Research Article

The Effects of Rosuvastatin on the Serum Cortisol, Serum Lipid, and Serum Mevalonic Acid Levels in the Healthy Indian Male Population

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Abstract. In this open-label, balanced, randomized, placebo-controlled, parallel study, healthy male volunteers were randomly divided into two groups. Each group received either a single oral dose of rosuvastatin 20 mg or placebo. Estimations were done at predose on day 1 of dosing (baseline) and 24 h postdose after days 7 and 14. Serum cortisol and serum lipid levels were estimated using enzyme-linked immunosorbent assay kits and serum mevalonic acid (MVA) levels were measured using validated liquid chromatography–tandem mass spectrometry method. Rosuvastatin produced a statistically significant ($P<0.05$) decrease in total cholesterol, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, and triglycerides. However, the increase in high-density lipoprotein cholesterol and decrease in cortisol and MVA were not statistically significant when compared to the placebo-treated group. The study showed that rosuvastatin at a dose of 20 mg/day for a period of 14 days was very potent as cholesterol-lowering agent, without any significant change in serum cortisol level in the healthy Indian male population.

KEY WORDS: healthy male volunteers; rosuvastatin; serum cortisol; serum lipid; serum mevalonic acid.

INTRODUCTION

Statins are 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, which is the key enzyme of cholesterol biosynthesis. Statins are the most widely used lipid-lowering therapy commonly used in clinical practice for familial hypercholesterolemia (1).

There are several marketed statins, such as simvastatin, pravastatin, lovastatin, fluvastatin, atorvastatin, and rosuvastatin. Atorvastatin is a highly efficacious inhibitor of HMG-CoA reductase. Atorvastatin (10–80 mg) has been shown to lower low-density lipoprotein cholesterol (LDL-C) from 41% to 61% in a dose–response study in hypercholesterolemic volunteers. Pravastatin, another drug of this type with comparable lipid-lowering efficacy, is structurally similar but its tissue specificity may vary (2,3).

Rosuvastatin (CRESTOR; Fig. 1) is the latest congener of HMG-CoA reductase inhibitors launched globally by Astra Zeneca in August 2003. It has been approved for the treatment of primary hypercholesterolemia, mixed dyslipidemia, hypertriglyceridemia, and homozygous familial hypercholesterolemia. The effects of rosuvastatin on LDL-C are dose-related. At the 10-mg dose, the average LDL-C reduction was found to be 46% in one trial. Increasing the dose from 10 to 40 mg gave a modest increase of an additional 9% absolute reduction in LDL levels (55% below the baseline levels) (4).

Rosuvastatin has an approximate elimination half-life of 19 h, its time to peak plasma concentration is reached in 3–5 h following oral administration, its bioavailability is 20%, and it is excreted in the urine and feces. The metabolism of rosuvastatin occurs in the liver (5).

In the present study, the use of additional markers in addition to lipid profile and cortisol levels has been explored during treatment with statin (rosuvastatin). Statins are widely used as lipid-lowering therapy in India. But there are very few clinical trials to substantiate the effect of statins in the Indian population. Due to intersubject and population variability to statin therapy, there is a need to evaluate or monitor the therapy using additional markers. Moreover, there is no published literature about the effect of rosuvastatin on the steroid hormone production in Indian subjects. Statins selectively inhibit cholesterol synthesis. Significant inhibition of endogenous cholesterol synthesis could influence steroid hormone production. Since cholesterol is the precursor for steroid hormones, agents that decrease exogenous or intracellular free cholesterol levels could influence steroidogenesis (6,7)

In the biosynthesis of cholesterol, conversion of HMG-CoA to mevalonic acid (MVA) by HMG-CoA reductase is an early and rate-limiting step. Statin class of drugs such as

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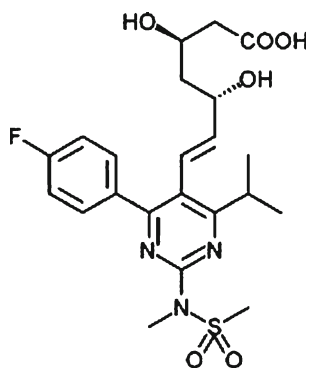
Fig. 1. Structure of rosuvastatin

simvastatin, atorvastatin, and rosuvastatin act on HMG-CoA reductase, resulting in the inhibition of biosynthesis of MVA. Understanding the reason for elevated cholesterol levels and interindividual variability to statin therapy can lead to better and monitored pharmacotherapy. Since the reduction in MVA levels is the indirect measure of decreased cholesterol levels, MVA can be used as a biomarker to measure the extent of statin activity.

