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Research Article
Effects of Different Forms of Statins on Lipid Profile in Hyperlipidemic Patients

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Abstract

Background and Objective: Statins are the cornerstone of dyslipidemia treatment. This class of drugs decreases all lipids, particularly LDL-C and non-HDL-C and consequently the risk of cardiovascular events. Different trials have, frequently, compared the effect of two statins, while very few studies have directly compared three statins in the same study. The aim of this trial was to evaluate the lipids-lowering effect of atorvastatin, rosuvastatin and pitavastatin, at moderate doses, in a head-to-head comparison, in patients with dyslipidemia. **Materials and Methods:** The current study was a prospective, randomized, open-label, parallel-group study with blinded endpoints (PROBE design) involving 221 patients. After clinical examination, patients were randomized to atorvastatin (20 mg dL^{-1}), rosuvastatin (10 mg dL^{-1}) or pitavastatin (2 mg dL^{-1}) and followed for 6 months. The primary endpoint of this trial was the change of lipids from baseline. Secondary endpoints included: The rate of subjects with LDL-C reduction >30% and 50% and the lowering effect on non-HDL-C. **Results:** At the end of this study atorvastatin, rosuvastatin and pitavastatin significantly ($p<0.001$) decreased plasma levels of lipids, compared with baseline values: (TC -30.1, - 39.1 and -26.8%), LDL-C (-39.1, -40.7 and -38.2%), TG (- 20.5, -17.6 and -13.4%), non-HDL-C (-36.4, -37.1 and -33.4%). No statistically significant difference was obtained between statins at the end of treatment. Differently from atorvastatin and rosuvastatin, pitavastatin increased the level of HDL (1.9%). **Conclusion:** The lipid-lowering efficacy of atorvastatin, rosuvastatin and pitavastatin is not statistically different, except for the HDL-C.

Key words: Dyslipidemia, statins, atorvastatin, rosuvastatin, pitavastatin

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Statins are the first-line treatment for dyslipidemia, a leading risk factor for cardiovascular morbidity and mortality[1,2]. Dyslipidemia; means that total cholesterol, Low-Density Lipoprotein (LDL) cholesterol, triglyceride, Lipoprotein a [Lp(a)] or apolipoprotein B levels are above reference values, or High-Density Lipoprotein (HDL) cholesterol or apolipoprotein A-1 levels are below reference values[3].

Statins prevent cholesterol synthesis via mevalonate by reversibly inhibiting the enzyme 3-Hydroxy-3-Methylglutaryl coenzyme A (HMG CoA) reductase, which is the rate-limiting step in cholesterol synthesis. Statins are the most powerful drugs currently used most frequently in primary and secondary prevention and whose cardiovascular disease preventive or risk-reducing effects have been demonstrated in numerous studies[4]. There are various forms of statins, some of which include atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin[5]. Among different available statins, atorvastatin (10-20 mg), rosuvastatin (5-10 mg) and pitavastatin (1-4 mg) are considered moderate-intensity statins[6] and, differently from high-intensity statins (atorvastatin 80 mg and rosuvastatin 20 mg), are indicated, for primary prevention, in patients with dyslipidemia at moderate-high cardiovascular risk[6].

In this study, the effects of atorvastatin, rosuvastatin and pitavastatin on TC, LDL-C, HDL-C and TG, which are important lipid values in the diagnosis and treatment of dyslipidemia, were investigated. Different head-to-head trials have, frequently, compared the lipids-lowering effect of two statins, particularly atorvastatin vs rosuvastatin[7-10] or vs pitavastatin[11-16], while very few studies have directly compared three statins in the same study e.g., atorvastatin, rosuvastatin and pitavastatin[17,18]. Therefore, the aim of this study was to assess in a head-to-head comparison trial, the lipids-lowering effect of atorvastatin, rosuvastatin and pitavastatin, at moderate doses, in patients with dyslipidemia.

MATERIALS AND METHODS

Study area: The study was carried out in Turkey between 03/2019 and 10/2019, with the coordinator center being the Faculty of Health Sciences, Istanbul Kartal Dr. Lütfi Kırdar Training and Research Hospital.

Study design: This study was comprised of prospective, randomized, open-label, parallel groups with a blinded-endpoints (PROBE design) design. A total of 234 male and female patients diagnosed with dyslipidemia were included in the study.

Inclusion criteria: Patients who agreed to participate in the study were older than 20 years of age and were diagnosed with hypercholesterolemia (total cholesterol (TC) $\geq$200 mg dL^{-1} and/or LDL-C $\geq$190 mg dL^{-1}) were included in the study.

