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Treatment with Fluvastatin Rapidly Modulates, via Different Pathways, and in Dependence on the Baseline Level, Inflammation in Hemodialysis Patients

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Key Words
Statins · Inteleukin-6 · Soluble interleukin-6 receptor · Interleukin-10 · Oxidized LDL · Inflammation in HD patients · Renal failure · Oxidant stress · Statins · C-reactive protein

Abstract
Background: Hemodialysis (HD) patients are frequently in an elevated inflammatory state which is correlated to the atherosclerosis-related and overall morbidity and mortality in this population. Statins, beyond their antilipidemic effects, are also considered to have anti-inflammatory, immunomodulating and antioxidant properties. The individual response of HD patients to a short course of fluvastatin, the mechanisms involved in the immunomodulating and anti-inflammatory effects of this drug and the time interval to the appearance of these effects are investigated in this longitudinal study. ***Methods:*** In a group of 51 HD patients, fluvastatin 40 mg/day was administered for 4 weeks. Serial measurements of the lipid profile, C-reactive protein (CRP), interleukin-6 (IL-6), soluble IL-6 receptor (sIL-6R), interleukin-10 (IL-10), and serum oxidized LDL (ox-LDL), were performed before, during, and after the treatment period. ***Results:*** Total cholesterol was significantly reduced after 14 days of treatment with fluvastatin (from mean ± SD 216.7 ± 34.3 to 179.2 ± 42.3 mg/dl, $p < 0.001$). IL-6 and ox-LDL were reduced on day 28 ($p < 0.001$ and $p < 0.01$, respectively) and IL-10 was increased on day 14 ($p = 0.05$); CRP did not change significantly during the treatment period while sIL-6R was increased on day 28 of fluvastatin administration ($p < 0.05$). In a subgroup of patients with CRP, IL-6, sIL-6R, and ox-LDL baseline serum values ≥ the median and IL-10 ≤ the median, CRP was reduced on day 28 of fluvastatin treatment ($p < 0.01$), IL-6 and ox-LDL were reduced earlier, on day 14 ($p = 0.05$ and $p < 0.05$, respectively) while sIL-6R did not change significantly during the treatment period. ***Conclusions:*** Treatment with fluvastatin rapidly modulates inflammation in HD patients. Enhancement of anti-inflammatory mechanisms and attenuation of the inflammatory and oxidative state contribute to this modulation. Patients in an elevated baseline inflammatory state respond more rapidly and effectively to the treatment. This immediate and multi-potent action of the statins could be clinically useful in acute atherosclerosis complications or in the treatment of chronic inflammation in HD patients.

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Introduction

Atherosclerotic cardiovascular disease (CVD) is a major cause of morbidity and mortality in hemodialysis (HD) patients [1]. Atherosclerosis is recognized as an inflammatory process and inflammation, frequently found to be elevated in end-stage renal failure patients, could be a risk marker or even a risk factor for this disease, in this high-risk population [2, 3]. Any therapeutic interventions that potentially modulate inflammation might also ameliorate atherosclerosis-related complications and overall outcome in these patients.

Statins, beyond their well-known anti-lipidemic effect, seem to have a degree of anti-inflammatory and anti-oxidant action [4]. Few studies have investigated the so-called pleiotropic effects of the statins in HD patients [5–7]. The time needed for these effects to become apparent as well as the mechanisms by which these drugs eventually modulate the inflammatory process in renal failure patients have not been fully elucidated. The exploration of the timing of appearance, of the mechanisms by which the statins exert their pleiotropic actions as well as the investigation of the probability for a differential response to this treatment between HD subjects, could be of importance for the CVD – and overall – management of these patients.

In the present study with a longitudinal design, the immunomodulating effects as assessed by serial changes in serum of C-reactive protein (CRP), interleukin-6 (IL-6), soluble IL-6 receptor (sIL-6R), and interleukin-10 (IL-10), as well as potential anti-oxidant ones, as assessed by the serum level modification of oxidized low density lipoproteins (ox-LDL), observed after a short-term treatment with fluvastatin, the time interval for the appearance of these actions as well as the magnitude of the patients' response to this treatment, in a group of stable HD patients are investigated.