Therefore, the current study was designed with the objective to evaluate the pharmacodynamic effects of rosuvastatin on the serum cortisol levels, serum MVA levels, and serum lipid levels in healthy, adult, male volunteers with above optimal or borderline LDL-C.

METHODS

Study Design and Subjects

This was an open-label, balanced, randomized, placebo-controlled, parallel study to evaluate the effects of multiple doses of rosuvastatin 20 mg on the serum cortisol, serum lipid, and serum MVA levels for 14 days in healthy male volunteers. The study protocol and informed consent form were approved by the Jamia Hamdard Institutional Review Board (New Delhi, India) prior to study initiation. Male subjects of the age range of 18–45 years were included in the study. The subjects had cholesterol levels between 150 and 300 mg/dl. Subjects were neither overweight nor underweight for their height as per the Life Insurance Corporation of India height/weight chart for nonmedical cases. All subjects voluntarily gave written informed consent to participate in this study and were of normal health as determined by the medical history and physical examination of the subjects performed within 28 days prior to the commencement of the study.

Subjects were excluded if they had history of allergy to rosuvastatin and/or related drugs; any evidence of organ dysfunction or any clinically significant deviation from the normal, in physical or clinical determinations; history of myopathy/rhabdomyolysis, myalgia, myositis, serious gastrointestinal, hepatic, renal, cardiovascular, pulmonary, neurological, pulmonary, and hematological disease, diabetes or glaucoma, and any psychiatric illness, which may impair the ability to provide written informed consent. Subjects were also excluded if they had positive results to the tests for drugs of abuse or alcohol or if they tested positive for

hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus antibody. Subjects were also excluded if they had consumed enzyme-modifying drugs within 30 days or any systemic medication (including over-the-counter preparations) within 14 days prior to day 1 of this study, participated in any clinical trial within 6 weeks preceding day 1 of this study, volunteers who, through completion of this study, would have donated more than 350 ml of blood in the past 3 months, and subjects without adequate venous access in their left or right arm to allow collection of blood samples via venous cannula in the three periods. Based on the above inclusion and exclusion criteria, only 12 healthy volunteers were selected for this study because it was a pilot study.

The volunteers were randomly divided into two groups ($n=6$) volunteers and each group received either a single oral dose of rosuvastatin 20 mg or placebo for a period of 14 days. All the subjects were on normal diet. They were instructed not to take any prescription, over-the-counter, as well as herbal medicines for at least 2 weeks prior to onset of study and during the study.

For the brief clinical examination, vital signs of oral temperature, sitting blood pressure, and radial pulse were measured prior to drug administration on all 14 days of treatment period. Clinical examinations were conducted on days 1, 7, and 14, at admission, and predose by a qualified medical designate on duty after subject check-in, prior to dosing of drug, and before checkout. Subjects were advised to promptly report in case they developed unexplained muscle pain, tenderness, or weakness accompanied by malaise and fever to the physician in-charge or clinical pharmacologist.

Sampling Schedule

Blood samples (6 ml) were collected after an overnight fast of 10 h at predose on day 1 of dosing. After dosing on days 7 and 14, 24-h postdose blood was withdrawn for estimation of serum lipid, serum MVA, and serum cortisol levels. For each subject, a total of three blood samples (6 ml) each were collected during the study. And the blood loss for each subject did not exceed 50 ml including 16 ml for screening and loss during blood withdrawal.

