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EFFECT OF ATORVASTATIN AND ROSUVASTATIN ON INFLAMMATORY MARKERS IN HYPERLIPIDEMIC PATIENTS

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Abstract: **Objective:** To make a comparative assessment in terms of Inflammatory markers among two different drugs: atorvastatin (10 mg) and rosuvastatin (10 mg) in patients with hyperlipidemia. **Methods:** The study was observational, prospective, nonrandomized, open label and single centric study involving 54 patients affected by hyperlipidemia without concomitant diseases: 23 patients in atorvastatin group and 31 patients in rosuvastatin group. The effects of 8-week statin treatment on inflammatory markers like hsCRP (high sensitivity C-reactive protein), WBC (white blood cell count), RDW (red blood cell distribution width), MPV (mean platelet volume) and ESR (erythrocyte sedimentation rate) were evaluated. **Results:** The % reduction in inflammatory markers like hsCRP, WBC and RDW from baseline to week 8 by atorvastatin was 30.29%, 44.25% and 10.20% and that by rosuvastatin was 38.19%, 47.64% and 24.92% which were significantly higher. The % decrease in the ESR and MPV with atorvastatin group was 43.87% and 10.65% and that with rosuvastatin was 58.17% and 15.15%. rosuvastatin showed a statistically significant improvement in lipid profile as compared to atorvastatin. **Conclusion:** A significant reduction was found in the level of inflammatory markers like WBC, RDW and MPV as well as lipid profile with rosuvastatin treatment as compared to atorvastatin treatment. Since these inflammatory markers have been associated with an increase in cardiovascular events, treatment with rosuvastatin can be of benefit in reducing cardiovascular events in patients with hyperlipidemia as compared to atorvastatin.

Keywords: Atorvastatin, Rosuvastatin, Hyperlipidemia, Inflammatory Markers

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INTRODUCTION

Hyperlipidemia is a heterogeneous group of disorders characterized by an abnormally elevated level of any or all lipids and/or lipoproteins in the bloodstream. These lipids include cholesterol, cholesterol esters, phospholipids, and triglycerides [1]. Lipids are transported in the blood as large 'lipoproteins'. Inflammation is an important feature of atherosclerotic disease, which is involved in all stages of atherosclerotic events. It has been shown that an effective reduction of inflammatory marker presents the two promising strategies in controlling the rate of morbidity and mortality of atherosclerotic diseases [2].

Statins (hydroxymethyl glutaryl–coenzyme A reductase inhibitors) are the most effective pharmacologic intervention for hypercholesterolemia. Statins have also been reported to attenuate chronic low-grade inflammation [3]. Statins have now become one of the more widely used therapeutic classes in clinical practice. It has been demonstrated that statin-related cardiovascular benefits are not only through their effects on lipid profile but also through their anti-inflammatory effects, which are believed to play an important role as well. The side effects and cost issue of statins are clinically major concerns in real world cardiovascular practice, which are associated with statin dosing used [3]. Generally, statins are remarkably well tolerated, but can produce myalgia, muscle cramps, and weakness in some patients. rosuvastatin has been shown to reduce Low Density Lipoprotein- Cholesterol (LDL-C) in a dose-dependent fashion by 46% to 55%, and has a similar safety profile to other statins [4].

Elevated serum inflammatory marker levels especially C-reactive protein (CRP), WBC count and others like Platelet count, Mean Platelet Volume (MPV), Erythrocyte Sedimentation Rate (ESR) and Red Blood Cells Distribution Width (RDW) have been associated with a greater risk of cardiovascular events in many epidemiological and clinical studies [5]. Activation of platelets occurs in hypercholesterolaemic patients. Enhanced platelet responsiveness has been noted when exposed to aggregatory agonists ex vivo [6]. Elevated serum inflammatory marker levels may identify individuals more likely to derive a greater relative benefit from some treatments. Evidence is growing that the statins have anti-inflammatory properties which is in part independent of their effect on lipids [7].