Exclusion criteria: Triglycerides (TG) >= 500 mg dL^{-1}, having atherosclerotic cardiovascular disease (heart failure, previous myocardial infarction or coronary revascularization, cerebrovascular accident, ischemic heart disease and peripheral arterial disease), abnormal thyroid function, uncontrolled diabetes, kidney disease, liver functional impairment, pregnancy and concomitant use of medications that could affect lipid levels were exclusion criteria for the study.

Studied parameters: First, demographic, medical history and total cardiovascular risk assessment were performed on the patients, then they were examined and informed about healthy nutrition. To measure lipid levels, blood samples were taken from the patients twice while fasting. Blood lipids were measured using the available enzymatic colorimetric method. Patients on treatment with statins were switched to the study drug immediately after they were eligible for the trial. The current study included 86.7% of patients with controlled diabetes, without target organ damage, therefore they were assigned to moderate doses of statins[6].

Patients included in the study and followed-up were randomized to pitavastatin (2 mg), rosuvastatin (10 mg) and atorvastatin (20 mg) treatment once daily for 6 months. Research statin drugs and doses were stable during the 6 months. After 3 months, patients who required a change of statins, or dosage were excluded from the research.

The primary endpoint of this trial was the change of lipids (TC, LDL-C, HDL-C, LDL-C and TG) from baseline. Secondary endpoints included: The rate of subjects with LDL-C reduction >30% and 50%[6,19] and the lowering effect on non-HDL-C, calculated as TC-HDL-C[2].

Ethical consideration: The study was approved by a local independent Ethics Committee and was conducted in accordance with the Declaration of Helsinki.

Statistical analysis: Statistical analysis was performed per protocol using the software (SAS version 9.0). The distribution

of data was tested using the Kolmogorov-Smirnov test. Continuous and categorical variables are expressed as Mean±SD and as percentages, respectively. The ANOVA with Bonferroni correction, paired t-test and Chi-square test were used to compare continuous and categorical variables. Two-sided p<0.05 were considered statistically significant.

RESULTS

At the beginning of the study 234 patients were screened. However, 22 subjects were excluded from the analysis because lost to follow-up. Therefore, 221 patients, randomized to atorvastatin (n = 75), rosuvastatin (n = 70) and pitavastatin (n = 73), respectively, completed the 6 months therapy. The baseline demographic, clinical and laboratory characteristics of patients were reported in Table 1. The three groups were homogeneous, particularly regarding age, gender, body mass index, treatment allocation, rate of hypertension, previous cardiovascular disease and plasma lipids. At the end of the study (Table 2) atorvastatin, rosuvastatin and pitavastatin significantly (p<0.001) decreased plasma levels of lipids, compared with baseline values: TC (-80.3, -79.7 and -74.0 mg dL^{-1}), LDL cholesterol (-71.4, -73.5 and -70.8 mg dL^{-1}) and TG (-36.5, -30.4 and -31.3 mg dL^{-1}), respectively. No statistically significant difference in all lipids parameters was obtained between statins (Table 2) at the end of the

Table 1: Demographic, clinical and biochemical characteristics of patients

Parameter	Atorvastatin (n = 75)	Rosuvastatin (n = 70)	Pitavastatin (n = 73)	p
Male (%)				
Age (years)	60.5±9.9	60.4±10.6	59.3±10.0	0.59
Diabetes, n (%)	68 (90%)	55 (78.6)	66 (90.4)	
Hypertension n (%)	23 (30.6)	22 (31.4)	13 (17.8)	
Cardiovascular disease n (%)	2 (2.60)	0	0	
Total cholesterol (mg dL^{-1})	266.4±46.8	265±48.6	272.3±46.5	0.61
LDL-C (mg dL^{-1})	182.2±39.1	180.5±39.7	185.5±34.8	0.73
Triglycerides (mg dL^{-1})	177.6±70.3	173.1±65.9	181.6±94.0	0.84
HDL (mg dL^{-1})	48.6±9.94	49.5±10.1	51.3±11.2	0.27
Non-HDL-C (mg dL^{-1})	218.3±44.8	216.1±43.9	220.9±42.6	0.8

