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Effects of Intensive Atorvastatin and Rosuvastatin Treatment on Apolipoprotein B-48 and Remnant Lipoprotein Cholesterol Levels

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Abstract

Atorvastatin and rosuvastatin at maximal doses are both highly effective in lowering low density lipoprotein cholesterol (LDL-C) and triglyceride (TG) levels. Rosuvastatin has been shown to be more effective than atorvastatin in lowering LDL-C, small dense LDL-C and in raising high density lipoprotein (HDL) and its subclasses. Intestinal lipoproteins containing apolipoprotein (apo) B-48 are also thought to be atherogenic particles. Our purpose in this study was to compare the effects of daily oral doses of atorvastatin 80 mg/day and rosuvastatin 40 mg/day over a 6-week period on serum apo B-48 (a marker of intestinal lipoproteins) and remnant lipoprotein cholesterol (RemL-C) levels (a marker of partially metabolized lipoproteins of both intestinal and liver origin), using novel direct assays in 270 hyperlipidemic men and women. Both atorvastatin and rosuvastatin caused significant ($p < 0.0001$) and similar median decreases in TG (–33.0%, –27.6%), RemL-C (–58.7%, –61.5%), and apoB-48 (–37.5%, –32.1%) as compared to baseline. Our findings utilizing a specific immunoassay and a fairly large number of subjects extend prior studies indicating that statins significantly lower apolipoprotein B containing lipoproteins of both intestinal and liver origin.

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Keywords

Statins; lipoproteins; apolipoprotein B-48 and remnant lipoprotein cholesterol

INTRODUCTION

The Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin (STELLAR) trial was a 6-week trial that compared the effects of a newer statin, rosuvastatin, with atorvastatin, pravastatin, and simvastatin in hypercholesterolemic patients. Not only was rosuvastatin more effective than other statins in reducing calculated low density lipoprotein cholesterol (LDL-C) across the dose ranges, but it also was more effective in raising high density lipoprotein cholesterol (HDL-C) (1,2). In this trial, rosuvastatin at 40 mg/day had the greatest effect on HDL-C (+9.6%) while atorvastatin at 80 mg/day had the least effect (+2.1%). We have previously examined the effects of atorvastatin and rosuvastatin on HDL subpopulations as assessed by two dimensional gel electrophoresis, and found that both statins lowered pre-beta 1 HDL by approximately 40%, and that rosuvastatin 40 mg/day was twice as effective in raising large alpha 1 HDL particles (+24%) versus atorvastatin 80 mg/day (+12%) in a subset of STELLAR participants (3). We view these as very favorable effects on HDL subpopulations, based on our research on these particles in the Framingham Offspring Study, the Veterans Affairs HDL Intervention Trial, and the HDL Atherosclerosis Treatment Study (4-6). In addition we have compared maximal doses of atorvastatin and rosuvastatin and found rosuvastatin to be significantly more effective than atorvastatin in lowering direct LDL-C and small dense LDL-C (7).

The purpose of the current study was to compare the effects of atorvastatin 80 mg/day and rosuvastatin 40 mg/day on remnant lipoprotein cholesterol (RemL-C) and apolipoprotein (apo) B-48 levels, using novel assays and serum samples from the STELLAR study. This study was carried out in order to improve our understanding of the differences in the effects of the two drugs on lipoprotein subpopulations and to explore possible relevance to their clinical benefits.

METHODS

Study Design and Subjects

The details of the design and conduct of the STELLAR study and of the patient population have been published (1, 2). It was an open-label; randomized, parallel group study in hypercholesterolemic patients conducted in 182 centers in the United States. The primary objective was to compare the efficacy of rosuvastatin in the reduction of LDL-C with other statins across dose ranges. Secondary objectives included a comparison of the effects of the statins on other lipoprotein parameters such as HDL-C, apolipoprotein (apo) A-I and B, and lipid ratios (1). Men and non-pregnant women (adults aged 18 or more) with hypercholesterolemia were asked to follow a National Cholesterol Education Program step 1 diet for 6 weeks. Those who were compliant with the diet and had fasting calculated LDL-C levels ≥ 160 mg/dl and < 250 mg/dl and TG < 400 mg/dl were randomized to the different statin doses as described (1,2). Blood samples were collected on at least 3 occasions before

randomization and after 4 and 6 weeks of treatment and sent to a central lab (Medical Research International (MRI), Highland Heights, KY) for the measurement of lipid and lipoprotein parameters that included total cholesterol (TC), triglyceride (TG) calculated LDL-C, HDL-C, apo A-I and apo B measurements as described (1,2).