Over the past few years, it has become clear that over and above their effects on lipids, statins have other effects, usually described under the term pleiotropic. These include anti-inflammatory properties which may play an important role in the prevention of cardiovascular events. Statin therapy may attenuate the effect of inflammation on risk of cardiovascular events [8]. The findings also suggested that patients with evidence of inflammation, including an increased WBC count, may obtain a greater benefit from statin therapy. But till date there are too few studies and evidences to recommend the anti-inflammatory effects of statins.

There are many general reviews but only a few actual reports describe the effect of statins on platelet function.

Thus, the aim of our study was to evaluate the impact of atorvastatin (10 mg/day) and rosuvastatin (10 mg/ day) on inflammatory markers like hsCRP, ESR, WBC, RDW and MPV in patients with hyperlipidemia. The primary objective was to determine the change in the levels of inflammatory markers (hsCRP, WBC, MPV, ESR and RDW) from baseline to endpoint (week 8)].

MATERIALS AND METHODS

Patients:

We included 54 hypercholesterolemic subjects [37 males, 17 females, mean age 58.55 ± 9.815 years] with a baseline LDL-C between 130 - 250 mg/dl and Total Cholesterol (TC) between 200 - 240 mg/dl. Subjects were excluded if they had a history or evidence of hypersensitivity to statins, history of smoking and alcohol, any other endocardial or metabolic disease, renal disease or any other clinical condition, case of homozygous familial hypercholesterolemia or Subjects on recent ongoing intercurrent infection or using concomitant medication (cyclosporine, systemic glucocorticoids or ketoconazole, erythromycin or clarithromycin, glucocorticoids or verapamil) known to affect the lipid profile or with potencial safety concern were also excluded. The subjects were administered either atorvastatin or rosuvastatin once daily orally. The study protocol was approved by the ethics committee of the recruiting center.

Study design:

This was an observational, prospective, non randomized, open label and single centric study comparing the effects of two structurally different statins: atorvastatin and rosuvastatin. Eligible subjects, meeting entry criteria, were asked to return for a pretreatment visit. After this, patients returned to obtain either atorvastatin 10 mg/day or rosuvastatin 10 mg/day as instructed by the physician. Study assessment took place after 4 and 8 weeks of therapy. Data obtained at each subsequent visit included fasting blood work, adverse event reporting and study medication return to assess compliance. Laboratory analysis included lipid analysis and assessment of inflammatory biomarkers. All the results are expressed as mean ± SD and statistical tests were performed using paired and unpaired t-test.

RESULTS

Demographic Characteristics:

Table 1 shows the baseline demographic characteristic of patients. There were total 37 males and 17 females. The mean age of patients was similar in both groups which was 58.39 ± 11.43 and 58.71 ± 8.20 for atorvastatin and rosuvastatin, respectively. There were 15 males and 08 females in atorvastatin group as compared to 22 males and 09 females in rosuvastatin group. The graphical presentation of demographic characteristics is shown in fig. 1.

Baseline Characteristics of the patients:

Table 2 shows the baseline characteristics of the patient which were recorded in both the groups during the screening time and includes inflammatory markers like hsCRP, WBC, RDW, ESR and MPV. No statistically significant difference was observed between both the groups.

Change in Inflammatory markers from baseline to week 8

As shown in Table 3, rosuvastatin significantly decreased hsCRP, RDW and MPV as compared to atorvastatin. Both the drugs significantly decreased ESR but there was no statistically significant difference between both the groups. No statistically significant difference was found in the reduction of hsCRP between the groups.

Table 4 shows the percentage reduction in the inflammatory markers like hsCRP, WBC, RDW, ESR and MPV by atorvastatin which is 30.29%, 44.25%, 10.20%, 43.87% and 10.65% compared to 38.19%, 47.64%, 24.92%, 58.17% and 15.15% in patients with rosuvastatin group, respectively. These data indicate that rosuvastatin is able to improve the level of inflammatory markers to a greater extent as compared to atorvastatin. Its graphical representation is shown in fig. 4.

Change in Lipid profile from baseline to week 8

Changes from baseline in the various lipid parameters are shown in Table 5. Reduction in low density lipoprotein (LDL) and triglyceride (TG) was significantly more with rosuvastatin as compared to atorvastatin. Treatment with both the drugs also resulted in a significant increase in the level of HDL but the increase in high density lipoprotein (HDL) was significantly more with rosuvastatin as compared to atorvastatin.