Methods

Study Design – Patients

In a group of 69 hyper- or normolipidemic stable HD patients, fluvastatin (Lescol, Novartis) 40 mg was administered – in a single daily dose at night – for a time period of 4 weeks. High-sensitivity CRP, serum total cholesterol, HDL cholesterol, and triglycerides were measured and LDL cholesterol was calculated weekly for 2 consecutive weeks prior to treatment initiation as well as for 2 weeks after treatment termination; the average of the 2-weekly measurements was considered as the baseline pre- and post-treatment level for these parameters (in this way the considerable temporal variability of CRP and the potential variance in time of the lipid fractions were taken into consideration [8]). Immediately before treatment initiation, at the end of the second and fourth week of treatment with fluvastatin, as well as 2 weeks after treatment was discontinued, IL-6, sIL-6R, IL-10, serum ox-LDL, creatine kinase (CK) and serum glutamic-oxaloacetic transaminase (SGOT) were also measured.

The inclusion criteria were absence of a recognized inflammatory event (due to infection, trauma, surgical operation, myocardial infarction, active collagen disease, neoplasia, etc.) on initiation of the study and normal liver function. Patients were required to not have been on any anti-lipidemic treatment. They were on a stable normolipidemic diet throughout the study. Compliance to treatment was monitored on every dialysis day. Patients were allowed to continue the study medication and were included in the analysis if they remained free of any inflammatory event for the duration of the study, if they were free of any rhabdomyolysis symptoms, if their CK and SGOT values remained within 2–4 times the upper normal limit and if they were compliant to treatment. All patients gave informed consent before they were included in the study.

According to these criteria, 51 out of 69 patients were finally included in the study. Thirteen patients were excluded because of a clinical inflammatory event (9 patients had common upper respiratory tract infections and 4 had other infections, mainly related to the vascular access); 2 patients were excluded because of non-compliance to the treatment, 1 because of his transfer to another renal unit, 1 because of a trauma followed by CK elevation, and 1 because of nausea after the second day of treatment. In all of these patients, treatment was stopped on the day of the event and no further blood collections were done.

The study was performed between February and April 2003. Of the 51 patients finally included in the study, 39 were from the HD unit of the Dragini Clinic and 12 from the Blue Cross Hospital. All patients were white, 22 female, (mean ± SD) 63.00 ± 11.52 years old (range 25–81 years) and on HD for 40.21 ± 36.18 months (range 3–148 months). Eleven patients were diabetics, 21 had hypertension and 11 were smokers. Atherosclerosis (coronary, cerebrovascular or peripheral vascular disease) of any grade, as assessed using the CVD portion of the index of coexisting disease [1], was present in 16 out of 51 patients. The body mass index was 25.18 ± 4.19 kg/m^2. Causes of end-stage renal failure were chronic glomerulonephritis in 15 patients, polycystic disease in 12, diabetic nephropathy in 10, hypertensive nephrosclerosis in 6, other causes in 4, and unknown in 4. HD access was provided by an arteriovenous fistula in 34 patients and by a vascular graft in 7. All patients were on conventional HD and were dialyzed with bicarbonate dialysate. Water processing was performed by central reverse osmosis water treatment system. The type of dialyzer was EVAL (polyethylene-vinyl-alcohol membrane, Kawasumi Laboratories Inc.) for 39 patients and a modified cellulose membrane (Polysynthane, Baxter) for the remaining 12 patients. The dialyzer ultrafiltration coefficient was >10 ml/h mm Hg in 11 patients and <10 ml/h mm Hg in the remaining 40 patients. Of the subjects, 12 were being treated with angiotensin-converting enzyme inhibitors, 11 with acetylsalicylic acid (100 mg/day), 9 with intravenous ferrum (maintenance treatment, 100 mg once per week, for the duration of the study) and 22 patients with sevelamer hydrochloride.