Pharmacodynamic Analysis

The following pharmacodynamic parameters were calculated for rosuvastatin:

Estimation of Total Serum Cholesterol

Cholesterol was measured in the serum with the help of the cholesterol Flex® reagent cartridge. It is an *in vitro* diagnostic test used for quantitative determination of total cholesterol in serum and plasma. The cholesterol method is based on the principle first described by Roschlau in 1974 ([8]). The test was performed on the Dimension® clinical chemistry system after the method was validated and the instrument was calibrated. The CHOL Flex® reagent cartridge was required to perform the CHOL test. Sampling, reagent

Table I. Percent Difference of Mean Cholesterol Levels (in Milligrams per Deciliter) and Mean LDL-C Levels Following Rosuvastatin and Placebo Treatment

	Mean ± SD total cholesterol			Mean ± SD LDL-C		
	Placebo	Rosuvastatin	Percent difference	Placebo	Rosuvastatin	Percent difference
Predose (baseline)	189.17±20.86	156.75±27.21	17.14	118.7±14.34	102.65±16.05	13.52
Postdose (7 days)	173.50±18.77	110.50±20.86	36.31*	115.73±14.58	59.75±16.50	48.37*
Postdose (14 days)	174.67±20.98	107.75±27.77	38.3*	104.40±16.96	61.4±16.50	41.19*

*$P<0.05$, significant in the rosuvastatin-treated group, and $P>0.05$, insignificant in the placebo group, using ANOVA

delivery, mixing, processing, and printing of the results were automatically performed by the Dimension® system.

Estimation of Serum Triglycerides

Triglycerides were measured in the serum with the help of the triglyceride Flex® reagent cartridge. It is an *in vitro* diagnostic test used for quantitative determination of triglycerides in serum and plasma. Triglycerides are water insoluble lipids consisting of three fatty acids linked to one glycerol molecule. Triglycerides are transported in the blood as core constituents of all lipoproteins, but the greatest concentration of these molecules is carried in the triglyceride-rich chylomicrons and very low-density lipoproteins (VLDL) (9). The lipases, bile acids, and triglycerides are hydrolyzed into glycerol and fatty acids which are absorbed by adipose tissue for storage or by other tissues requiring a source of energy. A peak concentration of chylomicron-associated triglycerides occurs within 3–6 h after ingestion of a fat-rich meal; however, the rate of absorption of fats is highly variable, depending on the individual and dietary composition of the fat. After absorption, triglycerides are resynthesized in the epithelial cells and combined with cholesterol and a number of apolipoproteins to form chylomicrons (10).

The test was performed on the Dimension® clinical chemistry system after the method was validated and the instrument was calibrated. The TGL Flex® reagent cartridge was required to perform the TGL test. Sampling, reagent delivery, mixing, processing, and printing of the results were automatically performed by the Dimension® system.

Estimation of Serum HDL Levels

High-density lipoprotein cholesterol (HDL-C) was measured in the serum with the help of the HDL-C Flex® reagent cartridge. It is an *in vitro* diagnostic test used for quantitative determination of HDL-C in pretreated serum and plasma. The HDL-C method is based on the separation of lipoproteins by a polyanion reagent followed by enzymatic cholesterol analysis. LDL and VLDL are quantitatively precipitated by a buffered phosphotungstate reagent. The HDL-C fraction present in the supernatant is then analyzed by the enzymatic cholesterol method (11).

The test was performed on the Dimension® clinical chemistry system after the method was validated and the instrument was calibrated. The HDL Flex® reagent cartridge was required to perform the HDL test. Sampling, reagent delivery, mixing, processing, and printing of the results were automatically performed by the Dimension® system.

Estimation of LDL Cholesterol

LDL-C was calculated by the Friedewald formula (12):

$$\text{LDL cholesterol} = \text{total cholesterol} - \text{HDL cholesterol} - 1/5\,\text{triglyceride}.$$

