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Comparison of atorvastatin versus fenofibrate in reaching lipid targets and influencing biomarkers of endothelial damage in patients with familial combined hyperlipidemia

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Abstract

Statins and fibrates have different effects on lipid abnormalities of familial combined hyperlipidemia (FCHL); thus, the selection of the first-line drug is troublesome. We evaluated to what extent monotherapy with a potent statin is more effective than fibrate in reaching the recommended lipid targets in FCHL. Fifty-six patients were randomized to receive optimal dosage of atorvastatin (n = 27) or 200 mg/d micronized fenofibrate (n = 29) for 24 weeks. To reach the optimal dosage, atorvastatin was up-titrated at each follow-up visit if low-density lipoprotein (LDL) cholesterol >130 mg/dL (>100 mg/dL in patients with coronary or cerebrovascular disease). The effects of fenofibrate and atorvastatin on lipoprotein fractions as well as on plasma levels of endothelin-1 (ET-1) and adrenomedullin (AM) were also evaluated. At end of trial, a greater proportion of patients on atorvastatin (average dosage, 20.8 mg/d) reached lipid targets in comparison with those on fenofibrate (64% vs 32.1%, $P = .02$). Atorvastatin was significantly more effective in reducing total cholesterol, LDL cholesterol, apolipoprotein B, and non–high-density lipoprotein (HDL) cholesterol. Conversely, triglycerides decreased and HDL increased more during fenofibrate. Nevertheless, atorvastatin produced a marked reduction in very low-density lipoprotein and very low-density lipoprotein remnants. Atorvastatin lowered all LDL subtypes, although fenofibrate appeared to be more effective on denser LDL. Compared with 43 normolipemic controls, FCHL patients presented increased baseline plasma levels of ET-1 ($P = .007$) but not of AM. Fenofibrate, but not atorvastatin, significantly lowered ET-1 levels by 16.7% ($P < .05$). Neither drug significantly affected plasma concentrations of AM. In summary, although fenofibrate showed superiority in raising HDL and reducing ET-1, atorvastatin was more effective in reaching lipid targets in FCHL so that it can be proposed as the first-line option in the management of this atherogenic hyperlipidemia.

1. Introduction

Familial combined hyperlipidemia (FCHL) is a common atherogenic dyslipidemia characterized by elevated concentrations of triglyceride-rich lipoproteins (TGRLs) (mainly very low-density lipoprotein [VLDL]) and/or low-density lipoproteins (LDLs) [1-3]. Other features of FCHL are increased concentration of apolipoprotein (apo) B and the preponderance of small dense LDL subfractions (sdLDL) [4]. Current guidelines recommend lowering both LDL cholesterol (LDL-C) and TGRL to reduce cardiovascular risk in these patients [5].

The first-line drug for FCHL patients is still uncertain. Statins are very effective in reducing LDL-C, but do not always correct increased TGRL [6]; on the other hand, fibrates markedly lower plasma total triglycerides (TGs), but modestly lower total cholesterol (TC) and LDL-C [7]. Given that combination therapy with statin plus fibrate confers an increased risk of myopathy and rhabdomyolysis [8], a

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possible alternative might be to use more potent statins. Atorvastatin is one of the most potent statins [9], and its efficiency in reducing TGRLs has also been demonstrated [10]. However, the dosage of atorvastatin that is effective in most FCHL patients has not been clearly established.

Besides their effects on blood lipid levels, the ability of these drugs to influence additional vascular risk factors may be relevant for the selection of the optimal treatment. It has been noted that FCHL patients present abnormalities in the endothelial function [11,12]. Several factors have been associated to endothelial dysfunction, the most investigated of which is the endothelial-derived nitric oxide (NO) [12,13]. Endothelin (ET-1) acts as the natural counterpart to the endothelium-derived NO. In fact, ET-1 has been demonstrated to inhibit endothelial NO release, thereby impairing endothelium-dependent relaxation and promoting atheroma formation [14]. Few data are available in humans on changes in plasma levels of ET-1 during atorvastatin or fenofibrate therapy. More recently, attention has been focused on adrenomedullin (AM). It is a vasodilator peptide having a wide range of biological actions such as reduction of oxidative stress and inhibition of endothelial cell apoptosis [15]. Overexpression of AM suppressed intimal thickening, fatty streak formation, and perivascular hyperplasia in rodent models for vascular remodeling or atherosclerosis [16]. No data about the influence of atorvastatin and fenofibrate on plasma levels of AM are available.

