Rosuvastatin: An Effective Lipid Lowering Drug against Hypercholesterolemia

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Citation

Abstract

Hypercholesterolemia (HC) is primarily implicated in the progression of coronary heart disease (CHD) and its treatment is essential. Statin such as rosuvastatin, the lipid-lowering agent, is well known for its ability to normalize patient's serum cholesterol level. The study was designed, to compare the lipid-modifying efficacy of rosuvastatin across HC. The efficacy of rosuvastatin (10mg) was found in 162 patients who met the inclusion criteria [fasting Total cholesterol (TC) concentration ≥ 200mg/dl, low density lipoprotein-Cholesterol (LDL-C) ≥ 130mg/dl and triglyceride (TG) ≤ 300 mg/dl]. Selected patients were subdivided into two groups (group 1 - TC ≤ 240 mg/dl and group 2 - TC > 240 mg/dl). The efficacy was determined by measuring changes from baseline in lipid parameters including LDL-C, TC, TG, high density lipoprotein-Cholesterol (HDL-C) and non-high density lipoprotein-Cholesterol (NHDL-C). TC, LDL-C, and NHDL-C significantly (p<0.001) reduced over their baselines. Mean changes at 8 weeks were -24 to -28.3% for TC, -19.5 to -20.1% for TG, -33.3 to -38.7% for LDL-C, -31.3 to -35.6% for NHDL-C, 6.5 to 6.9% for HDL-C, - 28.9 to - 33.2% for TC/HDL-C, - 37.6 to - 42.9% for LDL-C/HDL-C and - 35.8 to -40% for NHDL-C/HDL-C. Rosuvastatin produces good reduction in TC and beneficial changes in other lipid fractions in hypercholesterolemic patients and is well tolerated.

INTRODUCTION

A novel statin rosuvastatin has been introduced in market recently. Its high inhibitory potency has been shown against the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase in vitro and in vivo ([1]). In European patients rosuvastatin has produced marked beneficial changes in other lipid variables. It has been shown to reduce LDL-C significantly more than atorvastatin and other statins in a no. of studies in western population ([2]).

HC is the main cause of coronary atherosclerosis ([3]). Several cholesterol lowering interventions have reduced CHD events in primary and secondary prevention clinical trial ([4,5,6]). Expert panels in Europe and the USA have therefore recommended dietary changes and if, necessary addition of drugs to reduce high cholesterol concentrations-specifically low density lipoprotein (LDL) cholesterol ([7,8]) — especially in patients with CHD. In epidemiological studies total cholesterol (TC) and low density lipoprotein cholesterol (LDL) correlated well with risk of CHD ([8]). In other population studies (e.g. The Munster Heart Study; PROCAM) while the primacy of LDL as a risk factor was clear, the triglyceride (TG) and HDL levels also played a significant role in predicting the risk of a vascular event ([9]).

The significance of TGs as a risk factor is often overlooked because of it's high inverse correlation with HDL and association with other risk factors ([9,10]).

Thus, the study was designed, to assess the lipid-modifying efficacy of rosuvastatin across hypercholesterolemia.

MATERIALS AND METHODS
PATIENT POPULATION

162 consecutive patients with hypercholesterolemia who met the study criteria and willing to give written informed consent to participation were prospectively assigned to treatment with rosuvastatin (10mg/day) for 8 weeks. The drug was administered once daily after the evening meal and concomitant use of any drug that could influence the serum lipid concentrations was prohibited. The enrollment criteria were: TC concentration ≥ 200mg/dl, LDL-C ≥ 130mg/dl and TG ≤ 300 mg/dl. Patients who had active liver or renal disease were excluded.

The study group was divided into 2 subgroups based on the serum TC concentration at the baseline. Group 1 had TC level less than 240 mg/dl and group 2 had TC level was above 240 mg/dl.

The study was approved by the institution's Ethics Committee. Placebo control was not possible for ethical and feasibility reason.

The primary objective was to assess percentage reduction in TC from baseline in hypercholesterolemic patients. Secondary objectives were to assess changes from baseline in TG, LDL-C, NHDL-C, HDL-C, TC/HDL-C, LDL-C/HDL-C and NHDL-C/HDL-C and to assess safety of study treatment.

BLOOD SAMPLE ANALYSIS

Fasting lipids were measured at 0, 4 and 8 weeks of therapy. Blood samples were drawn after more than 12 h of fasting. All lipid analyses were performed in Clinical Biochemistry Laboratory, L.T.M.M.C. in Mumbai. Blood samples (5ml) were centrifuged at 1,500 g for 10 minutes. TC and TG were measured by the enzymatic kit method; HDL-C by the selective precipitation method; LDL-C by the Friedewald equation. NHDL-C was calculated by the formula (NHDL-C = TC – HDL-C). All biochemical investigations were done on Ciba Corning Express Plus clinical chemistry analyzer, USA.