Estimation of Serum Cortisol

Serum cortisol was measured in the serum with the help of the enzyme-linked immunosorbent assay kit. The Lilac
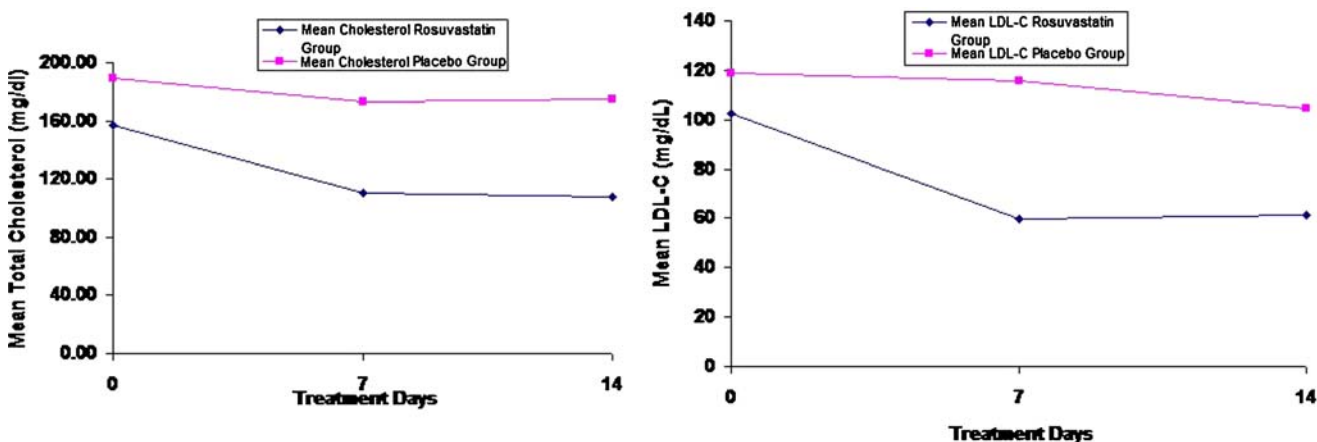

Fig. 2. Change in mean total cholesterol levels and mean LDL-C levels from baseline (day 0) in the rosuvastatin-treated and placebo groups following 14 days of treatment

Table II. Percent Difference of Mean VLDL-C Levels and Mean Triglyceride Levels (in Milligrams per Deciliter) Following Rosuvastatin and Placebo Treatment

	Mean ± SD VLDL-C			Mean ± SD triglycerides		
	Placebo	Rosuvastatin	Percent difference	Placebo	Rosuvastatin	Percent difference
Predose (baseline)	32.67±16.35	22.60±10.25	30.82	152.17±95.56	113.00±51.24	25.74
Postdose (7 days)	25.77±7.92	14.80±9.20	42.57	128.33±66.60	81.25±49.68	36.68
Postdose (14 days)	37.27±13.32	16.25±9.94	56.40*	186.33±66.60	64.25±27.93	65.51*

*$P>0.05$, insignificant change in both the rosuvastatin-treated and the placebo groups using ANOVA

cortisol kit was used for the quantitative determination of cortisol levels in human serum.

Estimation of Serum MVA

Serum MVA concentrations were quantified by liquid chromatography–tandem mass spectrometry method provided by the Metabolism and Pharmacokinetics Department of Ranbaxy Research Laboratories.

The method was validated over the linearity range of 0.5–50.0 ng/ml ($r^2>0.99$) using deuterated MVA (D7-MVA) as internal standard. The lower limit of quantification was 0.5 ng/ml. The assay procedure involved the isolation of MVA from plasma samples using solid phase extraction. Chromatographic separation was achieved on a Hi Purity Advance column with a mobile phase consisting of ammonium formate buffer (10 mM, pH 8.0) and acetonitrile (70:30, v/v). Excellent precision and accuracy was observed. MVA and deuterated mevalonolactone (D7-MVAL) were stable in water and plasma under different storage and processing conditions. The recovery observed was low, which was attributable to a significant matrix effect. The calibration range was 0.5 to 50 ng/ml. Quality control samples were prepared by taking into consideration the endogenous MVA levels. MVA was extracted as mevalonolactone (acidic pH) from plasma using the solid phase extraction procedure and was converted to acid form (basic pH) and read as m/z 147/59. D-7 was the internal standard and read as m/z 154/59. The concentrations were read using Analyst® software (13).

Assay Procedure

The assay was done at least 1 h before use; all reagents, standards, and samples were brought to room temperature (18–30°C) and mixed carefully on the vortex. Calibration was set and samples were distributed in duplicate. Distribution and incubation times were the same for all the wells in the same analysis. Long interruptions at each step were avoided. The color in the last incubation was stable for at least 30 min in the dark. The samples were analyzed in the Biomaster Junior Autoanalyzer.

Statistical Analysis

The repeated measures for intragroup variance "analysis of variance (ANOVA)" were tested by the application of F test. Besides the intragroup variance, paired comparisons were done by using Student's paired t test. Furthermore, Student's t test was used for measuring the difference between the rosuvastatin-treated and placebo groups. A confidence interval of 95% was used.