Laboratory Measurements

Blood samples were taken before dialysis from the vascular access. All measurements were performed in the same laboratory (Department of Medical Biopathology, Eginition Hospital, Medical School, University of Athens). IL-6, sIL-6 R and IL-10 serum levels were quantified with a sandwich enzyme immunoassay technique based on a monoclonal-polyclonal antibody pair (R&D Systems, Minneapolis, Minn., USA). For IL-6, the coefficient of variation (CV) for the intra-assay precision varies between 4.2 and 2% at the corresponding serum concentrations of 16.8 and 186 pg/ml, while for the inter-assay precision it varies between 6.4 and 3.8% for the same serum concentrations. For sIL-6R the intra-assay CV value is 6% at a level of 134 pg/ml and 2.3% at a level of 1,669 pg/ml (the inter-assay precision was 6.4 and 4.7% respectively). For IL-10 the intra-assay CV was 5 and 1.7% at the levels of 23.9 and 231 pg/ml respectively, while for the same levels the inter-assay precision was 7.3 and 5.9%. For the determination of ox-LDL a sandwich enzyme immunoassay technique based on a monoclonal-monoclonal antibody pair was used (Mercodia, Uppsala, Sweden). The intra-assay precision varies between 5.5 and 6.2% at the corresponding serum concentrations of 8.5 and 32 mU/l, while the inter-assay precision varies between 6.2 and 4.0% for the same serum concentrations.

Serum levels of all biochemical markers (total cholesterol, HDL cholesterol, triglycerides, CK and SGOT) were determined utilizing Olympus AU 560 random access analyzer (Olympus Corp., Japan). LDL cholesterol levels were calculated using the Friedwald formula. Serum levels of high sensitivity CRP were determined by particle-enhanced immunonephelometry on Behring Nephelometer II (Dade Behring, Marburg, Germany). All assays were carried out in the same run and in duplicate.

Statistical Analysis

Data are presented as mean ± SD or median with range. Spearman's correlation coefficient was calculated for the univariate analysis between baseline values. Student's t test was used for determining the differences between subgroups of patients. To compare values obtained at baseline, at 2 and 4 weeks of treatment and at 2 weeks after treatment termination, ANOVA test for repeated measurements was used. Due to skewed distribution, CRP, IL-6, sIL-6R, IL-10 and ox-LDL were transformed to their natural logarithms. All statistical analyses for the above-mentioned parameters were performed using log-transformed values. The natural numbers are presented in the tables and in the text. A significance level of 0.05 was used for all statistical tests.

Results

No statistically significant differences were observed at baseline regarding the lipid levels or the inflammatory markers between patients with different demographic data, co-morbidities, dialysis conditions or medical treatment, except that patients treated with sevelamer hydrochloride had lower total and LDL cholesterol (202.36 ± 24.16 and 111.04 ± 27.71 mg/dl) than patients not on this treatment (229.33 ± 37.66 and 144.64 ± 36.48 mg/dl) ($p = 0.005$ and 0.001). In the same subgroup of patients (on sevelamer hydrochloride treatment) no statistically significant differences were observed at baseline regarding CRP in comparison to patients not on this treatment (CRP 5.86 ± 4.45 and 6.75 ± 7.44 mg/l, $p = 0.638$) but ox-LDL was significantly lower in these patients compared to those not on sevelamer (76.36 ± 25.92 and 96.64 ± 32.43 mg/l, $p = 0.031$).

No correlations were found between lipid values and inflammatory markers in the cohort of patients except that, baseline total cholesterol, LDL cholesterol, LDH cholesterol and triglycerides were significantly correlated to serum ox-LDL levels ($r = 0.583$, $p < 0.001$, $r = 0.518$, $p < 0.001$, $r = -0.366$, $p < 0.01$ and $r = 0.565$, $p < 0.001$ respectively), and CRP was inversely correlated to HDL cholesterol ($r = -0.339$, $p = 0.015$). Furthermore, a significant correlation was found between baseline sIL-6R and ox-LDL serum levels ($r = 0.334$, $p = 0.017$).

Lipid and enzyme serum levels at baseline, at 2 and 4 weeks of fluvastatin treatment, and after the treatment period are shown in table 1. Serum inflammation markers and ox-LDL before, during and after fluvastatin treatment are shown in table 2. In order to examine if patients with a higher pretreatment level of inflammation have a different response to the short treatment course than the ones with a lesser level of inflammation, we analyzed separately the changes of the inflammatory markers in those patients with serum levels equal or superior (or equal or inferior for IL-10) to the median found at baseline for each marker within the whole group of patients included in this study. The results of this separate statistical analysis are shown in table 3.

