 13 HIV-positive patients receiving HAART. As shown in Figure 1, total cholesterol could be lowered significantly from 6.8 ± 1.6 mmol/l at baseline (n = 12) to 6.3 ± 0.9 mmol/ll after 12 weeks (n = 13, p = 0.02). However, the mean level of total cholesterol could not be lowered below the upper limit of 3.9 mmol/l. There was no sustained lipid lowering effect in the patients treated with pravastatin. Furthermore, only a transient decrease of LDL could be observed, which did not reach statistical significance between baseline (3.80 ± 1.25 mmol/l; n = 11) and week 12 (3.68 ± 0.99 mmol/l; n = 11; p = 0.17). The levels of HDL cholesterol remained virtually unchanged and were around 1.0 mmol/l.

Triglyceride levels were unaffected by pravastatin as well (Figure 1). Triglyceride levels were highly variable and ranged between 5.82 ± 3.79 mmol/l at baseline (n = 12), 4.01 ± 2.80 mmol/l (n = 13) in week 12 (p = 0.09).

As with fluvastatin, no severe adverse event or laboratory abnormality could be observed.

Effects on Plasma Levels of Indinavir

In the group of 13 patients treated with pravastatin, four received an antiretroviral combination of IDV and two nucleosides (d4T/ddI n = 2; 3TC/d4T n = 1; AZT/3TC n = 1). Two patients had IDV (800 mg twice daily) combined with ritonavir (100 mg twice daily) in order to boost plasma levels of IDV. Figure 2b shows that pravastatin had no effect on IDV plasma levels in the four patients (baseline: 4.080 ± 3.429 ng/ml [n = 3], week 12: 5.883 ± 4.159 ng/ml [n = 4], week 24: 4.325 ± 4.183 ng/ml [n = 4], week 36: 1.053 ± 1.204 ng/ml [n = 4], week 48: 2.645 ± 356 ng/ml [n = 4], week 60: 1.992 ± 1.682 ng/ml [n = 4], week 72: 1.595 ± 1.642 ng/ml [n = 3]). One patient had to stop IDV due to nephrotoxicity. There was no difference between IDV and IDV/r regimens and also no effect on ritonavir plasma levels in the patients receiving pravastatin.

Table 3
Effects of fluvastatin and pravastatin in different doses on total and LDL cholesterol.

	Fluvastatin 20 mg	Fluvastatin 40 mg	Fluvastatin all patients	Pravastatin 10 mg	Pravastatin 20 mg	Pravastatin all patients
Total cholesterol (% reduction)	25.3	17.4	19.0	9.5	17.1	13.9
LDL cholesterol (% reduction)	35.8	31.2	30.2	13.6	14.0	14.4

Discussion

In order to treat diet-resistant hypercholesterolemia in 25 HIV-infected patients under HAART, the CSE inhibitors fluvastatin (12 patients) and pravastatin (13 patients) were used. Both substances exerted lipid lowering effects by reducing elevated cholesterol levels. Based on the 12-week data, the effect was statistically significant for fluvastatin and pravastatin, whereas the second compound failed in significantly affecting LDL cholesterol. HDL cholesterol and triglycerides remained unaffected. In comparison with other studies on the treatment of hyperlipidemia, pravastatin was not as effective as expected [2–4].

Another study in HIV-negative patients showed a percentage decrease in plasma concentration of low density lipoprotein by fluvastatin of 17% (20 mg/d) and 23% (40 mg/d), respectively. [9]. In this study, the effect of fluvastatin was even more pronounced and independent of the administered dose (Table 1). The data for pravastatin [9] show a lowering of LDL by 19% (10 mg/d) and 24% (20 mg/d). However, in the patient collective observed in our study, the reduction of LDL cholesterol by pravastatin was not this effective and, as seen with fluvastatin, independent of the administered dose. Therefore, in this study, treatment of HAART-related hypercholesterolemia was