Measurement of Biochemical Parameters

For this sub-study, available serum samples that had been never thawed and had been frozen at -80°C , corresponding to the baseline (week 0) and the 6-week time points of the atorvastatin 80 mg/day and rosuvastatin 40 mg/day arms of the main study were sent on dry ice to the Cardiovascular Research Laboratory, Tufts University, in Boston, MA. In the rosuvastatin 40 mg and atorvastatin 80 mg arms of the STELLAR study, 158 and 167 patients, respectively were randomized and 152 and 160 patients had data recorded at baseline and after 6 weeks treatment. Archived serum samples corresponding to the randomization and 6-week time points were available for this study of lipoprotein subpopulation in 136 (89%) and 134 (84%) of these patients. These were serum samples that had been previously thawed at 37°C for assessment of HDL populations in our laboratory (3), and then had been rapidly refrozen at -80°C until use. We have documented that this procedure does not effect the results obtained with homogeneous direct assays of lipoprotein cholesterol content, HDL subpopulation analysis, or the apoB-48 enzyme linked immunosorbent assay (ELISA), and all samples were treated in identical fashion. Homogeneous direct LDL-C (using kits obtained from Kyowa Medex Corporation, Tokyo Japan), HDL-C and RemL-C (using kits obtained from Kyowa Medex Corporation, Tokyo Japan), and TC and TG (using kits obtained from Roche Diagnostics, Indianapolis, IND, and Wako Diagnostics, Richmond, VA) were measured on a Hitachi 911 analyzer. The characteristics and development of these assays have been previously described (8-12). The apoB-48 ELISA kits used for this study were purchased from the Shibayagi Company of Gunma, Japan (www.shibayagi.co.jp). The assay uses a monoclonal antibody that only recognizes apoB-48 and not apoB-100 (13). The antibodies were produced against a C terminal decapeptide with homology to apoB-48, and the assay is standardized with apoB-48 synthesized by recombinant technology. Recovery of added apoB-48 in serum was in excess of 95%, and mean values in fasting serum were 0.46 mg/dl, with marked increases in the post-prandial state. The characteristics and development of this assay have been previously described (13). To further validate the apoB-48 ELISA we measured apoB-48 in plasma and in the TG-rich lipoprotein fraction (TRL, density $< 1.006\text{ g/ml}$) after ultracentrifugation using samples from an atorvastatin kinetic study in which subjects were sampled in the fasting and fed state, and in which TRL apoB-100 and apoB-48 were quantitated by a total apoB assay and densitometric gel scanning of the TRL fraction after gel electrophoresis as previously described (14). In this prior study atorvastatin at 80 mg/day lowered TRL apoB-48 by about 25% in the fed state as compared to placebo. Moreover the results obtained by direct ELISA measurement versus the gel scanning method correlated significantly ($r=0.82$, $p<0.001$) based on 75 samples, but mean values (standard deviation) were 1.01 (0.43) and 0.50 (0.20) mg/dl, respectively. If one assumes that apoB-48 ELISA represents the true value, then the gel scanning methodology underestimates TRL apoB-48 levels by a factor of 2.02. These data indicate that our previously reported TRL apoB-48 values based on gel scanning need to be corrected by this factor. In addition the mean values

(standard deviation) for plasma and TRL apoB-48 as assessed by direct ELISA in this study based on 50 samples obtained in the fed state were 1.78 (0.72) and 1.09 (0.44) mg/dl, respectively. These results indicate that even in the fed state (hourly isocaloric feeding) only 61.2% of total plasma apoB-48 is found in the TRL fraction, with the remainder presumably being found in intermediate and low density lipoproteins.

The direct LDL-C assay has intra-, and Inter- assay coefficients of variation of 0.77% and 1.3%, respectively, while for the direct HDL-C assay these values were 0.82% and 0.76%, for RemL-C the values were 1.55% and 3.79%, respectively. For the apoB-48 ELISA they were 0.96% and 2.17%, respectively. Our laboratory maintains lipid standardization with the Centers for Disease Control, Atlanta, GA. Our analysis of STELLAR represents a post hoc analysis of an open labeled study, but all laboratory personnel were blinded from treatment information until all analyses were completed.

Data Analysis

The primary objective of this investigation was to compare the effects of atorvastatin 80 mg/day with rosuvastatin 40 mg/day on the changes in triglycerides, RemL-C and apoB-48 levels. Changes in all parameters from baseline and by treatment were compared using Mann-Whitney U test non-parametric statistical testing using Statview, version 5.0 (SPSS, Cary, NC). A p values of < 0.05 was considered statistically significant.

