

Comparison of anti-inflammatory effect of atorvastatin with rosuvastatin in patients of acute coronary syndrome

Sushant Khurana, Surabhi Gupta, HiraLal Bhalla, Shefali Nandwani¹, Varad Gupta¹

Departments of Pharmacology and ¹Medicine, Subharti Medical College, Meerut, Uttar Pradesh, India

Received: 16-07-14

Revised: 17-10-2014

Accepted: 14-02-2015

ABSTRACT

Objectives: To compare anti-inflammatory effect of atorvastatin and rosuvastatin in patients of acute coronary syndrome. **Materials and Methods:** The study was a prospective, open-labeled, randomized and single-center study conducted on 100 patients of acute coronary syndrome. Patients were assigned to atorvastatin 40 mg daily or rosuvastatin 20 mg daily for 4 weeks. C-reactive protein (CRP) levels, lipid profiles, erythrocyte sedimentation rate (ESR) and adverse effects were measured at beginning and at the end of 4 weeks. **Results:** Baseline parameters and clinical profile did not differ between the two groups. CRP levels significantly decreased from beginning to the end of 4 weeks in both atorvastatin and rosuvastatin groups (from 35.48 to 23.07 mg/l and from 35.88 to 19.91 mg/l respectively, both $P < 0.001$). However, there was significant difference between the levels of CRP in patients of the rosuvastatin group as compared to the atorvastatin group (19.91 ± 6.32 vs 23.07 ± 7.47 , $P < 0.05$). In addition, both the drugs were associated with a reduction in total cholesterol, LDL levels and ESR at the end of 4 weeks as compared to the beginning ($P < 0.001$ for all comparisons). **Conclusion:** Both atorvastatin (40 mg) and rosuvastatin (20 mg) are effective in decreasing CRP and LDL cholesterol levels even in a short duration of 4 weeks. Rosuvastatin was found to be more effective in decreasing CRP levels.

Key words: Acute coronary syndrome, inflammation, statins

INTRODUCTION

Cardiovascular diseases are a leading cause of morbidity and mortality in both developed and developing countries and account for around 17 million deaths worldwide and 1.5 million

deaths in India.^[1] The most dramatic presentation of coronary artery disease resulting in increased mortality is acute coronary syndrome (ACS) which covers a group of clinical conditions including acute ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA).^[2]

Inflammation plays an important role in the onset and development of atherosclerosis which is the underlying cause of ACS.^[3,4]

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Address for correspondence:

Surabhi Gupta, Department of Pharmacology, Subharti Medical College, Meerut, Uttar Pradesh, India.
E-mail: surabhi.gupta32@gmail.com

How to cite this article: Khurana S, Gupta S, Bhalla H, Nandwani S, Gupta V. Comparison of anti-inflammatory effect of atorvastatin with rosuvastatin in patients of acute coronary syndrome. J Pharmacol Pharmacother 2015;6:130-5.

Recently markers of inflammation are being investigated as predictors of coronary ischemic events suggesting the key role of inflammation in progression of atherosclerosis. C-reactive protein (CRP), an acute phase reactant, is most consistently associated in predicting subjects with greater risk of both first and recurrent cardiovascular events.^[5-8]

Apart from having cholesterol-lowering effect, a wide spectrum of statin-mediated actions like attenuation of inflammation, plaque stabilization and improvement of endothelial dysfunction may contribute to potential benefits of statin therapy in ACS. Such multiple actions of statins which are independent of cholesterol lowering have been collectively termed as “pleiotropic effects”.^[9,10]

Lack of studies supporting anti-inflammatory effect of rosuvastatin, in Indian population, which is one of the commonly prescribed statins was one of the factors to undertake this study. Hence, this study was planned to compare the anti-inflammatory effect of atorvastatin and rosuvastatin in the patients of ACS.

MATERIALS AND METHODS

Study design

The study was a prospective, open labeled, randomized and single center study to compare the anti-inflammatory effect of atorvastatin and rosuvastatin in the patients of ACS conducted on 100 patients admitted in Chatrapati Shivaji Subharti Hospital, Subharti Medical College (SMC), Meerut (UP). The duration of the study was from December 2010 to July 2012.

Study population

A total of 100 patients of ACS participated in the study. Eligible patients were adults above 18 years of age, of either sex and those who fulfilled WHO criteria for the diagnosis of ACS (STEMI, non-STEMI, UA).^[2] Patients excluded were those who were already taking statins and/or other hypolipidemic drugs or those who had severe cardiac dysfunction (EF < 30%), severe anemia, chronic liver disease, chronic renal failure, pregnancy or lactation or if coronary revascularization was planned or anticipated at the time of screening and those with any history of hypersensitivity or allergy to statins or any contra indication to the use of statins. Approval was taken from ethical committee of the institute. The study was conducted in accordance with the GCP guidelines. The study was registered with CTRI (registration no. CTRI/2013/02/003385).