STATISTICAL ANALYSIS

Descriptive statistics were performed and data were presented as mean (SD). Paired student's test was used to compare the results of same groups. Correlation coefficients for the relationship between two variables were determined using Pearson correlation methods. A value of $p<0.05$ was considered statistically significant. All statistical calculations were performed using Sigma stat software (V. 3.0)

The primary efficacy variable was the percent change in TC from baseline to endpoint. Secondary variables included the percent change from baseline in TG, HDL-C, LDL-C, NHDL-C, TC/HDL-C, LDL-C/HDL-C and NHDL-C/HDL-C. Both groups showed statistically significant changes in the lipid profile from baseline.

RESULTS

Demographic and baseline characteristics are given in table1. In total 162 patients 46.91 percentage (%) were male, and the mean patient age was 51.42 years.

Figure 1

Table 1: Demographic and Baseline Characteristic

Variables	Total Cholesterol	
	TC below 240 mg/dl	TC above 240 mg/dl
Sex, n (%) Male	n = 67 61.76%	n = 95 36.17%
Age, mean (SD), (Range)	52.69 (10.26) 37 - 65	50.27 (8.99) 35 - 63
Body weight, mean (SD), Kg	62 (9.8)	64 (10.42)
Body Mass Index, mean (SD), Kg/ m²	24.22 (4.9)	25.47 (5.3)
Obesity, (%)	23.53 %	14.89 %
Diabetes, (%)	26.47%	51.06%
Hypertension, (%)	0%	34.04%
Smokers, (%)	23.53%	12.77%
Alcohol consumers, (%)	14.7 %	17.02%
History of any CHD	23.53%	6.38%

LIPOPROTEIN FRACTIONS

Changes in lipid measures based on TC at 8 weeks with rosuvastatin are shown in Table 2. At the end of the 8 week treatment TC in group 1 dropped by 24% ($p<0.001$) and in group 2 dropped by 28.3% ($p< 0.001$). TG was decreased by 19.5% and 20.1% ($p<0.05$) in Group 1 and 2 respectively. LDL-C level of group 1 was higher to that of group 2 at baseline and after the end of 8 week treatment LDL-C was decreased by 33% and 37.56% ($p<0.01$) in group 1 and 2 respectively. Following the ATP III guidelines, we analyzed the effect of rosuvastatin treatment on NHDL-C. In group 1 the NHDL-C was reduced by 31.57 % and 35.28% in group 1 and 2 ($p<0.001$). HDL-C level was increased by 10.79% and 11.29% in group 1 and 2 respectively ($p<0.001$).

Figure 2

Table 2: Changes in lipid measures at 8 weeks

	TC below 240 mg/dl n = 67	TC above 240 mg/dl n =95
TC		
Baseline, mg/dl	226.29 (11.19)	264.04 (20.16)
Week ,8 mg/dl	172.08 (11.42) *	189.23 (15.09) *
TG		
Baseline, mg/dl	140.82 (76.55)	188.95 (65.73)
Week 8, mg/dl	107.38 (54.06) *	143.59 (49.56) *
LDL - C		
Baseline, mg/dl	157.65 (19.92)	186.84 (21.74)
Week 8, mg/dl	105.55 (15.93) *	116.66 (15.62) *
HDL - C		
Baseline, mg/dl	40.67 (6.12)	39.40 (4.69)
Week 8, mg/dl	45.05 (5.96) *	43.85 (4.97) *
Non HDL - C		
Baseline, mg/dl	185.61 (14.81)	224.63 (21.44)
Week 8, mg/dl	127.02 (12.98) *	145.38 (16.32) *
TC/HDL - C		
Baseline, mg/dl	5.70 (1.015)	6.80 (1.05)
Week 8, mg/dl	3.88 (0.582) *	4.37 (0.65) *
LDL-C/HDL - C		
Baseline, mg/dl	3.99 (0.94)	4.82 (0.90)
Week 8, mg/dl	2.39 (0.53) *	2.74 (0.54) *
Non HDL – C/HDL-C		
Baseline, mg/dl	4.70 (1.01)	5.80 (1.05)
Week 8, mg/dl	2.88 (0.58) *	3.37 (0.65) *

Results are expressed as Mean (SD)
* $p < 0.001$ as compared to Base-line

The % change in TC was well correlated with % change in NHDL-C (r = 0.97, 0.95) and then to LDL-C (r = 0.95, 0.94) in both the groups. Inverse correlation was found with the % change in HDL-C of group 1 (r = - 0.66) while in group 2 (r = - 0.06) there was no correlation with HDL-C. In group 1 TC was well correlated with the ratios TC/HDL-C, LDL-C/HDL-C and NHDL-C/HDL-C (r = 0.94, 0.93, and 0.93) and in group 2, it showed poor correlation (r = 0.67, 0.70, and 0.66). The % change in TG didn't show any correlation with other lipids. The % change in LDL-C was well correlated with the % change in NHDL-C (r = 0.98, 0.96) in both the groups. Like TC, LDL-C showed inverse correlation with the % change of HDL-C in group 1 (r = -0.66) and poor correlation in group 2 (r = -0.24). In group 1, the % change in ratios were well correlated with the % change in LDL-C (r = 0.91, 0.97 and 0.94). Also good correlation was found between % change in LDL-C and ratios (TC/HDL-C, LDL-C/HDL-C and NHDL-C/HDL-C) in group 2 (r = 0.77, 0.85 and 0.78) Similar results were seen with NHDL-C (r = -0.67, -0.25) and HDL-C. NHDL-C was well correlated with the % change in ratios (TC/HDL-C, LDL-C/HDL-C and NHDL-C/HDL-C) (r = 0.92, 0.96 and 0.96) and (r = 0.78, 0.82 and 0.81) in group 1 and 2. % change in HDL-C showed inverse good correlation with the ratios (TC/HDL-C, LDL-C/HDL-C and NHDL-C/HDL-C) in Group I (r = - 0.87, - 0.81 and – 0.84) and in Group II (r = -0.76, - 0.70 and – 0.76).