RESULTS

Subject Characteristics at Baseline

Tables 1 summarize the characteristics of patients randomized to the atorvastatin 80 mg and rosuvastatin 40 mg arms of the STELLAR study. The two groups of patients were well-matched according to gender, age, and disease characteristics, except that those placed on rosuvastatin had a somewhat higher prevalence of diabetes (9.5% versus 5.4%). The sample sizes presented in the tables represent the number of patients who both completed treatment and had serum samples available for measurement of lipoprotein subpopulations. The two groups were also reasonably well-matched with regard to baseline levels of lipoproteins (see table 2).

Changes and Percent Changes in Biochemical Variables

Data presented in table 2 represents values of all biochemical parameters measured at baseline off treatment and at 6 weeks on treatment. Data are presented as mean values with standard deviations, except for non-normally distributed variables (TG, RemL-C, and apoB-48) where the data are presented as the median values and the inter quartile ranges). As can be seen in table 2 both statins significantly altered all parameters measured versus baseline, except that only rosuvastatin significantly increased HDL-C levels. In table 3 we provide data on all biochemical variables for percentage changes with standard deviations for normally variables, and for the non-normally distributed variables as mean percent change with inter quartile ranges. As can be seen in table 3 both atorvastatin and rosuvastatin caused significant ($p<0.0001$) and similar percentage decreases in TC (-39.0% , -41.0%), TG (-33.0% , -27.6%), RemL-C (-58.7% , -61.5%), and apoB-48 (-37.5% ,

32.1%) levels. Moreover rosuvastatin treatment resulted in significantly greater reductions than atorvastatin in non-HDL-C (-48.2% versus -51.6% , $p=0.037$), and calculated LDL-C (-51.4% versus -55.4% , $p=0.020$). Reductions in direct LDL-C for both atorvastatin and rosuvastatin were highly correlated with reductions in calculated LDL-C ($r = 0.951$, $p < 0.001$), indicating that in general calculated LDL-C is sufficient for LDL-C assessment provided that the subjects are fasting and the serum triglyceride levels are < 400 mg/dl. Figure 1 shows the marked variability in treatment responses of TG, RemL-C and apoB-48 levels for all individuals (see Figure 1). We see the same marked degree of variability with both statins.

DISCUSSION

In the post-prandial state there are significant increases in levels of TG-rich lipoproteins of both intestinal and liver origin (15,16). Patients with coronary heart disease (CHD) not only have higher LDL-C and lower HDL-C levels, but they have elevated levels of TG and remnant lipoprotein cholesterol in both the fasting and fed state than controls (16). In addition elevated remnant lipoprotein cholesterol levels are an independent CHD risk factor for CHD, especially in women (17,18). Moreover patients with diabetes mellitus are clearly at increased CHD risk, and usually have normal LDL-C levels, but have elevated TG and remnant lipoprotein cholesterol levels, increased small dense LDL, and decreased HDL (19,20). It is important to emphasize that these earlier studies were all done using the remnant like particle cholesterol assay (RLP-C) developed and marketed by Otsuka Pharmaceutical Company, and not the present assay (RemL-C) that we utilized in this study, which was provided by Kyowa Medex. There may well be significant differences between the two methodologies in terms of results obtained on the same samples. The Kyowa Medex assay however does not require sample pre-treatment, in contrast to the Otsuka assay. However elevated remnant lipoprotein cholesterol values have also been reported with the RemL-C assay as compared to controls (12). Elisa Campos and colleagues have carefully examined the properties of triglyceride-rich and cholesterol-rich lipoproteins in the remnant-like particle fraction as isolated by the RLP kit methodology (21). These investigators have documented the about 25% of these particles contain apoB-48, with the remainder containing apoB-100 (21).

In our view atorvastatin and rosuvastatin are more effective than other statins such as simvastatin, lovastatin, pravastatin, and fluvastatin in lowering TRL and remnant lipoproteins because of their longer residence times in plasma. It is for this reason that these agents are probably also more effective than other statins in lowering triglyceride-rich lipoproteins and their remnants. We have previously documented that atorvastatin is more effective than other statins in lowering triglycerides, remnant lipoprotein cholesterol, and small dense LDL cholesterol and raising large HDL than the other statins that were tested (fluvastatin, lovastatin, pravastatin, and simvastatin) in both the fasting and fed state (22,23). Moreover we have previously documented that rosuvastatin raises large alpha 1 HDL twice as effectively as atorvastatin, and increases in this fraction have been linked to less progression and some regression of coronary atherosclerosis in patients treated with the simvastatin/niacin combination (3-6). We have also documented that maximal dose rosuvastatin is more effective than maximal dose atorvastatin in lowering small dense LDL

cholesterol (7). We have now extended our studies to compare the effects of rosuvastatin with atorvastatin at maximal doses on remnant lipoproteins and apoB-48, the only known biochemical marker specific for intestinal lipoproteins.