As shown in table 2, CRP levels did not change significantly after 28 days of treatment with fluvastatin 40 mg in the cohort of the HD patients examined but IL-6 and ox-LDL serum levels were significantly reduced in the same period of treatment. IL-10 had increased significantly already by day 14 of treatment and this increment was even stronger after the 28 days of fluvastatin administration. Finally, the sIL-6R serum level, although unchanged at 14 days, increased significantly on the 28th day of treatment. In a separate statistical analysis the response to fluvastatin treatment in patients on sevelamer hydrochloride was similar to the patients not treated with this medication regarding inflammatory indexes measured (data not shown) except that sIL-6R was not increased ($p = 0.806$) and ox-LDL was not decreased ($p = 0.107$) significantly on the 28th day of treatment.

In the patients with a higher CRP at baseline, this protein decreased significantly after 28 days of treatment with fluvastatin (table 3). IL-6 and ox-LDL were already

Table 1. Changes in the biochemical markers of the 51 hemodialysis patients on fluvastatin treatment for 28 days

	Baseline	14 days of treatment	28 days of treatment	After treatment	p
Total cholesterol, mg/dl	216.7 ± 34.3	179.2 ± 42.3[a]	175.7 ± 36.2[b]	208.9 ± 38.4	<0.001
LDL cholesterol, mg/dl	129.6 ± 36.3	104.5 ± 36.6[a]	100.9 ± 36.1[b]	126.7 ± 34.6	<0.001
HDL cholesterol, mg/dl	42.1 ± 11.2	44.0 ± 10.8	46.5 ± 11.5[b]	41.8 ± 10.2	<0.001
Triglycerides, mg/dl	185.7 ± 78.5	176.5 ± 80.8	179.4 ± 84.7[c]	190.2 ± 81.2[c]	<0.05
Creatine kinase, U/l	70.0 ± 54.7	71.1 ± 54.0	84.0 ± 106.0	75.1 ± 63.4	0.521
SGOT, U/l	19.8 ± 9.9	20.8 ± 8.7	21.7 ± 9.9	21.8 ± 10.4	0.159

Values are expressed as mean ± SD.
SGOT = Serum glutamic-oxaloacetic transaminase.
[a] $p < 0.001$ between baseline and 14 days of treatment.
[b] $p < 0.001$ between baseline and 28 days of treatment.
[c] $p < 0.05$ between 14 and 28 days of treatment and after treatment.

Table 2. Changes in the inflammatory markers and oxidized-LDL in 51 hemodialysis patients under fluvastatin treatment for 28 days

	Baseline	14 days of treatment	28 days of treatment	After treatment	p
C-reactive protein, mg/l	4.5 (0.5–38.1)	4.3 (0.4–37.8)	4.5 (0.8–12)	5.6 (1.1–19.65)[a]	0.046
Interleukin-6, pg/ml	7.2 (3.4–140.3)	7.6 (0.7–60.8)	5.8 (2.5–50.6)[b]	10.6 (4.6–37.4)	<0.001
Soluble IL-6 receptor, ng/ml	72.1 (1.2–148.1)	71.4 (1.4–134.2)	82.9 (52.2–411.9)[c]	61.5 (1.4–107.1)	<0.001
Interleukin-10, pg/ml	5.3 (4.1–12.3)	5.5 (3.9–11.0)[d]	6.0 (4.8–9.4)[b]	5.3 (4.5–8.0)	<0.001
Serum oxidized LDL, U/l	79.0 (35.0–149.0)	80.0 (37.0–88.0)	67.0 (9.7–151.0)[e]	90.0 (16.0–170.0)[f]	<0.015

Values are expressed as median (range).
[a] $p < 0.05$ between 28 days of treatment and after treatment and between baseline and after treatment.
[b] $p < 0.001$ between 28 days of treatment and baseline and between 28 days of treatment and after treatment.
[c] $p < 0.05$ between 28 days of treatment and baseline, $p < 0.001$ between 28 days of treatment and after treatment, $p < 0.01$ between 28 and 14 days of treatment.
[d] $p = 0.05$ between 14 days of treatment and baseline.
[e] $p < 0.01$ between 28 days of treatment and baseline and between 28 and 14 days of treatment.
[f] $p < 0.01$ between after treatment and 28 days of treatment.

significantly reduced on the14th day of treatment in the patients with higher levels of these molecules at baseline. IL-10 also increased more significantly than in the whole cohort at 14 days of treatment, in the subgroup of patients having lower initial levels of this cytokine. Serum ox-LDL was more significantly reduced at 28 days in this subgroup of patients than in the whole cohort. Finally, serum sIL-6R did not change significantly in the group of patients that had higher initial levels for this molecule.