RESULTS AND DISCUSSION

Subject's Demographics

The subjects ranged in age from 21 to 41 years with mean + standard deviation (SD) age of 29.67 + 6.47, body weight ranged from 47 to 80 kg with mean + SD weight of 60.67 + 8.54,
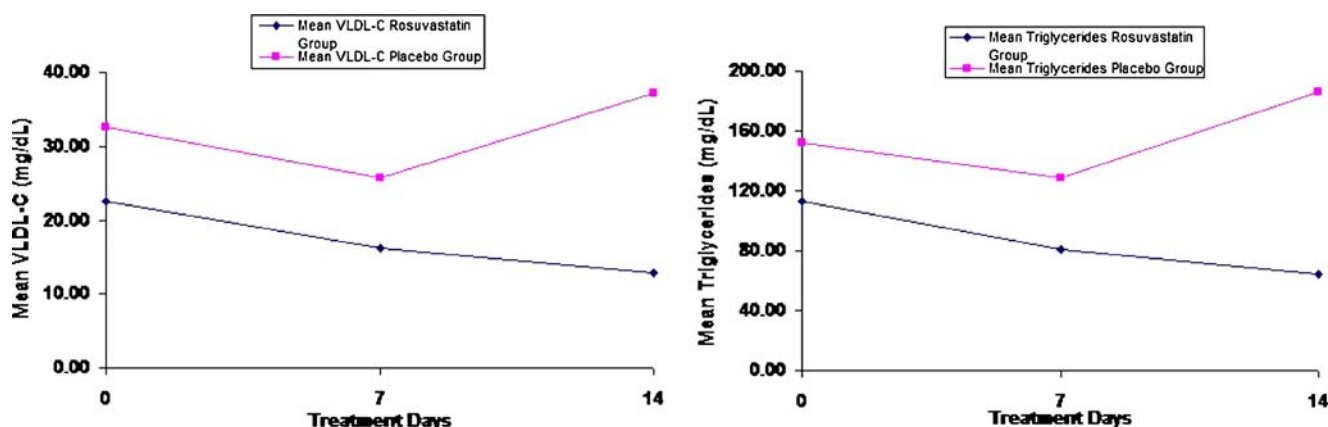

Fig. 3. Change in mean VLDL-C levels and mean triglyceride levels from baseline (day 0) in the rosuvastatin-treated and placebo groups following 14 days of treatment

Table III. Percent Difference of Mean HDL-C Levels and Mean Cortisol Levels (in Nanograms per Milliliter) Following Rosuvastatin and Placebo Treatment

	Mean ± SD HDL-C			Mean ± SD cortisol		
	Placebo	Rosuvastatin	Percent difference	Placebo	Rosuvastatin	Percent difference
Predose (baseline)	39.03±4.61	31.50±6.14	19.29*	195.84±35.70	184.27±42.01	6.27*
Postdose (7 days)	32.00±3.16	34.50±9.26	7.8*	161.27±27.34	149.04±27.98	8.20*
Postdose (14 days)	33.00±3.22	33.50±11.47	1.5*	148.09±23.22	141.63±28.87	4.56*

*$P>0.05$, insignificant change in both the rosuvastatin-treated and the placebo groups using ANOVA

and height ranged from 154 to 172 cm with mean + SD height of 164.58 + 5.78. They were neither overweight nor underweight as per the Life Insurance Corporation of India height/weight chart for nonmedical cases. They were found to be in normal health and their clinical laboratory values are within the normal range.

The study was conducted in 12 subjects. There were no dropouts in the study. Two subjects, subject numbers 4 and 5 were withdrawn from the study. Subject number 4 was withdrawn on the fourth day of dosing. The subject reported with burn injury (scald) over the dorsal and medial aspect of his right hand, including the thumb and index fingers. Local examination showed a grade 1 superficial burn with blister formation over the dorsal and medial aspects of the right hand. The subject was referred to a surgery consultant for management. On discussion with the chief supervisor and clinical research physician, the subject was withdrawn. Follow-up of the subject for dressing was done till the wound healed. Subject number 5 was withdrawn in the evening of the 14th day of the dosing. The subject reported with a history of fall with located wound on the left heel and abrasions on the right side of the chest. The subject was referred to an expert for opinion. On discussion with the chief supervisor and clinical research physician, the subject was withdrawn. Follow-up of the subject for dressing was done till the wound healed.