We designed this study with the primary aim of comparing the efficacy of fenofibrate vs the optimal LDL-lowering dosage of atorvastatin in reaching lipid targets in patients with FCHL. To identify the optimal dosage of atorvastatin, its daily dose was titrated up to 80 mg/d according to attaining LDL-C <130 mg/dL (or <100 mg/dL in patients with coronary or cerebrovascular disease). As an additional objective, the ability of these 2 drugs to correct lipoprotein abnormalities in FCHL was also compared. Finally, we took the opportunity of this drug trial to evaluate the effects of fenofibrate and atorvastatin on plasma levels of ET-1 and AM.

2. Methods

2.1. Study population

Patients between 30 and 75 years old with diagnosis of FCHL were selected for the study. They were enrolled from FCHL kindreds identified in the framework of a genetic study on this hyperlipidemia. The FCHL status was diagnosed according to previously reported criteria [17-19]. Briefly, FCHL-affected individuals were required to have TC and/or TG levels greater than or equal to that of age- and sex-specific 90th Italian population percentiles, and/or *hyperapobetalipoproteinemia*, defined as isolated elevation of plasma apo B concentrations (>130 mg/dL corresponding to the 90th Italian population percentile). Only families with at least 2 affected members presenting different lipid phenotypes were enrolled. Individuals with type III hyperlipidemia, diagnosed by the presence of a broad β band on electrophoretogram and apo E-2/E-2 genotype, were excluded. Family members were tested twice for plasma lipids during ad libitum diet and were considered affected only if both samples were greater than cutoff values. Other acquired causes of dyslipidemia were ruled out by standard laboratory tests. Individuals with obesity (body mass index >30 kg/m^2) or poorly controlled diabetes mellitus (blood glucose >120 mg/dL and/or glycosylated hemoglobin >6.0%) and those taking lipid-affecting drugs were excluded.

2.2. Study design

The study was designed as a randomized, open-label trial. Eligible patients entered a washout phase where they were instructed to maintain a standard lipid-lowering diet for 6 weeks before the baseline blood analysis. Thereafter, they were randomly assigned to receive either 10 mg atorvastatin or 200 mg micronized fenofibrate daily. Follow-up visits that included clinical assessment, blood drawings, and compliance evaluation were scheduled at 6, 12, 18, and 24 weeks. In the atorvastatin group, drug dosage was doubled at each visit (up to 80 mg/d) if LDL-C levels remained >130 mg/dL (or >100 mg/dL in patients with coronary or cerebrovascular disease). Conversely, in the fenofibrate group, the dosage of 200 mg/d remained unchanged throughout the treatment period. Compliance to drug treatment was evaluated by counting returned pills and expressed as percentage of taken over scheduled doses.

Sample size was estimated assuming a 2-sided level of statistical significance of .05, 80% power, and a between-group difference of responders of 100%. This resulted in a requirement of 30 subjects for each treatment group.

The study was approved by the institutional Ethical Committee, and all subjects gave written informed consent to participate into the study.

2.3. Lipid, lipoprotein, and apo measurements

Blood samples were collected early in the morning after an overnight fast in EDTA-containing tubes. Plasma was obtained by centrifugation at 4°C and added with EDTA (0.04%), NaN_3 (0.05%), and phenylmethylsulfonyl fluoride (0.015%) to prevent lipoprotein modification. Some aliquots were immediately used, and others were stored at −80°C for future measurements.

Plasma and lipoprotein fractions were assayed for TC and TG using enzymatic reagents, and HDL-C was determined as reported [17]. Total protein content of lipoprotein fractions was assayed by a modified Lowry's procedure [20]. Lipoproteins were isolated from fresh plasma by sequential ultracentrifugation as described [21]. Briefly, plasma samples (4 mL) were spun at 40 000 rpm at 10°C for 16 hours to isolate VLDL and intermediate-density lipoprotein fraction (density, <1.019 g/mL), for 18 hours for light LDL (density, 1.019-1.035 g/mL), and for 20 hours for dense