Discussion

The main findings of this study are that treatment with fluvastatin rapidly modulates inflammation in HD patients by influencing pro- and anti-inflammatory and oxidative stress-related mechanisms as well as that the initial patients' inflammation level is correlated with the time interval of the appearance and strength of the response.

Total and LDL cholesterol were reduced by about 18–19% on day 14 of treatment with fluvastatin with a small further reduction by 1–3% on day 28 while HDL choles-

Table 3. Changes in the inflammatory indexes with fluvastatin treatment in patients with higher level of inflammation (≥ median for CRP, IL-6, sIL-6R, ox-LDL, and ≤ median for IL-10) at baseline

At baseline	Baseline	14 days of treatment	28 days of treatment	After treatment	p
CRP ≥4.5 mg/l (26 patients)	8.4 (4.5–38.1)	8.3 (0.9–37.8)	6.6 (3.2–12.0)[a]	7.7 (3.9–19.6)	0.04
IL-6 ≥7.2 pg/ml (26 patients)	11.6 (7.2–140.3)	10.7 (2.0–60.8)[b]	7.4 (3.7–50.6)[c]	13.1 (5.5–37.4)	0.01
sIL-6R ≥72.1 ng/ml (26 patients)	94.5 (72.1–148.1)	89.0 (1.5–134.2)	88.5 (52.2–133.3)	61.7 (1.4–107.1)[d]	0.001
IL-10 ≤5.3 pg/ml (29 patients)	4.9 (4.1–5.3)	5.9 (3.9–10.1)[e]	5.9 (4.8–8.7)[f]	5.2 (4.5–7.0)[g]	0.000
Ox-LDL ≥79 U/l (26 patients)	110.0 (79.0–149.0)	95.0 (37.0–188.0)[h]	77.5 (20.0–151.0)[i]	107.5 (40.0–170.0)	0.004

Values are expressed as median (range).
CRP = C-reactive protein; IL-6 = interleukin-6; sIL-6R = soluble IL-6 receptor; IL-6 x sIL-6R = ox-LDL, oxidized LDL.
[a] $p < 0.01$ between 28 days of treatment and baseline and $p < 0.05$ between 28 days of treatment and after treatment.
[b] $p = 0.05$ between 14 days of treatment and baseline and $p < 0.05$ between 14 and 28 days of treatment.
[c] $p < 0.001$ between 28 days of treatment and baseline and between 28 days of treatment and after treatment.
[d] $p = 0.000$ between after treatment and baseline.
[e] $p < 0.01$ between 14 days of treatment and baseline.
[f] $p < 0.001$ between 28 days of treatment and baseline.
[g] $p < 0.001$ between after treatment and 28 days of treatment and $p < 0.05$ between after treatment and baseline.
[h] $p < 0.05$ between 14 days of treatment and baseline.
[i] $p < 0.001$ between 28 days of treatment and baseline and $p < 0.05$ between 28 days of treatment and after treatment.

terol increased. These results are similar to those obtained in other studies with renal failure patients after 8 weeks of treatment with the same or other statin [9, 10].

CRP did not change significantly during the 28 days of treatment when the whole cohort was analyzed. However, the results changed when the response to fluvastatin treatment in patients with CRP ≥4.5 mg/l at baseline was separately analyzed; a significant reduction of this protein at 28 days of treatment was observed and this decrement was significantly different from the baseline and the post-treatment CRP values (table 3); both values were the average of two measurements on 2 consecutive weeks before and after the treatment period; this method of CRP calculation takes in consideration and corrects for significant variability with time of this acute phase reactant [8]. This difference in CRP reduction in patients included in the present study is in contrast to the results of other studies in renal failure patients [5, 7, 10] and could be attributed either to the short treatment period which may not have allowed all patients to respond or to the different method used for CRP estimation – the average of two consecutive measurements – in the present study. In any case, a direct comparison to other studies is difficult because the CRP measurements were done at different time intervals after statin initiation [5, 7, 10]. For the more inflamed patients included in this study, CRP reduction was significant and this finding is in accordance to the stronger response to statins observed in patients at higher CRP quartiles in studies with non-renal failure patients [11].