Table 2: Change in lipids from baseline

Parameter	Statins	Mean (SD)	*p	p between statins
TC (mg dL^{-1})	ATV	-80.3 (36.8)	<0.01	0.09
	%	-30.1		
	ROS	-79.7 (36.2)	<0.01	
	%	-39.1		
	PTV	-74.0 (46.7)	<0.01	
	%	-26.8		
LDL-C (mg dL^{-1})	ATV	-71.4 (27.2)	<0.01	0.36
	%	-39.1		
	ROS	-73.5 (30.6)	<0.01	
	%	-40.7		
	PTV	-70.8 (41.6)	<0.01	
	%	-38.2		
HDL-C (mg dL^{-1})	ATV	-1.0 (5.5)	<0.01	0.03**
	%	2.1		
	ROS	-0.36 (4.8)	<0.01	
	%	-0.8		
	PTV	+1.0 (5.6)	<0.01	
	%	1.9		
TG (mg dL^{-1})	ATV	-36.5 (56.5)	<0.01	0.31
	%	-20.5		
	ROS	-30.4 (57.8)	<0.01	
	%	-17.6		
	PTV	-31.3 (74.4)	<0.01	
	%	-17.2		
Non-HDL (mg dL^{-1})	ATV	-79.4 (38.7)	<0.01	0.27
	%	-36.4		
	ROS	-80.1 (36.9)	<0.01	
	%	-37.1		
	PTV	-74.9 (45.8)	<0.01	
	%	-33.9		

TC: Total cholesterol, LDL-C: Low Density Lipoproteins, HDL: High Density Lipoproteins, TG: Triglycerides, Non-HDL-C: Non-HDL cholesterol, *p vs baseline, **Atorvastatin vs Rosuvastatin (p = 0.68), **Atorvastatin vs Pitavastatin (p = 0.01) and **Rosuvastatin vs Pitavastatin (p = 0.21)

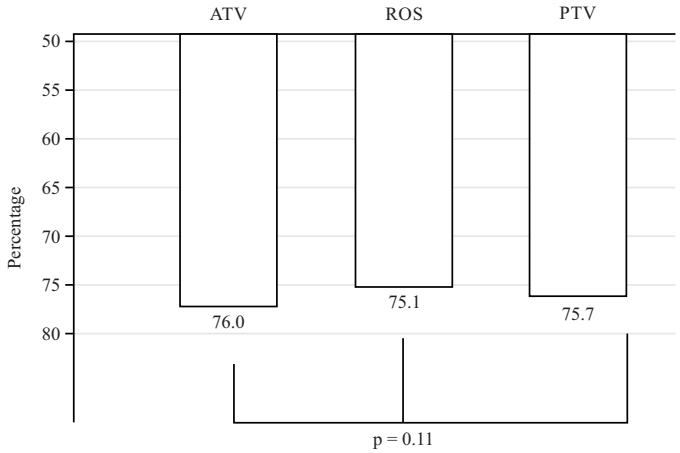

Fig. 1: Patients (%) with LDL-C reduction >30%
ATV: Atorvastatin, ROS: Rosuvastatin and PTV: Pitavastatin

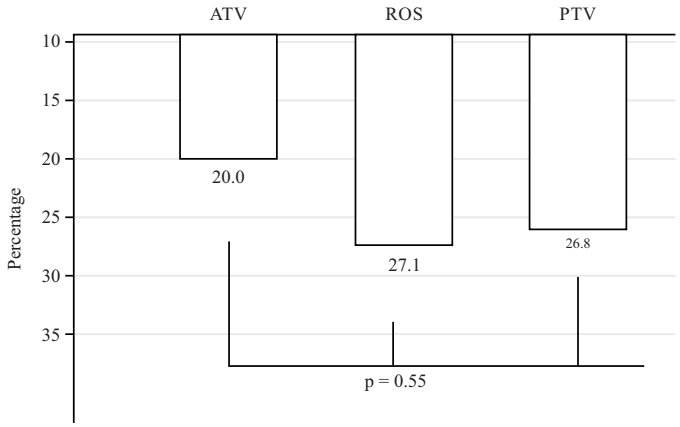

Fig. 2: Patients (%) with LDL-C reduction $\geq$ 50%
ATV: Atorvastatin, ROS: Rosuvastatin and PTV: Pitavastatin

treatment. However, there were important differences in HDL-C plasma concentrations between statins. Indeed, while HDL-C decreased with atorvastatin (-1 mg dL^{-1}) and with rosuvastatin (-0.36 mg dL^{-1}), it was not significantly ($p = 0.45$) increase with pitavastatin (1 mg dL^{-1}), therefore the comparison between the three statins resulted statistically significant ($p = 0.03$). Particularly the difference between atorvastatin and pitavastatin was statistically significant ($p = 0.01$), while there was no significant difference between pitavastatin and rosuvastatin ($p = 0.21$).