Table 1
Baseline characteristics of the study population

Variables	FCHL patients (n = 56)
Age (y)	53.2 ± 9.0
Sex (M/F)	38/18
Body mass index (kg/m^2)	26.0 ± 2.9
Current smoking (n [%])	11 (19.6)
Hypertension (n [%])	18 (32.1)
Diabetes mellitus (n [%])	6 (10.7)
Coronary heart disease (n [%])	6 (10.7)
Cerebrovascular disease (n [%])	4 (7.1)
HLP phenotypes [a] (n [%])	
IIA	12 (21.4)
IIB	4 (7.1)
IV	14 (25.0)
Isolated hyperapo B	26 (46.4)
Plasma lipids (mg/dL)	
TC	264.7 ± 46.7
LDL-C	170.3 ± 32.3
HDL-C	44.9 ± 13.1
TG	270.9 ± 367.5
Apo B	159.3 ± 23.7
Apo E genotypes (n [%])	
E-3/E-3	33 (58.9)
E-3/E-4	15 (26.8)
E-3/E-2	7 (12.5)
E-4/E-4	1 (1.8)

Values are expressed as means ± SD and numbers, (%).

[a] HLP indicates hyperlipidemic; IIA phenotype is defined as TC >90th and TG <75th percentile; IIB phenotype as TC and TG >90th percentile; type IV phenotype as TC <75th and TG >90th percentile; isolated hyperapo B phenotype as plasma apo B concentrations >130 mg/dL.

LDL (density, 1.035-1.068 g/mL). It has been reported that light LDL included predominantly LDL-I and LDL-II particles (>25.5 nm) and dense LDL included predominantly LDL-III particles (<25.5 nm) [21].

Total plasma apo B, apolipoprotein A-I (apo A-I), apolipoprotein A-II (apo A-II), and Lp(a) were measured by an immunoturbidimetric method (Kone Instruments, Espoo, Finland). To avoid assay drift, these measurements were performed at the end of the study in one assay.

2.4. Plasma ET-1 and AM measurements

Plasma concentrations of ET-1 and AM were determined in 47 FCHL patients (21 randomized to atorvastatin and 26 to fenofibrate) on blood sample obtained at baseline and after 6 and 24 weeks of treatment. Forty-three normolipemic subjects were included as controls (mean age, 57.0 ± 5 years; TC, 149 ± 21 mg/dL; and TG, 138 ± 20 mg/dL). Plasma ET-1 was determined by a specific radioimmunoassay using rabbit anti-endothelin-1 antibody (Peninsula Laboratories, Belmont, CA) according to a previously described method [22]. Interassay and intraassay variabilities of ET-1 measurements were 13% and 9%, respectively. Adrenomedullin was measured by using commercially available radioimmunoassay (Phoenix Pharmaceuticals, Mountain View, CA) as previously described [23]. The intraassay and interassay coefficients of variation were 5.1% and 12%, respectively. The AM and ET-1 measurements were performed in duplicate on frozen samples at the end of the study.

2.5. Other laboratory methods

Serum creatinine, uric acid, and the other safety parameters were determined during the lipid-lowering treatment using the standard laboratory methods. Apolipoprotein E genotype was determined as reported [17].

2.6. Statistical analysis

For the purpose of the present analysis, only baseline, 6-week, and 24-week lipid and lipoprotein values are reported. Data are expressed as mean ± SD or as percentages where appropriate.

For all efficacy analyses, a modified intention-to-treat model was used that included all randomized and treated patients with a baseline and at least one valid on-treatment measurement. Missing values were replaced using the "last observation carried forward" technique. Within treatment, parameters were compared by using Student t test for paired data; mean changes from baseline and their 95% confidence intervals (CIs) were also calculated. Categorical variables were analyzed by χ^2 test. Comparison between treatment groups was performed by the analysis of covariance method, and sums of squares type III were used. Baseline value of the response variable was considered as a covariate.

Nonparametric tests (Mann-Whitney test) were used to compare parameters showing skewed distribution. To describe association between variables, correlation coefficients were calculated by using Pearson's test. A logistic regression analysis including, age, sex, baseline lipid parameters, apo E genotype, and treatment as independent variable was carried out to identify factors predicting the response to therapy.

All analyses were performed using SAS Software (version 8.02, TS level 01M0; SAS, Cary, NC). A probability value of less than .05 was taken as statistically significant.

3. Results

3.1. Participant enrollment and characteristics

Four patients withdrew consent during the washout phase; and therefore, 56 patients were randomized to treatment. Their clinical characteristics are reported in Table 1.