A number of other investigators have examined the effects of statins on levels of apolipoprotein (apo) B-48 within TRL in the fed state by using immunoassays for total apoB and gel scanning after gel electrophoresis in small numbers of hyperlipidemic or diabetic subjects. Cabezas et al reported that simvastatin lowered apoB-48 in TRL in 6 patients with familial combined hyperlipidemia in the post-prandial state as assessed by gel electrophoresis (24). Battula et al reported that cerivastatin reduced post-prandial apoB-48 in TRL in 8 patients with type 2 diabetes (25). Dane-Stewart et al documented that 80 mg/day of atorvastatin lowered post-prandial TRL apoB-48 in 10 CHD patients, and that this decrease was associated with an increase in LDL receptor activity as measured in peripheral monocytes (26). Verseyden et al reported that atorvastatin lowered both apoB-48 and apoB-100 in large TRL in 12 patients with familial combined hyperlipidemia following intravenous injection of Intralipid (27). We have previously documented that atorvastatin at both 20 mg/day and 80 mg/day significantly lowered TRL apoB-48 by about 25% in the fed state as compared to placebo, and that this reduction was linked to enhanced fractional clearance in 9 patients with combined hyperlipidemia (14). In contrast Hogue et al recently reported that atorvastatin reduced apoB-100 levels in lipoproteins by enhancing their fractional catabolism, but reduced TRL apoB-48 levels as assessed by gel electrophoresis due to decreased production in 12 patients with type 2 diabetes (28).

In the current study we examined the effects versus baseline of both atorvastatin 80 mg/day and rosuvastatin 40 mg/day given orally to a total of 270 patients with combined hyperlipidemia on both plasma apoB-48, triglyceride level, total B, and remnant lipoprotein cholesterol levels. In this study LDL cholesterol was reduced by more than 50% versus baseline by both statins, while median apoB-48 was decreased by 37.5% with atorvastatin 80 mg/day, and by 32.1% with rosuvastatin 40 mg/day. Plasma triglyceride levels were reduced by a similar amount (median reduction -33.0% on atorvastatin and -27.6% on rosuvastatin). Remnant lipoprotein cholesterol levels utilizing the RemL-C assay were reduced by a median of -58.7% on atorvastatin and -61.5% on rosuvastatin.

In contrast to previous studies, in this study we used a newly developed enzyme linked absorbent assay (ELISA) for apoB-48, that we have correlated with TRL apoB-48 values obtained from gel electrophoresis (see methods, $r=0.82$). However it should be noted that the gel scanning methodology substantially underestimated the TRL apoB-48 concentration, and that such values need to be multiplied by a factor of about 2 to obtain actual values. These data are consistent with the studies of Cohn et al which have documented differences in change in chromogenicity of apoB-48 and apoB-100 when TRL samples subjected to serial dilution are run on gel electrophoresis and stained with Coomassie blue (15). Other investigators have suggested identical chromogenicity of apoB-100 and apoB-48 on gels after staining with Coomassie blue, so there may other reasons for these discrepant absolute value. In addition we have shown that even in the fed state only about 60% of plasma apoB-48 is in the TRL fraction, consistent with studies of Hannia Campos et al which reported very substantial proportions of plasma apoB-48 not present in the TRL fraction

(29). In addition we have also documented that baseline plasma levels of apoB-48 are only 0.3% to 0.4% of total plasma apoB values in these hyperlipidemic subjects, and that significant and comparable reductions in plasma apoB-48 are induced by maximal doses of both atorvastatin and rosuvastatin.

Our data in a reasonably large number of hyperlipidemic individuals treated with maximal doses of the most effective available statins using an immunoassay specific for apoB-48 confirm and extend the current evidence that statin compounds lower the levels of intestinal as well as hepatic lipoproteins containing apoB. The major mechanisms whereby apoB-48 and apoB-100 fractional catabolism is enhanced by statins in our view is due to suppression of cellular cholesterol synthesis and compensatory upregulation of LDL receptor activity with increased clearance of both apoB-100 particles as well as apoB-48:apoE lipoproteins from the plasma space (14).