RATIOS

TC/HDL-C, LDL-C/HDL-C and NHDL-C/HDL-C ratio showed significant decrease in both the groups (p<0.001). In group 1, TC/HDL-C, LDL-C/HDL-C and NHDL-C/HDL-C ratio decreased by 31.93, 40.10 and 38.72% and 35.74, 43.15 and 41.89% in group 2 respectively.

The % change in TC/HDL-C showed a good correlation with LDL-C/HDL-C (r = 0.98, 0.97) and NHDL-C /HDL-C (r = 0.98, 0.98) in group I and group 2 respectively. The correlation between LDL-C/HDL-C with NHDL-C/HDL-C was best (r = 0.99, 0.98)

SAFETY

Safety was assessed by physical examination, evaluation of vital signs, and various laboratory parameters. Clinical laboratory assessment included biochemical investigations (including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, total protein, creatinine, creatine kinase (CK)). No adverse effect was seen during treatment. There was no death in the study. Few people had complaint about muscle paining but no increase was seen in CK level.

No apparent differences were observed in the safety profile in both the groups. Rosuvastatin was well tolerated.

DISCUSSION

This is one of the rare Indian clinical study showing efficacy of rosuvastatin. The study showed that rosuvastatin (10mg) could significantly reduce serum TC, TG, LDL-C and NHDL-C in Indian hypercholesterolemic Indian patients. The well-known LDL-C lowering effect was more in very high cholesterol containing group. The present study monitored 162 patients with hypercholesterolemia and effect of short term rosuvastatin treatment on lipoproteins. After 8 weeks treatment, the serum concentration of TC, LDL-C, NHDL-C, and TG were significantly (p<0.001) lower and the HDL-C concentration was significantly (p<0.001) higher than baseline values. This pattern of changes in lipid concentration during treatment was similar in both the groups.

Effectiveness of rosuvastatin in reducing TC and LDL-C was observed in various studies ([11,12,13,14]). Atherogenic lipoprotein fractions (TC/HDL-C, LDL-C/HDL-C and NHDL-C/HDL-C) were reduced significantly (p<0.001) at period of 8 week treatment. Our results are parallel to Saito et al 2003.

Reduction in TG and increase in HDL-C is seen in both the groups. These results are consistent with those previously reported for rosuvastatin treatment in hypercholesterolemic patients ($_{11}$). In study of 72 Japanese patients, rosuvastatin 1, 2 and 4 mg. significantly reduced TG by 8 to 17% and increase HDL-C by 3 to 7% at a period of 8 weeks by Yamamotto et al 2002. In another European study, rosuvastatin produced reduction in TG (10-35%) and increased in HDL-C (9-14%) across the 1 to 40 mg dose range ($_{12}$). A 6 week study by saito et al showed similar result.

An atherogenic NHDL-C contain VLDL-C, IDL, LDL-C and lipoprotein (a). The NHDL-C can be used as tool for lipproptein cholesterol screening ($_{15}$) and assessment of risk and therapy as per NCEP-III guideline ($_8$), reduction of NHDL-C is a secondary goal in reducing CHD events. It was seen that rosuvastatin significantly reduced NHDL-C overperiod of 8 weeks at the dose of 10mg/day.

A comparative study of atorvastatin Vs Simvastatin reduced ratio of NHDL-C.HDL-C (39 to 33%) at 16 week ($_{16}$). The same effect was produced by rosuvastatin (10 mg) in 8 week. Thus, efficacy of rosuvastatin in terms of lipoprotein fraction is observed.

% change in TC was well correlated with % change in LDL-C and NHDL-C even in severer hypecholeterolemic patients. TC shows better correlation with ratios in group 1 than group 2. Thus, LDL-C or NHDL-C can be taken as a risk factor.

% change in LDL-C or NHDL-C when correlated with other lipid and ratios, NHDL-C has shown better correlation than LDL-C. Thus, NHDL-C can be taken as a fundamental risk factor to make more effective approach for risk reduction.

CONCLUSION

From the data we conclude that Rosuvastatin produces good reduction in TC and beneficial changes in other lipid fractions in hypercholesterolemic patients. To make risk reduction more effective NHDL-C can be taken as a risk factor. Rosuvastatin did not produce any serious adverse effect thus, can be used as better lipid lowering drug.

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