Twenty-seven patients received atorvastatin and 29 fenofibrate. Their baseline clinical characteristics did not differ significantly in all tested parameters (data not shown). Two patients in either group prematurely interrupted the study, one for acute myocardial infarction and one for creatine phosphokinase increase in the atorvastatin group, and one for sudden death and one for mild elevation of hepatic transaminases in the fenofibrate group. Atorvastatin at the dosage range of 10 to 40 mg/d allowed reaching LDL-C targets in all FCHL patients so that none

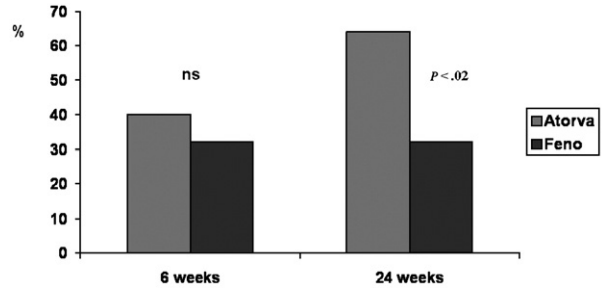

Fig. 1. Percentage of FCHL patients reaching the therapeutic goals during atorvastatin and fenofibrate treatment. Results of the intention-to-treat analysis in 27 patients on atorvastatin and 29 on fenofibrate. *Therapeutic goal* is defined as LDL-C <130 mg/dL (or <100 mg/dL in patients with coronary or cerebrovascular disease) and TG <200 mg/dL. At week 24, the average dosage of atorvastatin was 20.8 mg/d and that of fenofibrate was 200 mg/d.

required 80 mg/d. In particular, 10 patients (40.0%) maintained the starting dose of 10 mg/d, 9 patients (36.0%) received 20 mg/d, and 6 (24.0%) received a dose of 40 mg/d. At week 24, the average dose in the atorvastatin group was 20.8 mg/d. Compliance to test drug was comparable in the treatment groups (94.6% [range, 73.8%-102%] in the atorvastatin group and 96.5% [range, 83.4%-100.6%] in the fenofibrate group).

Body weight did not change during fenofibrate, whereas during atorvastatin, it showed a slight but significant increase at week 24 compared with baseline (74.7 ± 10.7 kg vs 73.8 ± 9.4 kg, $P < .05$). Plasma creatinine remained unchanged in the atorvastatin group, whereas it showed a significant increase in the fenofibrate group (from 1.05 ± 0.2 mg/dL at baseline to 1.18 ± 0.2 mg/dL at week 24, $P < .001$). However, no patients presented values greater than 1.3 mg/dL (data not shown).

3.2. Effects of treatments on plasma lipids and lipoproteins

At week 24, 16 patients (64.0%) in the atorvastatin group and 9 (32.1%) in the fenofibrate group reached the recommended lipid targets; and this difference was statistically significant ($P = .02$) (Fig. 1). Compared with fenofibrate, atorvastatin was more effective in obtaining therapeutic successes also at 10 mg/d (40% vs 31.2% at week 6); but the difference did not reach statistical significance ($P = .552$) (Fig. 1).

Treatment was considered successful when LDL-C <130 mg/dL (or <100 mg/dL in patients with coronary or cerebrovascular disease) and TG <200 mg/dL. After applying the LDL-C <100 mg/dL cutoff also to diabetic patients, a more pronounced difference in the percentage of responders was seen between treatment groups (64.0% in atorvastatin vs 28.6% in fenofibrate, $P < .01$). Moreover, when patients with severe hypertriglyceridemia (TG >400 mg/dL; 4 on fenofibrate and 3 on atorvastatin) were excluded from the analysis, the between-group difference in responders was only marginally affected ($P < .03$).

In the logistic regression analysis, the assignments to atorvastatin (positively at $P = .014$) and baseline TGs (negatively at $P = .009$) were the only variables predicting the therapeutic response (data not shown). We determined that baseline TGs <300 mg/dL was associated with the highest probability (odds ratio = 8.5; 95% CI, 2.3-15.3; $P < .001$) to correct lipid profile during treatment.

Table 2 reports the effects of both medications on lipids, apoproteins, and other biochemical parameters. Total cholesterol and LDL-C showed a statistically significant decrease in both treatment groups ($P < .001$ at any time point). However, atorvastatin was significantly more effective than fenofibrate in reducing both TC and LDL-C levels. In fact, the mean percentage changes of TC from baseline to

Table 2
Changes of plasma lipids and apoproteins and other biochemical parameters during atorvastatin and fenofibrate treatment in FCHL patients