Study process

Patients who fulfilled inclusion criteria were enrolled after

they signed an informed written consent. After enrolment, history was taken and a thorough systemic examination and laboratory investigations were done. After selecting the patients, participants were randomized into either of the two groups as follows:

Group A received standard therapy + atorvastatin (40 mg/d).

Group B received standard therapy + rosuvastatin (20 mg/d).

Standard therapy included: Aspirin, clopidogrel, β -blocker, nitrates, ACE inhibitors.

The patients were followed up for one month time and all the investigations were repeated and all the results were tabulated.

All the adverse events either reported or observed by the patients were recorded in the case record form (CRF) with information about severity, onset, duration and action taken regarding the study drug.

End points

Primary outcome measures included levels of CRP and lipid profile after 4 weeks of treatment. Secondary outcome measures included recurrent myocardial infarction (MI), recurrent angina, stroke, treatment of emergent side effects and mortality.

Biochemical tests

Estimation of CRP (quantitative) was done at baseline and end of treatment using *Turbox CRP kit* (for protein analyzer Turbox plus) by *turbidimetry method*. The reference value in serum was 0-6.0 mg/l. Lipid profile was also measured at baseline and at the end of treatment using *Vitros 250* automatic analyzer (measured by dry chemistry). Erythrocyte sedimentation rate (ESR) was also measured at baseline and the end of treatment using *Westergren method*.

Statistical analysis

The data was analyzed using Microsoft Excel worksheet and SPSS 17.0 software. Data was tabulated as mean \pm S.E.; percentage change was also calculated. Results were analyzed using paired *t*-test to compare the baseline and end of treatment readings within each group. Unpaired Student *t*-test was applied to compare the significant difference between the groups. A *P* value of < 0.05 was considered significant.

RESULTS

Effect on CRP in both groups

Table 1 shows changes in CRP levels in the patients of both groups.

Atorvastatin 40 mg treatment caused highly significant decline ($P < 0.001$) in CRP levels in group A at the end of treatment. The level of CRP decreased from 35.48 to 23.07 mg/l. The mean percentage decrease in CRP as compared to baseline after 4 weeks of treatment was about 35%. Rosuvastatin 20 mg treatment also caused highly significant decline ($P < 0.001$) in CRP levels in group B at the end of treatment. The level of CRP decreased from 35.88 to 19.91 mg/l. The mean percentage decrease in CRP as compared to baseline after 4 weeks of treatment was about 44%. There was significant difference between the levels of CRP in patients of group B as compared to group A (19.91 ± 6.32 vs 23.07 ± 7.47 , $P < 0.05$).

Effect on ESR in both groups

Table 2 shows changes in ESR levels in the patients of both groups.

Atorvastatin 40 mg treatment caused highly significant decline ($P < 0.001$) in ESR levels in group A at the end of treatment the level of ESR decreased from 25.66 to 22.57 mm/hr. The mean percentage decrease in ESR as compared to baseline after 4 weeks of treatment was about 12%. Rosuvastatin 20 mg treatment also caused highly significant decline ($P < 0.001$) in ESR levels in Group B at end of treatment. The level of ESR decreased from 25.45 to 22.45 mm/hr. The mean percentage decrease in ESR as compared to baseline after 4 weeks of treatment was about 11%. There was no statistically significant difference between the levels of ESR in the patients of both groups.

Effect on lipid profile in patients of both groups

Table 3 shows changes in lipid profile in both groups.

There was statistically significant decline in all the components of lipid profile in group A. Total cholesterol decreased from 190.92 to 140.62 mg/dl ($P < 0.001$) and LDL cholesterol from 101.91 to 64.08 mg/dl ($P < 0.001$). HDL cholesterol showed a very mild decline from 38.74 to 38.44 mg/dl ($P = 0.001$). VLDL cholesterol decreased from 50.27 to 32.60 mg/dl ($P < 0.001$), while triglycerides showed a small but significant decrease from 143.66 to 140.32 mg/dl ($P < 0.001$).

There was statistically significant decline in all the components of lipid profile in group B also. Total cholesterol decreased from 209.14 to 149.90 mg/dl ($P < 0.001$) and LDL cholesterol from 109.13 to 66.73 mg/dl ($P < 0.001$). HDL cholesterol showed a very mild decline from 40.82 to 40.54 mg/dl ($P = 0.002$). VLDL cholesterol decreased from 59.19 to 35.18 mg/dl ($P < 0.001$) and triglycerides showed a small but significant decrease from 138.66 to 134.04 mg/dl ($P < 0.001$).