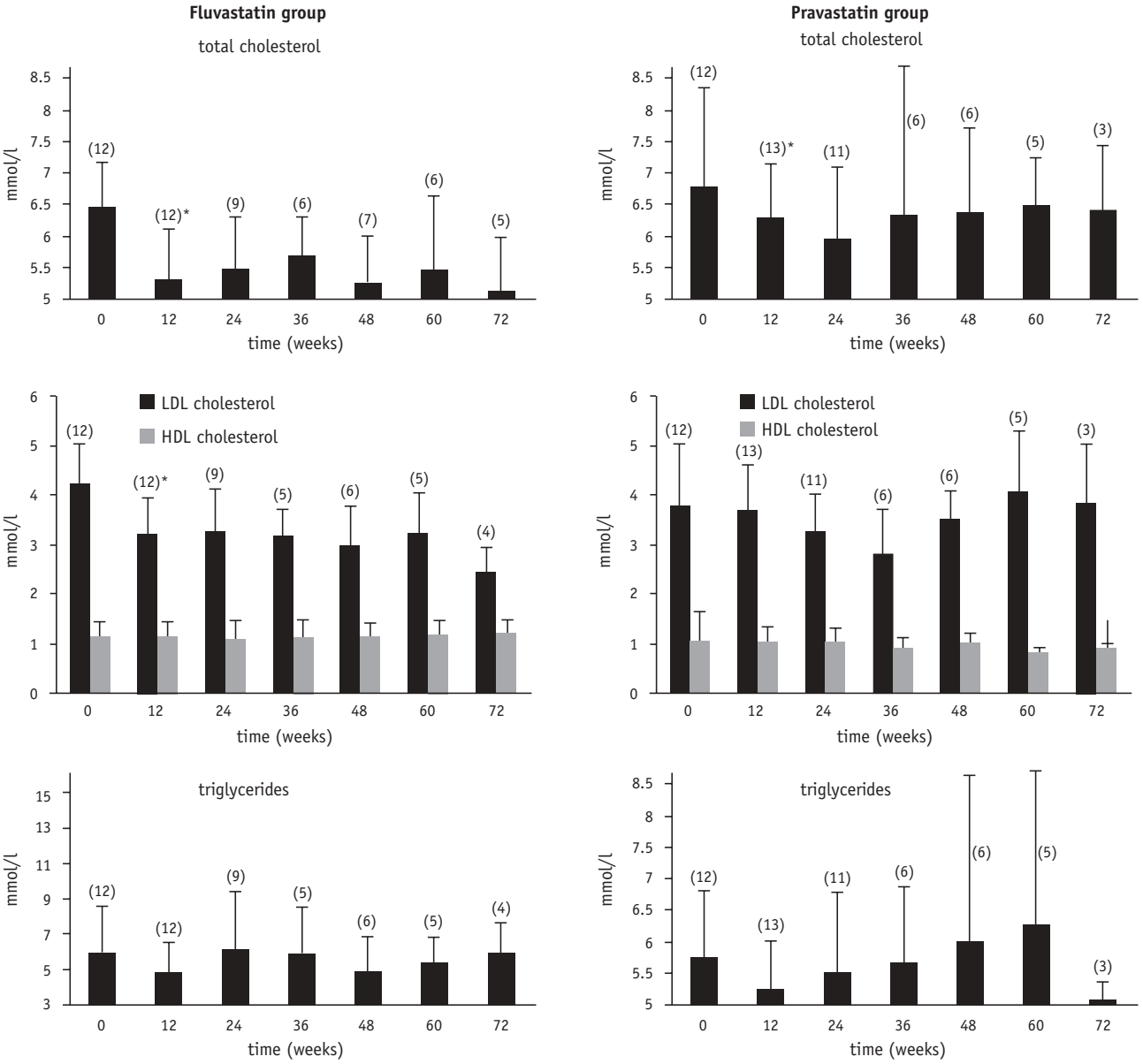
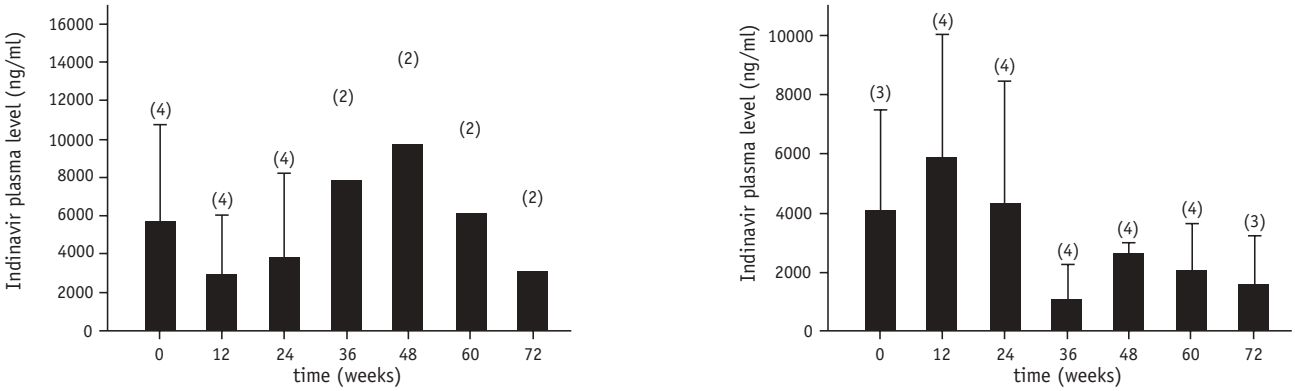


Figure 1. Effects of treatment with fluvastatin (left panel) and pravastatin (right panel) on total cholesterol, LDL and HDL and triglycerides over a time period up to 72 weeks. (number of patients in parentheses, *p < 0.05).



Figures 2a and 2b. Indinavir plasma levels during CSE-inhibitor therapy (fluvastatin: Figure 2a; pravastatin: Figure 2b); number of patients in parentheses.

very effective with fluvastatin, whereas pravastatin showed only a transient effect and did not lower LDL and total cholesterol satisfactorily. However, the significance of these observations is limited by the small number of patients participating in this study. Another possibility to explain the unexpected small and only transient effect of pravastatin would be an interaction between HAART and pravastatin. The plasma levels of fluvastatin and pravastatin were not determined, but this could be the focus of further studies.

None of the two compounds lowered triglyceride levels. Neither fluvastatin nor pravastatin significantly influenced the plasma levels of the PI IDV. The IDV plasma levels measured before and during statin therapy varied widely, but remained within ranges, according to our formerly published results [14].

The effects of fluvastatin and pravastatin on cholesterol (total and LDL) were independent of the individual HAART regimen. The effects in patients with NRTI/NNRTI, NRTI/PI, and IDV regimens against combinations with other PIs were comparable to the overall effects shown in table 3 and figure 1.

In conclusion, therapy of hypercholesterolemia with fluvastatin and pravastatin is effective in HIV-positive patients under ongoing HAART. There were no influences on plasma levels of IDV. Therefore, both lipid lowering agents seem to be a viable treatment option in HAART-induced hypercholesterolemia.

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