The rate of patients with LDL-C plasma level reduced by 30% (Fig. 1) was no different between the statins (atorvastatin 76.0%, rosuvastatin 75.1%, pitavastatin 75.7%, $p = 0.11$), as well (Fig. 2) the reduction $\geq$50% (atorvastatin 20.0%, rosuvastatin 27.1% and pitavastatin 26.8%, $p = 0.55$).

Non-HDL cholesterol (Table 2) was similarly lowered by all statins, compared with basal values: -36.4, -37.1 and -33.9% with atorvastatin, rosuvastatin and pitavastatin, respectively ($p<0.01$), without significant difference at end of the follow-up ($p = 0.27$).

No clinical adverse events, particularly muscle symptoms or abnormal liver function have been reported during the treatments.

DISCUSSION

The main findings of this study showed that in patients with dyslipidemia under stable treatment, the lipids-lowering effect of moderate doses of atorvastatin, rosuvastatin and pitavastatin, has not been significantly different. This result was in agreement with previous studies that have

demonstrated a comparable effect between atorvastatin, rosuvastatin and pitavastatin in a wide range of patients with primary or combined dyslipidemia[11-13,16,17,20,21]. The LDL-C was decreased by 30% (Fig. 1) in a large proportion of patients treated with atorvastatin, rosuvastatin and pitavastatin (76.0, 75.1 and 75.7%, p = 0.11), while the reduction $\geq$50% (Fig. 2) was reached in fewer patients: 20.0, 27.1 and 26.8% (p = 0.55). The moderate doses of statins, in this study, can explain this finding. However, even with high-intensity statins, only about 50%, or less, of patients achieve the target recommended by the guidelines[22,23]. The only difference, in this study, has been the change in plasma levels of HDL-C between atorvastatin, rosuvastatin and pitavastatin. Indeed atorvastatin and rosuvastatin decreased plasma level of HDL (-2.1 and -0.8%), while pitavastatin increased it by 1.9%. However, the rise in HDL-C concentration is lower than reported in previous studies[13-15,24,25], particularly in patients with low HDLs at baseline (<40 mg dL^{-1}). Nevertheless, the marginal increase of HDL with pitavastatin is statistically significant, compared with atorvastatin (p = 0.01). This effect of pitavastatin seems to be related to an increase in apolipoprotein A1 plasma levels and therefore HDL-C function[14,15,24-26]. Atorvastatin, rosuvastatin and pitavastatin significantly decreased the non-HDL-C from baseline (p<0.01), without any significant difference at the end of the follow-up (p = 0.27). This was an important finding because non-HDL-C is considered much more suitable, than LDL-C, for assessing the risk of cardiovascular disease[2,27].

The current study has some potential limitations and strengths:

- **Limitations:** (i) Sample size was not calculated, (ii) Trial was not performed double-blind, however, a PROBE design was used and the treatment was randomized
- **Strengths:** Study was one of the few studies that assessed simultaneously head-to-head comparison between atorvastatin, rosuvastatin and pitavastatin

CONCLUSION

The results showed that atorvastatin, rosuvastatin and pitavastatin all significantly reduced TC, LDL cholesterol and TG levels. Lipid lowering efficacy of these 3 drugs was not statistically different. In addition, it was observed that atorvastatin and rosuvastatin decreased the level of HDLs, whose high plasma levels are known to be associated with a lower risk of CV events and therefore atheroprotective properties, while pitavastatin increased it. Globally these data suggested no difference in the lipids parameters and calculated endpoints, pitavastatin, differently from atorvastatin and rosuvastatin was associated with an increase in HDL-C.

SIGNIFICANCE STATEMENT

Dyslipidemia is a major public health problem worldwide and a major risk factor for cardiovascular disease. Statin-group drugs are widely used in the first-line treatment of dyslipidemia and are among the most prescribed drugs in the world. While there are many studies in the literature comparing the effects of two statins, very few studies have compared three statins. The aim of this study was to evaluate the lipid-lowering effect of moderate doses of atorvastatin, rosuvastatin and pitavastatin in patients with dyslipidemia. Data from the study: Atorvastatin, rosuvastatin and pitavastatin all significantly reduced TC, LDL cholesterol and TG levels, without a statistically significant difference between them. It was observed that while atorvastatin and rosuvastatin decreased the HDL level, which is very beneficial and closely related to cardiovascular health, pitavastatin increased it.

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