Variables (mg/dL)	Atorvastatin (n = 27)			Fenofibrate (n = 29)			Treatment difference with respect to percentage changes *	
	Baseline	6 wk	24 wk	Baseline	6 wk	24 wk	Estimate (95% CI)	*P*
TC	258.3 ± 42.2	192.6 ± 33.4 *	182.2 ± 29.8 *	273.4 ± 50.8	223.3 ± 35.3 §	211.0 ± 31.2 §	− 9.0 (−15.1, −3.0)	.004
LDL-C	166.2 ± 33.7	108.9 ± 32.5 *	105.8 ± 21.8 *	176.4 ± 32.6	148.0 ± 29.5 §	135.5 ± 31.7 §	−17.0 (−26.1, −8.0)	<.001
Non–HDL-C	213.7 ± 41.4	147.3 ± 34.9 *	137.2 ± 30.0 *	228.2 ± 50.8	174.4 ± 42.0 §	160.5 ± 36.6 §	−7.6 (−15.6, 0.3)	.059
Apo B	160.0 ± 25.2	122.7 ± 16.6 *	120.7 ± 24.7 *	161.2 ± 21.1	134.4 ± 26.5 §	130.0 ± 27.1 §	−5.8 (−14.5, 2.8)	NS
TG	239.3 ± 152.9	192.0 ± 119.0	158.1 ± 90.1 *	306.5 ± 490.6	144.5 ± 198.1 ‡	132.2 ± 105.2 †	15.5 (3.35, 27.7)	.013
HDL-C	44.7 ± 11.7	45.3 ± 14.2	45.0 ± 11.5	45.2 ± 15.2	48.9 ± 15.7 †	50.5 ± 14.1 †	−14.2 (−24.6, − 3.8)	.008
Apo A-I	132.5 ± 22.3	133.2 ± 20.6	132.6 ± 24.6	134.1 ± 16.3	139.8 ± 19.6 †	140.6 ± 18.4 †	−5.2 (−10.2, −0.1)	.044
Apo A-II	32.9 ± 3.7	33.8 ± 3.8	32.4 ± 2.7	33.4 ± 4.2	39.4 ± 4.0 §	39.7 ± 3.8 §	−22.0 (−27.2, −16.8)	<.001
Lp(a)	16.8 ± 20.1	17.9 ± 21.0	16.4 ± 19.3	18.2 ± 21.5	18.2 ± 22.0	18.5 ± 22.3	−16.1 (−49.9, 17.6)	NS
Fibrinogen	298.0 ± 22.4	294.4 ± 21.8	295.3 ± 24.6	286.7 ± 23.4	295.9 ± 29.6	299.2 ± 22.7 ‡	− 1.51 (−6.22, 3.19)	NS

Non–high-density lipoprotein cholesterol was calculated as TC − HDL-C. Data are reported as means ± SD. Atorvastatin vs fenofibrate difference between baseline and 24-week percentage changes. NS indicates not significant.

* $P < .001$ for comparison with baseline values in the atorvastatin-treated group.

§ $P < .001$ for comparison with baseline values in the fenofibrate-treated group.

‡ $P < .01$ for comparison with baseline values in the fenofibrate-treated group.

† $P < .05$ for comparison with baseline values in the fenofibrate-treated group.

Table 3
Changes in TGRL and in light and dense LDL subfractions during atorvastatin and fenofibrate treatment in FCHL patients

Variables	Atorvastatin (n = 27)			Fenofibrate (n = 29)			Treatment difference with respect to percentage changes *	
	Baseline	6 wk	24 wk	Baseline	6 wk	24 wk	Estimate (95% CI)	*P*
TGRL (mg/dL)								
Cholesterol	48.4 ± 22.0	34.3 ± 19.5 *	34.3 ± 23.2 *	53.5 ± 27.6	25.1 ± 12.0 ‖	25.4 ± 15.6 ‖	26.0% (1.85%, 50.1%)	.035
Triglycerides	165.8 ± 102	142.8 ± 114.0	112.3 ± 84.8 †	163.4 ± 112	68.4 ± 42.6 ‖	73.6 ± 66.0 ‖	28.7% (13.7%, 43.6%)	<.001
Light LDL (mg/dL)								
Cholesterol	140.6 ± 40.3	95.9 ± 27.9 †	86.4 ± 21.1 †	146.4 ± 36.1	130.9 ± 26.6 ‡	121.6 ± 26.4 §	−26.0 (−36.6%,−15.4%)	<.001
Triglycerides	28.0 ± 8.6	21.2 ± 5.8 †	17.7 ± 5.9 †	32.2 ± 12.8	23.1 ± 8.4 ‖	23.2 ± 7.6 ‖	−17.8 (−30.8%, −4.8%)	.008
Total protein	87.2 ± 31.7	56.1 ± 22.4 †	45.3 ± 11.2 †	80.4 ± 23.0	64.0 ± 19.3 ‖	57.5 ± 16.2 ‖	−14.8% (−25.9%,−3.8%)	.010
Dense LDL (mg/dL)								
Cholesterol	23.8 ± 14.3	20.6 ± 8.6	20.8 ± 7.8	27.8 ± 17.4	15.1 ± 7.1 ‖	17.3 ± 12.5 ‡	−7.0% (−81.9%, 67.3%)	NS
Triglycerides	7.0 ± 3.8	7.1 ± 3.6	6.4 ± 3.6	6.9 ± 4.8	3.8 ± 1.4 ‖	6.0 ± 4.7	−22.2 (−84.6%, 40.2%)	NS
Total protein	31.6 ± 14.9	32.0 ± 13.8	27.7 ± 14.7	30.4 ± 15.4	25.5 ± 15.4	19.2 ± 7.1 ‖	32.25 (12.4%, 52.0%)	.002