The percentage change in lipid parameters of atorvastatin group as compared with rosuvastatin group is shown in Table 6 and their graphical representation is shown in fig 3. The percentage decrease in lipid parameters like TC, LDL and TG were 30.29%, 44.25% and 10.20% in patients in atorvastatin group as compared to 38.19%, 47.64% and 24.92% in patients in rosuvastatin

group. The increase in HDL-C level was 43.87% in atorvastatin group as compared to 58.17% in rosuvastatin group. These data indicate that rosuvastatin is able to improve the lipid profile to a greater extent as compared to atorvastatin.

DISCUSSION

Hypercholesterolemia is a major risk factor for the development of coronary heart disease (CHD). Inflammatory-response has been considered predictors of cardiovascular events including hyperchlolesterolemia both in its early phases and in Acute Coronary Syndromes patients. Elevated serum inflammatory marker levels especially C-reactive protein (CRP), WBC count and others like platelet count, MPV, ESR and RDW have been associated with a greater risk of cardiovascular events in many epidemiological and clinical studies.

The present study was designed to compare the effect of atorvastatin and rosuvastatin on lipid profile and various inflammatory biomarkers in patients with Hyperlipidemia.

Paul et al (2010) determined the effect of rosuvastatin treatment on C-reactive protein (CRP) which is a circulating marker of inflammation. The study provided a novel and clinically relevant data describing the effects of rosuvastatin on mediators of inflammation, suggesting that rosuvastatin may influence monocyte/macrophage inflammatory response by increasing TLR4 expression on circulating monocytes. rosuvastatin treatment further lowers CRP, a clinical marker of inflammation [9].

Giuseppe et al (2009) analysed the relation between Red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. The study demonstrate for the first time a strong, graded association of RDW with hsCRP and ESR independent of numerous confounding factors and suggest that this association might provide a rationale to introduce the easy, inexpensive RDW in algorithms for cardiovascular risk prediction [10].

In the present study rosuvastatin significantly decreased the level of inflammatory markers like WBC, RDW and MPV as compared to atorvastatin. Both the drugs significantly decreased ESR but there was no statistically significant difference between both the groups. The percentage decrease in hsCRP from baseline to week 8 in rosuvastatin group was found to be more as compared to atorvastatin. The percentage reduction in the inflammatory markers like hsCRP, WBC, RDW, ESR and MPV by rosuvastatin was higher than atorvastatin.

In was also observed that rosuvastatin was significantly better in improving lipid parameters like TG, LDL and HDL from baseline to week 8 as compared to atorvastatin.

From the results of this study it can be concluded that rosuvastatin seems to be a better drug as compared to atorvastatin not only in terms of improvement in lipid profile but also in terms of

decrease in the level of inflammatory biomarkers. But since the present study is single centric, of short duration and since no correlative study between atorvastatin and rosuvastatin comparing their effect on inflammatory markers has been carried out, more evidences are required to elucidate the comparative anti inflammatory effects of Statins.

CONCLUSION

Both atorvastatin and rosuvastatin significantly decreased LDL and TG and significantly increased HDL cholesterol but rosuvastatin significantly decreased lipid profile to a better extent as compared to that of atorvastatin. A significant reduction was found in the level of inflammatory markers like WBC, RDW and MPV with rosuvastatin treatment as compared to atorvastatin treatment. The inflammatory markers have been associated with a greater risk of cardiovascular events and the anti-inflammatory effects of rosuvastatin may play an important role in the prevention of cardiovascular events. rosuvastatin seems to be a better drug as compared to atorvastatin in terms of improvement in lipid profile as well as decrease in the level of inflammatory biomarkers.