There was no statistically significant difference between the changes in lipid profile in both groups. All P values were > 0.05 .

Effect on secondary outcome measures in both groups

Three patients (6%) in group A and four (8%) in group B presented with recurrent angina. None of the patients in both the groups died or experienced MI, or stroke.

Adverse effect profile in both groups

Table 4 shows the adverse effect profile in both groups.

There were few adverse effects in group A, majority related to gastrointestinal system. There were five cases of constipation, four cases of dyspepsia and one case of pain in abdomen and myalgia in this group. All adverse effects were mild in severity and did not need alteration in treatment.

There were similar adverse effects in group B, majority related to the gastrointestinal system. There were four cases of constipation, four cases of dyspepsia, two cases of pain in abdomen and one case of myalgia in this group.

All adverse effects were mild in severity and did not need alteration in treatment. There was no statistically significant difference between the two groups on account of incidence of adverse effects.

DISCUSSION

This randomized study was undertaken to compare the anti-inflammatory effect of atorvastatin and rosuvastatin in the

Table 1: Level of CRP at baseline and at the end of 4 weeks

Groups	Baseline	4 weeks	Mean change (%)	P^*	$P^{\#}$
Group A (Atorvastatin=40 mg/d)	35.48±11.65	23.07±7.47	34.84±3.68	<0.001	0.02
Group B (Rosuvastatin=20 mg/d)	35.88±9.87	19.91±6.32 [#]	44.54±6.79	<0.001	

In each group as compared to baseline, ^{*}Inter group comparison, $n=50$ in each group, CRP=C-reactive protein, ESR=Erythrocyte sedimentation rate

Table 2: Level of ESR at baseline and at the end of 4 weeks

Groups	Baseline	4 weeks	Mean change (%)	P^*	$P^{\#}$
Group A (Atorvastatin=40 mg/d)	25.66±16.61	22.57±14.89	12.38±3.28	<0.001	0.96
Group B (Rosuvastatin=20 mg/d)	25.45±11.80	22.45±10.26	11.50±3.85	<0.001	

In each group as compared to baseline, ^{*}Inter group comparison, $n=50$ in each group, CRP=C-reactive protein, ESR=Erythrocyte sedimentation rate

Table 3: Effect on lipid profile (mg/dl)

Groups	Lipid profile	Baseline	4 weeks	Mean change (%)	P*	P†
Group A (Atorvastatin=40 mg/d)	TC	190.92±48.07	140.62±37.08	26.40±4.67	<0.001	0.21
	LDL	101.91±34.47	64.08±22.47	37.06±5.85	<0.001	0.54
	HDL	38.74±10.12	38.44±10.05	0.78±1.44	=0.001	0.24
	VLDL	50.27±24.34	32.60±15.77	34.90±4.33	<0.001	0.43
	TG	143.66±54.73	140.31±53.23	2.28±2.17	<0.001	0.51
Group B (Rosuvastatin=20 mg/d)	TC	209.14±48.92	149.90±36.60	28.36±4.21	<0.001	
	LDL	109.13±31.39	66.73±21.69	39.16±6.16	<0.001	
	HDL	40.82±7.52	40.54±7.56	0.68±1.43	=0.002	
	VLDL	59.19±27.21	35.18±17.35	41.02±5.35	<0.001	
	TG	138.66±43.86	134.04±41.95	3.18±3.32	<0.001	

*In each group as compared to baseline, †Inter group comparison; n=50 in each group; TC=Total cholesterol, LDL=Low density lipoprotein, HDL=High density lipoprotein, VLDL=Very low density lipoprotein, TG=Triglycerides

Table 4: Adverse effect profile

Type of ADR	Group (A/B)	Number (%)	Severity (no.)
Constipation	A	5 (10)	a
	B	4 (8)	a
Dyspepsia	A	4 (8)	a (2), b (2)
	B	4 (8)	a
Pain abdomen	A	1 (2)	a
	B	2 (4)	a
Myalgia	A	1 (2)	a
	B	1 (2)	a
Headache	A	0	-
	B	0	-

A=Atorvastatin, B=Rosuvastatin, a=Mild, b=Moderate

patients of ACS. The demographic characteristics of patients in two groups (group A—atorvastatin and group B—rosuvastatin) were comparable at baseline. The demographic profile in our study is consistent with previous studies in which ACS is reported to mainly affect middle-aged men.^[11,12]

The primary outcome parameter for efficacy comparison was alteration in CRP levels. In the present study, CRP levels decreased significantly (35%) in group A, which was treated with 40 mg of atorvastatin for 4 weeks and the level of CRP also decreased significantly (44%) in group B, which was treated with 20 mg of rosuvastatin for 4 weeks. A *P* value was <0.001 in both the groups. The fall in CRP was more significant in group B as compared to group A (*P* < 0.05).