Rosuvastatin has the lowest half maximal inhibitory concentration and is a significantly more potent blocker of hepatocytes sterol synthesis than all other statins currently available (14). It differs structurally from other statins, containing a polar methane sulfonamide group which confers

relative hydrophilicity, which in turn imparts greater selectivity for uptake into hepatic *versus* nonhepatic cells (14–16). Rosuvastatin is well tolerated when used alone or in combination, exhibiting a safety profile similar to that of other statins available. Previous findings indicated that rosuvastatin brought more hypercholesterolemic volunteers to their Joint European and ATP III LDL-C goals than did atorvastatin, simvastatin, and pravastatin (17).

Estimation of Total Serum Cholesterol and LDL Cholesterol

The cholesterol Flex® reagent cartridge was used for the quantitative estimation of serum cholesterol level and, at pH 5.7, LDL and VLDL are selectively precipitated by the addition of buffered phosphotungstate reagent, leaving HDL in the supernatant. Centrifugation of the pretreated serum results in a clear supernatant containing HDL which is assayed on the Dimension® system.

There was no significant decrease between postdose days 7 and 14 in total cholesterol levels and LDL-C levels on its pairwise comparison in both the rosuvastatin-treated and placebo groups as shown in Table I. However, the intragroup comparison for repeated measures by using ANOVA predicted a significant change $P<0.05$ in the rosuvastatin-treated group and an insignificant change $P>0.05$ in the placebo group (Fig. 2).

A significant decrease (40.19%; $P<0.05$) was observed in LDL-C and total cholesterol (31.26%; $P<0.05$) levels with respect to baseline levels following the 14-day treatment with rosuvastatin 20 mg in the healthy male volunteers compared
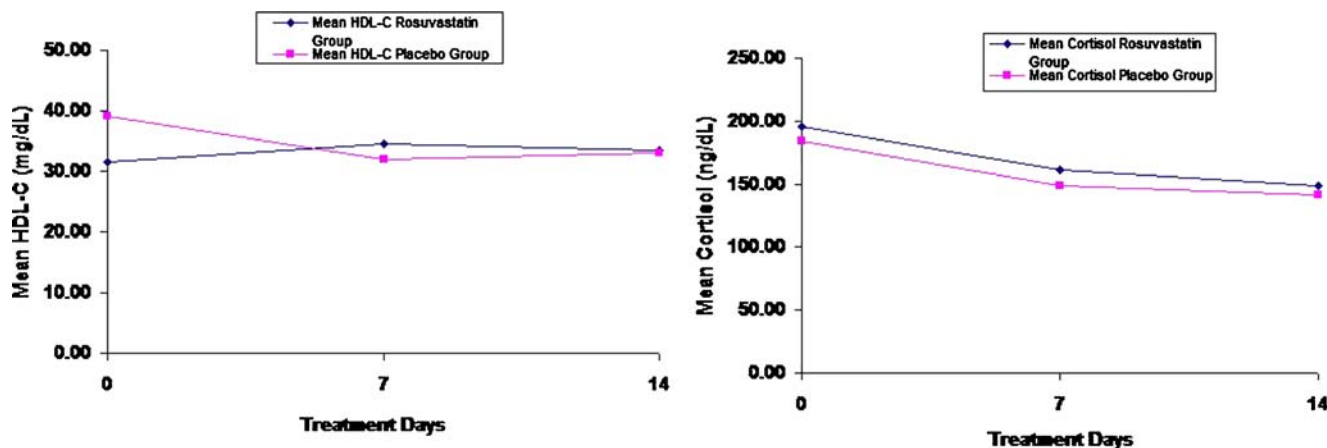

Fig. 4. Change in mean HDL-C levels and mean cortisol levels from baseline (day 0) in the rosuvastatin-treated and placebo groups following 14 days of treatment

Table IV. Percent Difference of Mean MVA Levels (in Nanograms per Milliliter) Following Rosuvastatin and Placebo Treatment

| | Mean ± SD MVA | | |
	Placebo	Rosuvastatin	Percent difference
Predose	12.28±2.54	10.82±4.64	11.88*
Postdose (7 days)	13.47±1.81	13.45±5.33	0.14*
Postdose (14 days)	12.58±2.79	12.09±4.29	3.89*

*$P>0.05$, insignificant change in both the rosuvastatin-treated and the placebo groups using ANOVA

to the placebo control group. The results are in agreement with earlier studies (18).