Table 1: Demographic characteristics

Characteristics		Atorvastatin (Group I) Mean ± SD	Rosuvastatin (Group II) Mean ± SD
No. of Patients		23	31
Age (yrs)		58.39 ± 11.43	58.71 ± 8.20
Sex	Male (n)	15	22
	Female (n)	08	09
Height (cm)		165.43 ± 7.01	165.81 ± 7.59
Weight (kg)		62.22 ± 9.81	65.29 ± 9.92

Table 2: Baseline characteristics of the patients

Parameters	Atorvastatin group Mean ± SD	Rosuvastatin group Mean ± SD
hsCRP (mg/L)	2.74 ± 1.16	2.88 ± 1.08
MPV (/cum)	10.80 ± 3.10	11.02 ± 3.35
RDW (%)	15.38 ± 5.63	15.97 ± 5.32
ESR (mm/hr)	24.48 ± 4.93	26.61 ± 3.76)
WBC (/cmm)	9276.39 ± 1749.97	8923.16 ± 1211.18
TC (mg/dl)	218.87 ± 13.06	221.97 ± 14.29

LDL (mg/dl)	144.91 ± 13.98	145.19 ± 9.05
TG (mg/dl)	211.26 ± 12.61	214.06 ± 15.12
HDL (mg/dl)	39.43 ± 7.47	40.58 ± 5.66

LDL= Low Density Lipoprotein, HDL= High Density Lipoprotein Cholesterol
TC= Total Cholesterol, TG= Triglyceride, RDW= Red blood cell distribution width,
ESR= Erythrocyte sedimentation rate, MPV= Mean platelet volume,
WBC= White blood cell count, hsCRP= High sensitivity C-reactive protein

Table 3: Reduction in inflammatory markers from baseline to week 8

Parameter	Atorvastatin Group		Rosuvastatin Group	
	Baseline Mean ± SD	Week 8 Mean ± SD	Baseline Mean ± SD	Week 8 Mean ± SD
hsCRP (mg/L)	2.74 ± 1.16	1.91 ± 0.75	2.88 ± 1.08	1.78 ± 0.77
WBC (/cmm)	9276.39 ± 1749.97	5171.4 ± 1099.18	8923.16 ± 1211.18	4672.48 ± 1055.69 *
RDW (%)	15.38 ± 5.63	13.81 ± 5.17	15.97 ± 5.32	11.99 ± 4.70 *
ESR (mm/hr)	24.48 ± 4.93	13.74 ± 4.29 #*	26.61 ± 3.76	11.13 ± 3.36 #*
MPV (/cum)	10.80 ± 3.10	9.65 ± 3.33	11.02 ±3.35	9.35* ± 3.04 *

p value <0.05 (between two groups), unpaired t-test.
* p value <0.0001 (baseline verses week 8), paired t-test.

Table 4: % Reduction in inflammatory markers from baseline to week 8

Parameter	Atorvastatin Group	rosuvastatin Group
	% change	% change
hsCRP	30.29	38.19
WBC	44.25	47.64
RDW	10.20	24.92
ESR	43.87	58.17
MPV	10.65	15.15

Table 5: Change in lipid profile from baseline to week 8

Para - meter	Atorvastatin Group		rosuvastatin Group	
	Baseline Mean (SD)	Week 8 Mean (SD)	Baseline Mean (SD)	Week 8 Mean (SD)
TC (mg/dl)	218.87 ± 13.06	149.70 ± 14.01 *	221.97 ± 14.29	117.55 ± 12.41*
LDL-C (mg/dl)	144.91 ± 13.98	88.78 ± 11.85 #*	145.19 ± 9.05	80.26 ± 8.69 #*
TG (mg/dl)	211.26 ± 12.61	155.95 ± 15.05#*	214.06 ± 15.12	146.48 ± 12.49#*
HDL-C (mg/dl)	36.87 ±7.47	43.17 ± 6.08 #*	40.58 ± 5.66	48.26 ± 5.53 #*

 # p value <0.05 (between two groups), unpaired t-test.

*** p value <0.0001 (baseline verses week 8), paired t-test.**

Table 6: % Change in lipid profile from baseline to week 8

Parameter	Atorvastatin Group	rosuvastatin Group
	% change	% change
TC	30.36	47.04
LDL	38.73	44.72
TG	16.27	26.9
HDL	9.49	15.91