Triglyceride-rich lipoprotein (TGRL) corresponds to density fraction <1.019 g/mL. Data are reported as means ± SD. Atorvastatin vs fenofibrate difference between baseline and 24-week percentage changes.

* $P < .01$ for comparison with baseline values in the atorvastatin-treated group.
† $P < .001$ for comparison with baseline values in the atorvastatin-treated group.
‡ $P < .05$ for comparison with baseline values in the fenofibrate-treated group.
§ $P < .01$ for comparison with baseline values in the fenofibrate-treated group.
‖ $P < .001$ for comparison with baseline values in the fenofibrate-treated group.

week 24 were −28.3 ± 13.8% in the atorvastatin group and −21 ± 12.4% in the fenofibrate group, resulting in a between-group difference of 9.05% ($P = .004$). Similarly, LDL-C decreased by 34.6 ± 13.9% in the atorvastatin group and 20.9 ± 21.3% in the fenofibrate group, resulting in a significant incremental difference of 17.0% in favor of atorvastatin ($P < .001$). Both treatments also significantly improved non–HDL-C ($P < .001$ at any time point), but the between-group difference was of borderline significance (Table 2). Conversely, in the fenofibrate group, HDL-C showed a significant increase at any time point, whereas no substantial changes were observed in the atorvastatin group. After 24 weeks of treatment, the mean percentage changes of HDL-C were +15.8 ± 25.3% with fenofibrate and +2.0 ± 15.5% with atorvastatin group, resulting in a significant 14.2% treatment difference in favor of fenofibrate ($P = .008$).

During fenofibrate, TGs showed a significant reduction at any time point, whereas in the atorvastatin group, the decreases were smaller and significant only at week 18 (data not shown) and at week 24. At this time point, mean percentage changes from baseline were −27.2 ± 26.2% ($P = .001$) in the atorvastatin group and −44.1 ± 20.9% ($P = .029$) in the fenofibrate group, resulting in an incremental 15.5% reduction during fenofibrate ($P = .013$).

Changes in the absolute concentrations of TGRL and LDL subfractions are reported in Table 3. After 24 weeks of therapy, TGRLs appeared to be more favorably affected by fenofibrate than atorvastatin. In fact, TC and TG in the density fraction <1.019 g/mL were reduced, respectively, by 50.5% and 54.8% with fenofibrate and by 22.8 and 26.2% with atorvastatin; and the treatment differences were all statistically significant in favor of fenofibrate ($P = .035$ for TC and $P < .001$ for TG). Although both treatments decreased large, buoyant LDL (light and intermediate-dense LDL subtypes), atorvastatin was significantly more effective than fenofibrate in reducing concentrations of cholesterol, triglycerides, and total protein in this LDL subfraction. Conversely, atorvastatin therapy showed only a modest effect on denser LDL, whereas fenofibrate resulted in a relative reduction of this LDL subtype. As evaluated in terms of cholesterol distribution, fenofibrate determined, at week 24, a shift of LDL subtypes from dense (−21.9%) to large, buoyant LDL (+4.2%), whereas atorvastatin produced opposite changes (+33.8% in dense and −5.8% in large LDL).