The inflammatory capability of IL-6 and its modification by fluvastatin treatment was investigated in the present study by this pro-inflammatory cytokine serum level measurement but also by its soluble receptor – sIL-6R – determination; this later molecule seems to influence essentially the real activity of IL-6 [12]. Our results were unexpected. Although IL-6 was reduced at the 28th day of the fluvastatin treatment and this reduction was more rapidly apparent (at the 14th day) in the more inflamed patients, sIL-6R was increased at the 28th day of the treatment in the whole cohort and remained unchanged in the more inflamed subgroup of patients. These results were unexpected because sIL-6R is postulated to have an agonistic and not an antagonistic role, enhancing and contributing to the IL-6 activity in cells that do not constitutively express the IL-6 membrane receptor (IL-6R) [12]. It was therefore reasonable to expect the immunomodulating effect of fluvastatin to modify the serum level of both molecules in the same direction, not in the opposite. Nevertheless, a recently published study showed that cellular cholesterol depletion triggers shedding of IL-6R from the cell surface [13]. Shedding of this receptor is one of two mechanisms postulated to induce sIL-6R production [12]. On the other hand, cellular cholesterol deple-

tion is a well-known mechanism of the hypocholesterolemic action of statins [14]. Finally, although the majority of the studies support the agonistic activity of sIL-6R on IL-6 responses, some recent studies found that this soluble molecule may potentiate the antagonistic activity of soluble gp130 – the main natural antagonist of IL-6 [15, 16]. Taking in consideration all the above data, it is possible that our results – namely the sIL-6R serum increases after fluvastatin treatment – although unexpected, may be of importance and more studies are needed to further clarify these findings.

The anti-inflammatory cytokine IL-10 was significantly increased on day 14 of fluvastatin administration and the response to this treatment was even stronger than in the subgroup of patients having lower initial levels of this molecule. This finding confirms recent experimental studies showing that statins promote T-helper 2 cells polarization [17] and underlines the fact that diverse pathways are activated by these drugs in the process of modulating inflammation.

The anti-oxidant effect of fluvastatin was also evident by the rapid and significant ox-LDL reduction. Circulating oxidized LDL measured by using the same specific monoclonal antibody – mAb-4E6 – used in the present study, was recently found by others to be correlated not only to clinically apparent but also to subclinical atherosclerosis [17].

Finally, although patients treated with sevelamer hydrochloride have lower lipid levels at baseline, their response to fluvastatin treatment was similar to the other patients, regarding inflammatory markers modification (with the exceptions of sIL-6R and ox-LDL that was already lower at baseline in this subgroup of patients).

Our study was limited by the absence of a control group. Although the baseline values of the parameters measured were obtained applying strict inclusion criteria for the patients and the post treatment values were determined after a wash-out period, this limitation is only partially corrected. Apart from the variability in time of the CRP that was corrected by the two consecutive measurements, this temporal variability may be valid as well for IL-6, sIL-6R, IL-10 and ox-LDL that were measured once at baseline and 2 weeks after fluvastatin treatment.

In conclusion, this study showed that the time interval for the appearance of fluvastatin's (a synthetic statin indicated for renal failure patients because it is least likely to provoke rhabdomyolysis [19]) pleiotropic effects is short and similar to that found in the non-renal failure patients [10, 20]. These effects are achieved by the modulation by this drug of the pro-inflammatory, anti-inflammatory and anti-oxidant mechanisms implicated in the inflammatory process. It appears that HD patients with a higher degree of inflammation, which represent a considerable percentage of HD patients, have a more rapid and stronger response to this treatment. The clinical usefulness of these findings, if confirmed in larger studies, might be that statins could be used both for treating acute atherosclerosis-related complications and as a chronic anti-inflammatory regimen capable of modulating inflammation, activating diverse mechanisms, in this patient population.

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