Estimation of VLDL-C and Serum Triglycerides

The triglycerides Flex® reagent cartridge was used for the quantitative estimation of serum triglyceride level. Triglycerides are determined quantitatively in the plasma and serum. The method is based on the enzymatic procedure in which the combination of the enzymes is employed. There was no significant decrease between postdose days 7and 14 in very low-density lipoprotein cholesterol (VLDL-C) levels and triglyceride levels on its pairwise comparison in both the rosuvastatin-treated and placebo groups as shown in Table II. However, the intragroup comparison for repeated measures by using ANOVA predicted insignificant change $P>0.05$ in both the rosuvastatin-treated and the placebo groups (Fig. 3).

The VLDL-C levels following 14 days of treatment with rosuvastatin 20 mg/day decreased by 43.14% when compared with the baseline levels. The intragroup comparison predicted that the change in VLDL-C levels was not statistically significant. The VLDL-C levels in the placebo group on its intragroup comparison predicted an insignificant change. However, on intergroup comparison between the treatment and placebo groups, the difference in the mean VLDL-C levels was not significant after 7 days of treatment; however, after 14 days of treatment, the difference was statistically significant.

The triglyceride levels following 14 days of treatment with rosuvastatin 20 mg/day decreased by 43.14% when compared with the baseline levels. The intragroup comparison predicted that the change in triglyceride levels was not statistically significant. The triglyceride levels in the placebo group on its intragroup comparison also predicted an insignificant change. However, on intergroup comparison between the treatment and placebo groups, the difference in the mean triglyceride levels was not significant after 7 days of treatment; however, after 14 days of treatment, the difference was statistically significant. The finding that rosuvastatin produced a greater percentage of decrease in triglycerides in volunteers with elevated baseline triglyceride levels is consistent with observations in studies with other statins. Statin therapy decreases triglycerides further in volunteers with lower triglycerides (19).

The insignificant decrease in the treatment group can be attributed to the fact that the treatment period was of very short duration; however, a decreasing trend was seen in the

VLDL and triglycerides and the lowering of these parameters was significant when compared to the placebo group after 14 days of dosing.

Estimation of Serum HDL and Cortisol Levels

The HDL-C Flex® reagent cartridge was used for the quantitative estimation of serum HDL-C level.

Cortisol (antigen) in the sample competes with horseradish peroxidase–cortisol (enzyme-labeled antigen) for binding onto the limited number of anticortisol (antibody) sites on the microplates (solid phase).

There was no significant decrease between postdose days 7 and 14 in HDL-C levels and cortisol levels on its pairwise comparison in both the rosuvastatin-treated and placebo groups as shown in Table III. However, the intragroup comparison for repeated measures by using ANOVA predicted insignificant change ($P>0.05$) in both the rosuvastatin-treated and the placebo groups (Fig. 4).

The HDL-C levels following 14 days of treatment with rosuvastatin 20 mg/day increased by 4.14% when compared to the baseline levels. The intragroup comparison predicted that the change in HDL-C levels was not statistically significant. The HDL-C levels in the placebo group on its intragroup comparison predicted a significant decrease. However, in the intergroup comparison between the treatment and placebo groups, the difference in the mean HDL-C levels was not statistically significant following 14 days of treatment. There was an increase in HDL-C levels after treatment with rosuvastatin; however, the increase was not statistically significant. Low HDL-C levels are recognized as an independent risk factor for coronary artery disease (CAD). Data from epidemiologic and clinical studies suggest that each 1 mg/dl increase in HDL-C is associated with a 2% to 3% reduction in CAD risk (20).