Both treatments significantly improved plasma concentrations of apo B ($P < .001$ at any time point). However, the difference between treatments was not statistically significant (Table 2). In concordance with changes in HDL-C levels, fenofibrate significantly increased plasma levels of apo A-I and apo A-II at any time point, whereas atorvastatin did not determine any significant variation of these parameters. After 24 weeks of fenofibrate therapy, apo A-I increased by 5.2 ± 10.1% and apo A-II by 20.0 ± 14.7% (Table 2). No significant changes were observed in plasma concentrations of Lp(a) during either atorvastatin or fenofibrate treatment. Although fibrinogen showed a slight but significant increase after 24 weeks of treatment with fenofibrate, no difference was observed when treatments were compared (Table 2).

3.3. Effects of treatments on ET-1 and AM levels

Baseline levels of ET-1 were significantly higher in FCHL compared with controls (10.9 ± 8.0 pg/mL vs 7.5 ± 2.6 pg/mL, $P = .007$). Conversely, no difference was observed in plasma levels of AM (16.1 ± 19.1 pg/mL vs 11.4 ± 4.4 pg/mL, $P = .59$). In the group of FCHL patients, inverse correlations was found between ET-1 and HDL-C ($r = −0.344$, $P < .05$) and between AM and LDL-C

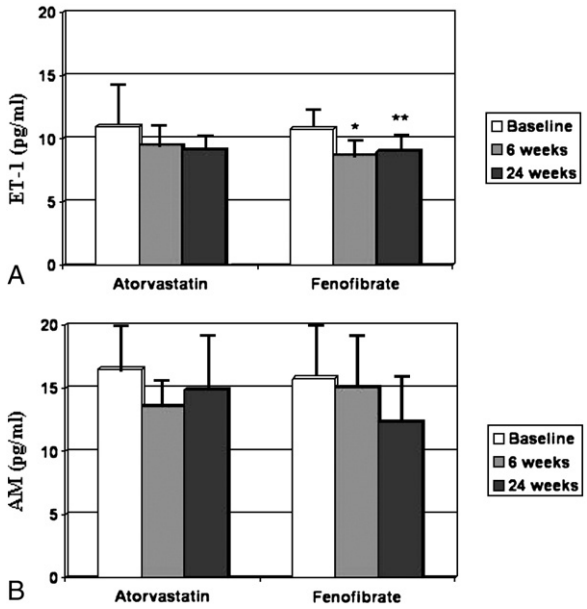

Fig. 2. Effect of treatment with atorvastatin (n = 21) or fenofibrate (n = 26) on plasma concentration of ET-1 (A) and AM (B). Data are presented as mean ± SE. *$P < .048$, **$P < .020$ for comparison with baseline values.

($r = -0.485$, $P = .001$), apo B ($r = -0.404$, $P = .005$), and HDL-C ($r = -0.342$, $P < .05$).

During both treatment regimens, no significant changes were observed in the plasma levels of AM (Fig. 2A). After 24 weeks of therapy, AM was reduced more by fenofibrate than by atorvastatin (−21.1% vs −9.7%); but this difference was not significant. Plasma ET-1 levels were marginally, but significantly, reduced during fenofibrate (−16.7%, $P < .05$), whereas these did not change during atorvastatin (Fig. 2B).

4. Discussion

It is still uncertain whether the first-line treatment of FCHL should consist of statin monotherapy or fibrate monotherapy. Other studies have compared atorvastatin and fenofibrate in mixed hyperlipidemia [24-27], but none have evaluated the effectiveness of these 2 drugs in obtaining lipid targets. Here we report that monotherapy with atorvastatin at the average dosage of 20 mg/d is more effective than 200 mg micronized fenofibrate in reaching recommended lipid targets in patients with FCHL. After 24 weeks of therapy, 64% of patients taking atorvastatin reached the therapeutic targets compared with only 32% of those taking fenofibrate. The superiority of atorvastatin over fenofibrate was found to be even more pronounced when more selective lipid targets were used.

This result was certainly due to the fact that atorvastatin, when compared with fenofibrate, produced an incremental reduction of TC, LDL-C, and apo B by 9%, 17%, and 5.8%, respectively. Although fenofibrate was more efficient in decreasing TGs, the overall better results observed during atorvastatin can be also attributable to the beneficial effect of this statin on the metabolism of TGRL. In agreement with previous observations [10,28], we found that atorvastatin significantly lowered VLDL and VLDL remnants and produced an additional 7.6% reduction of non–HDL-C compared with fenofibrate. Data from in vivo kinetic studies may provide the explanation for these effects of atorvastatin on TGRL metabolism in patients with mixed hyperlipidemias [29]. Besides increasing VLDL apo B removal, this drug has been demonstrated to reduce hepatic production of $VLDL_1$ and increase the delipidation of $VLDL_1$. It has been suggested that these effects of atorvastatin can be ascribed to the reduction of hepatocellular cholesterol and the stimulation of the LDL receptor pathway. In the same study [29], it was reported that fenofibrate lowered TGs and VLDL cholesterol by enhancing delipidation of $VLDL_1$ and $VLDL_2$ and increasing $VLDL_1$ catabolism, but not influencing VLDL production.