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Abbreviations

TC	Total cholesterol
TG	triglyceride
HDL-C	high density lipoprotein cholesterol
TC/HDL-C ratio	total cholesterol/HDL cholesterol ratio
LDL	low density lipoprotein
TC/HDL-C ratio	Total Cholesterol/HDL cholesterol ratio
RemL-C	remnant lipoprotein cholesterol
(apo) B-48	apolipoprotein
DM	Diabetes Mellitus
CHD	Coronary Heart Disease

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Figure 1.

The median value and the marked variability in percentage change responses from baseline of triglyceride, remnant lipoprotein cholesterol and apolipoprotein B-48 values following treatment with either atorvastatin 80 mg/day or rosuvastatin 40 mg/day are shown.

Table 1

Subjects Characteristics at Baseline

Variable	Atorvastatin 80mg (n= 134)	Rosuvastatin 40mg (n= 136)
Men / Women	67 / 67	70 / 66
Age (<i>years</i>)	58.6 ± 11.1	55.9 ± 12.8
BMI (<i>kg/m²</i>)	29.4 ± 6.2	29.5 ± 12.6
CHD (%)	20.4	19.6
Diabetes(%)	5.4	9.5*

Values presented as mean ± standard deviation, and percent , except for gender, which presented as the number of men and women.

* $p < 0.05$ for the comparison with the Atorvastatin group.

Table 2

Changes in lipoprotein subpopulations on Treatment

Variable	Atorvastatin 80mg (n= 134)		Rosuvastatin 40mg/dl (n= 136)		** P values for treatment
	Baseline	6weeks	Baseline	6weeks	
TC (mg/dl)	278.1(30.7)	168.5(29)*	282.9 (26.6)	166.1 (29.7)*	0.104
TG (mg/dl)	168 [124-224]	109.0 [89-144]*	176 [127-222]	120 [99.5-143]*	0.979
HDL-C (mg/dl)	52.3 (14.2)	52.9 (14)	50.1 (12.6)	54.3 (12.1)*	<0.001
TC/HDL-C ratio	5.7 (1.6)	3.4 (0.9)*	6.0 (1.4)	3.2 (0.7)*	0.001
Non HDL-C (mg/dl)	225.8 (31.4)	115.7 (27.7)*	232.8(25.2)	111.9 (28.5)*	0.014
Calculated LDL-C (mg/dl)	186 (25.1)	90.1 (22.7)*	191.5 (24.1)	85.8 (25)*	0.006
LDL-C (mg/dl)	198 (27.2)	91.7 (23.7)*	204.2 (27.2)	86.8 (26.8)*	0.069
RemL-C (mg/dl)	12.4 [7.3-17.4]	4.8 [3.5-7.0]*	11.8 [8.5-16.4]	4.6 [3.2-6.0]*	0.858
ApoB-48 (mg/dl)	0.6 [0.4-0.9]	0.4 [0.3-0.6]*	0.7 [0.6-1.1]	0.5 [0.4-0.7]*	0.951
ApoB (mg/dl)	172 (24.0)	98 (20.0)*	177 (23.0)	97 (21.0)*	0.004

Values are presented as mean $\pm$ (SD) or, Median [inter quartile range].

* p<0.001 versus baseline.

** P values for treatment differences between atorvastatin and rosuvastatin after 6 weeks.

Table 3

Percent Changes in lipoprotein subpopulations on Treatment

Variable	Atorvastatin 80mg (n= 134) % change	Rosuvastatin 40mg (n= 136) % change	^{**} P values for treatment
TC (mg/dl)	-39.0 (11.2) *	-41.0 (11.3) *	0.159
TG (mg/dl)	-33.0 [-46.1 to -9.8] *	-27.6 [-44.4 to -9.8] *	0.525
HDL-C (mg/dl)	+2.0 (12.4)	+9.8 (13.8) *	<0.001
TC/HDL-C ratio	-39.4 (13.3) *	-45.6 (11.3) *	<0.001
Non HDL-C (mg/dl)	-48.2 (13.4) *	-51.6 (13.0) *	0.037
Calculated LDL-C (mg/dl)	-51.4 (13.2) *	-55.4 (14.5) *	0.020
LDL-C (mg/dl)	-50.3 (13.2) *	-52.5 (14.5) *	0.186
RemL-C (mg/dl)	-58.7 [-73.3 to -38.5] *	-61.5 [-73.1 to -43.5] *	0.236
ApoB-48 (mg/dl)	-37.5 [-57.1 to -14.3] *	-32.1 [-50 to 0] *	0.071
ApoB (mg/dl)	-42.9 (12.1) *	-45.3 (13.3) *	0.003

Values are presented as mean $\pm$ (SD) or, Median [inter quartile range].*
p<0.01 versus baseline.**
P values for treatment differences between atorvastatin and rosuvastatin after 6 weeks.