The cortisol levels following 14 days of treatment with rosuvastatin 20 mg/day decreased by 24.05% when compared to the baseline levels. The intragroup comparison predicted that the change in cortisol levels was not statistically significant. The cortisol levels following 14 days of placebo administration decreased by 21.10% when compared with the basal levels. The intragroup comparison predicted that the change in cortisol levels was not statistically significant. On intergroup comparison between the treatment and placebo
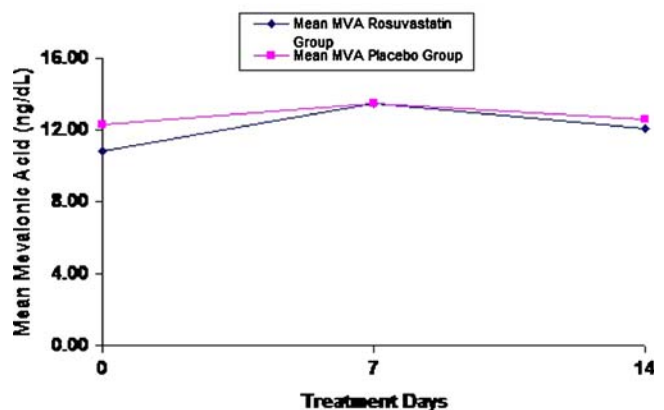

Fig. 5. Change in mean MVA levels from baseline (day 0) in the rosuvastatin-treated and placebo groups following 14 days of treatment

groups, the difference in the mean cortisol levels was not statistically significant following 14 days of treatment. The possible explanation as to why rosuvastatin and other HMG-CoA reductase inhibitors have no influence on steroidogenesis can be threefold:

1. Rosuvastatin does not fully inhibit HMG-CoA reductase enzyme, the endogenous cholesterol synthesis is still present, albeit reduced, and the residual partial enzymatic activity can provide a sufficient amount of cholesterol for hormonogenesis.
2. Rosuvastatin is capable of inducing a greater number of LDL receptors on the cellular surfaces so that it increases LDL receptor-mediated uptake and reduces serum cholesterol levels; the increase in the extracellular share could compensate for the lower quantity of cholesterol from endogenous biosynthesis.
3. Rosuvastatin is principally concentrated in the liver and, therefore, its concentrations in nonhepatic tissues play only a lesser part (6).

The effect of simvastatin (21), lovastatin (22), and pravastatin (3) on serum cortisol levels has been evaluated and none of the studies showed any significant change in the cortisol levels after treatment with statins.

Estimation of Serum MVA

There was no significant change between postdose days 7 and 14 in MVA levels on its pairwise comparison in both the rosuvastatin-treated and placebo groups as shown in Table IV. However, the intragroup comparison for repeated measures by using ANOVA predicted insignificant change ($P > 0.05$) in both the rosuvastatin-treated and the placebo groups (Fig. 5).

The MVA levels following the 14-day rosuvastatin administration did not show any significant decrease. The MVA levels following 14 days of placebo/rosuvastatin 20 mg administration increased compared to the baseline levels. The intragroup comparison predicted that the change in MVA levels was not statistically significant. On intergroup comparison between the treatment and placebo groups, the difference in the mean MVA levels was not statistically significant following 14 days of treatment. Measurement of plasma MVA or urinary excretion of MVA has been demonstrated to be good indicators of the *in vivo* rate of cholesterol biosynthesis. HMG-CoA reductase inhibitors decrease plasma concentration and urinary excretion of MVA (23). Findings in familial hypercholesterolemia volunteers in South Africa treated with high doses of atorvastatin, simvastatin, or pravastatin showed that, compared with good responders, poor responders had a lower basal level and a smaller decrease of plasma MVA on statins (24). Marked reductions in plasma and urine MVA following rosuvastatin treatment for 14 days were observed (25).

There was no significant decrease in the MVA levels except in one subject. The possible reasons for no significant difference in the treatment group are as follows.

- The decrease in MVA levels rebounds to its normal in 24 h but the samples for analysis of MVA was taken at 24 h postdose.

- The earlier studies were done in a higher number of volunteers ($n > 20$), whereas the sample size used in our study was small.
- Dietary influences could have played a role in the serum levels of MVA.
- Intersubject variability to statin therapy may have influenced the results.
- A single time-point for MVA cannot be used effectively as a biomarker as the study was not originally designed to measure the MVA levels, so there was only a single time-point.

CONCLUSION

In this pilot study, rosuvastatin at a dose of 20 mg/day was very potent as a cholesterol-lowering agent. Rosuvastatin was effective in significantly reducing LDL-C levels and also produced greater improvement in other elements of the lipid profile in healthy, adult, Indian volunteers. Rosuvastatin had no statistically significant effect on serum cortisol levels when compared to placebo. The limitations of the study are that the sample size in the study was small and the subjects were not kept in-house. Therefore, the study needs to be done in-house on a higher number of subjects.

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