The results of our study are in agreement with previous studies which have used different statins (pravastatin, simvastatin, lovastatin and atorvastatin) in different doses to show the effect of statin therapy on CRP. In studies comparing statin with placebo, patients with statin had a greater reduction of CRP than those receiving placebo. The percentage reduction was from 13% to 50% with various statins.^[13] Majority of studies have used higher doses of different statins and had longer follow-up period considering the thought that effect of statins on CRP develops over longer period.^[14]

Atorvastatin and rosuvastatin are two of the most commonly prescribed drugs for hypercholesterolemia and are a part of routine treatment of patients of ACS. Atorvastatin has been shown in clinical studies to produce reduction in CRP of 39% to 60% across the dose range of 10 to 80 mg.^[15,16] Few studies have assessed the effect of rosuvastatin in the patients with established coronary artery disease. So this comparative study was planned using doses, which are commonly prescribed clinically, for both the drugs. Earlier Russian study showed 10 mg/d rosuvastatin to be slightly inferior to 40 mg/d atorvastatin.^[17]

In JUPITER trial (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial) of apparently healthy persons without hyperlipidemia but with elevated high-sensitivity CRP levels, 20 mg rosuvastatin significantly reduced the incidence of major cardiovascular events. The CRP levels were reduced by 37%.^[18] In our study a decrease in CRP levels in rosuvastatin group was 44%. The exact reason of this difference could not be ascertained.

The exact mechanisms by which statins exert anti-inflammatory effect, thereby reducing CRP levels, are not known but postulated mechanisms are as follows-

- Statins inhibit lymphocyte adhesion to the intercellular adhesion molecule-1 (ICAM-1) and impair T-cell stimulation by directly binding to the lymphocyte function-associated antigen-1 site
- By inhibiting HMG-CoA reductase, statins inhibit the mevalonate pathway and consequently reduce the intracellular pools of isoprenoids, thereby downregulating the prenylation process
- A study showed that statins reduce IL-6-induced CRP in human hepatocytes via inhibition of protein glynylation.^[19-21]

Our study showed no significant difference between the secondary outcome measures of recurrent angina, recurrent MI, stroke and mortality between the two groups. There were

no cases of recurrent MI, stroke or mortality in either group. There were three cases of recurrent angina in group A and four cases in group B but the difference was not significant. The absence of any significant difference between clinical events in two groups in our study can be explained by short duration of study and that both the groups had been given statins, whereas most of the previous studies have compared various statins against placebos.

In the present study, there was a highly significant reduction in ESR levels in both the groups with no inter-group differences. The results were in accordance to study by Macin *et al.* which has also shown reduction in ESR rates with 40 mg/d of atorvastatin over 30 days.^[16] There is lack of data for the same with rosuvastatin.

In our study, atorvastatin and rosuvastatin had a favourable effect on lipid profile with a significant decrease in total cholesterol, LDL and triglycerides levels. These findings are in accordance with those in literature.^[22] There was a small decrease in HDL in both the groups. Atorvastatin has been shown to decrease HDL in initial period of 4-6 weeks followed by a steady increase in HDL thereafter in patients of ACS.^[23]

The adverse effect analysis in our study revealed that the overall incidence of adverse effects was low in the patients of both the groups. There were no cases of any serious adverse drug reaction including hepatic dysfunction or myositis. Most common adverse effects were related to gastrointestinal system like constipation, upper GI discomfort and pain in abdomen. All these adverse effects were mild in severity and none needed any change or termination of treatment. So our study showed that both 40 mg of atorvastatin and 20 mg of rosuvastatin were well tolerated and free of major adverse effects and drug interactions.

CONCLUSION

In conclusion, findings of our study showed that both atorvastatin (40 mg) and rosuvastatin (20 mg) are effective in decreasing CRP and LDL cholesterol levels even in a short duration of 4 weeks. It is tempting to suggest using CRP as a surrogate end point or monitoring variable for statin treatment in addition to LDL cholesterol. This dose of rosuvastatin was found to be more effective in decreasing CRP level. Both the drugs were effective, safe and offer an attractive approach for early treatment of ACS patients.

It is conceivable that clinical benefit afforded by statins if started early after ACS is partly due to other non-lipid-lowering effects, in which anti-inflammatory effect is primary as manifested by reduction in CRP levels. One common factor in all the studies which have shown clinical benefit from statin

treatment, associated with decline in CRP in patients of ACS, is that all the studies are large studies with bigger sample size and longer follow up.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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