The comparison of atorvastatin and fenofibrate on LDL composition is relevant because patients with FCHL typically present increased concentration of atherogenic sdLDL [4]. Atorvastatin and fenofibrate similarly decreased all LDL subfractions, although atorvastatin was more effective in lowering large, buoyant LDL (light and intermediate-dense LDL subtypes) and fenofibrate showed a more pronounced action on sdLDL. These results are in good agreement with a number of other studies reporting that LDL subfractions usually fall in concert with little changes in the size distribution profile during statin [25,30-33], whereas they shift composition toward larger LDL subclasses during fenofibrate therapy [34]. It must be noted that if all LDLs are atherogenic and if small dense LDLs are particularly atherogenic, it could be hypothesized that atorvastatin, which decreases all LDL, is more efficient than fenofibrate, which preferentially affects sdLDL, in reducing the LDL-dependent risk of atherogenesis. Indeed, clinical trials have demonstrated that a reduction in total LDL decreased coronary mortality and morbidity independently of LDL particle size [35].

Consistent with previous reports [25,32], fenofibrate was demonstrated to be more effective than atorvastatin in increasing HDL, thus providing a possible advantage in the management of FCHL. However, a still unanswered question is whether raising HDL over LDL may be more efficacious in reducing risk for CAD [36]. Several major prevention trials demonstrated that fibrate-induced raising of HDL significantly reduced progression of coronary atherosclerosis and cardiovascular events [36]. However, it must be noted that the most part of this benefit is confined to subjects showing baseline low HDL-C associated with high TG [37], a phenotype resembling atherogenic dyslipidemia (ALP) more than FCHL [38]. Moreover, with the only exception of the Helsinki Heart Study [37], none included patients with characteristics of FCHL. Finally, recent analyses of intervention trials suggested that raising HDL in patients with persistently elevated LDL may produce only limited benefits on cardiovascular risk reduction [39].

An interesting result of our study is that about one third of FCHL patients failed to reach the therapeutic targets even at the optimal dose of atorvastatin. We may estimate that this could be the proportion of FCHL patients requiring combination therapy. We further found that the lack of success of therapy was strongly related to the baseline levels of TG greater than 300 mg/dL. Although this finding may be biased because of the limited TG-lowering effect of atorvastatin, it strongly supports the notion that FCHL is a metabolically heterogenous disorder where a significant proportion of patients may present defects in hepatic TG metabolism not modifiable by reducing hepatocellular cholesterol availability with statins [31] or by activating peroxisome proliferator–activated receptor α–mediated pathways with fenofibrate [7].

In this study, we have examined whether and to what extent atorvastatin and fenofibrate may affect plasma concentration of AM and ET-1, 2 poorly investigated vasoactive peptides. We found that baseline plasma levels of AM were not increased in FCHL and that neither fenofibrate nor atorvastatin significantly influenced them. Conversely, ET-1 levels were elevated in FCHL; and fenofibrate, but not atorvastatin, significantly reduced them already after 6 weeks of therapy. To the best of our knowledge, this is the first report describing increased ET-1 in FCHL; and it is consistent with previous studies showing impaired endothelial function in these individuals [11,13].

The effect of statins on plasma ET-1 is controversial. Previous in vitro studies have shown that statins reduce the expression of ET-1 in endothelial cells [40]. However, atorvastatin decreased ET-1 levels in normolipemic diabetic patients but not in subject at risk of diabetes [41]; and pravastatin did not change plasma ET-1 in well-controlled hypertensive individuals [42]. Although these discrepancies might be due to differences in patients' characteristics, in our comparison study, we found that only fenofibrate significantly lowered ET-1 levels in FCHL, supporting previous observations in patients with hypertriglyceridemia [43].

In summary, the results of the present study proved that atorvastatin is more efficient than fenofibrate in reaching the recommended lipid targets in FCHL and thus can be proposed as the first-choice drug in the therapy for this atherogenic hyperlipidemia. Whether the superiority of fenofibrate in influencing HDL metabolism and reducing ET-1 could translate into clinical benefits in FCHL patients deserves further investigation.

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