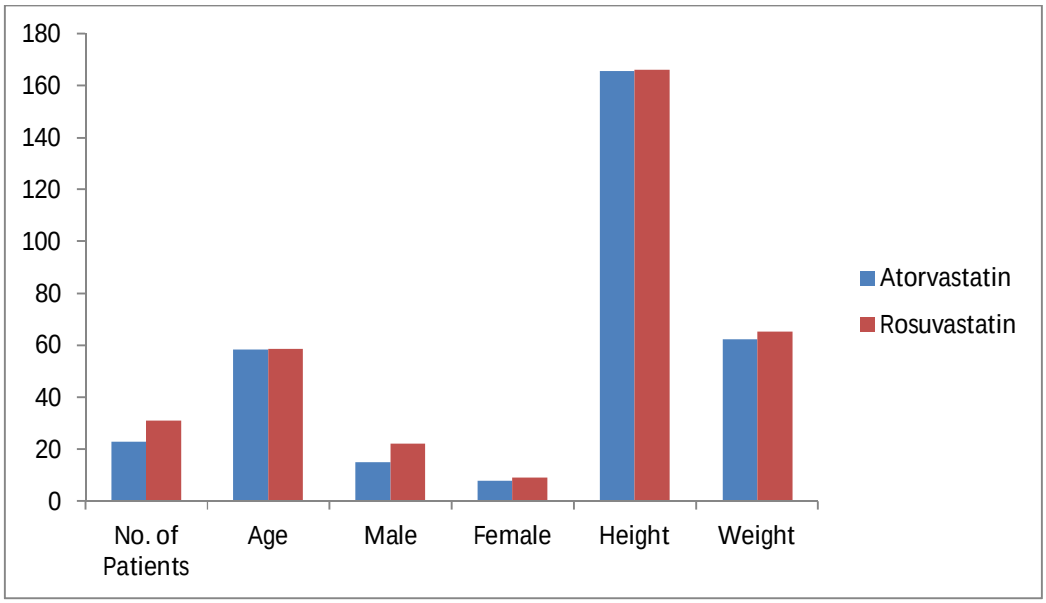

Figure 1: Demographic characteristics of patients

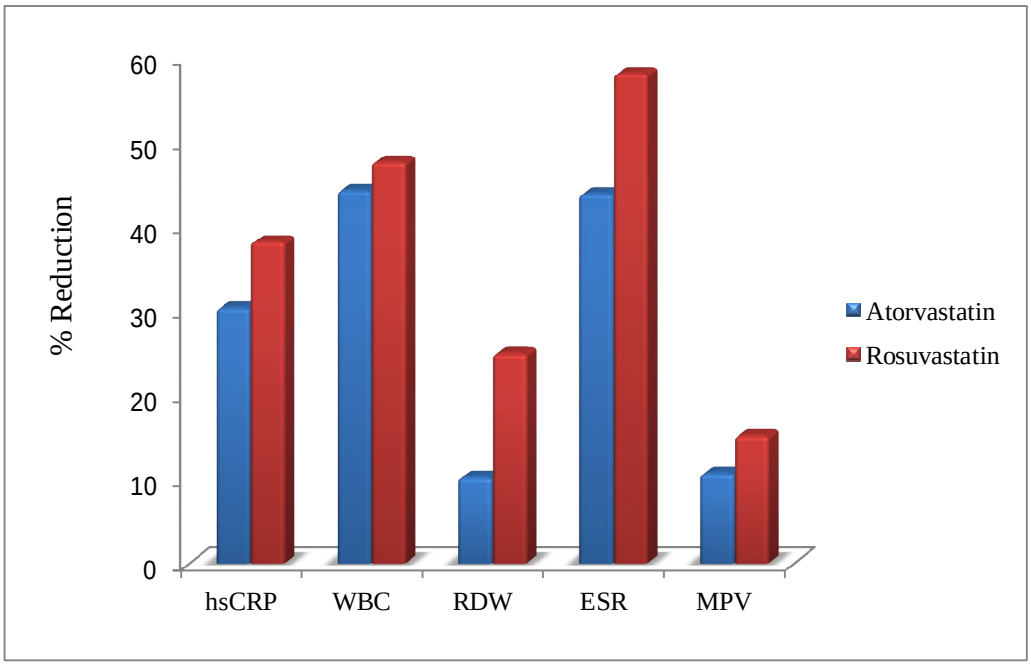

Figure 2: % Reduction in inflammatory markers from baseline to week 8

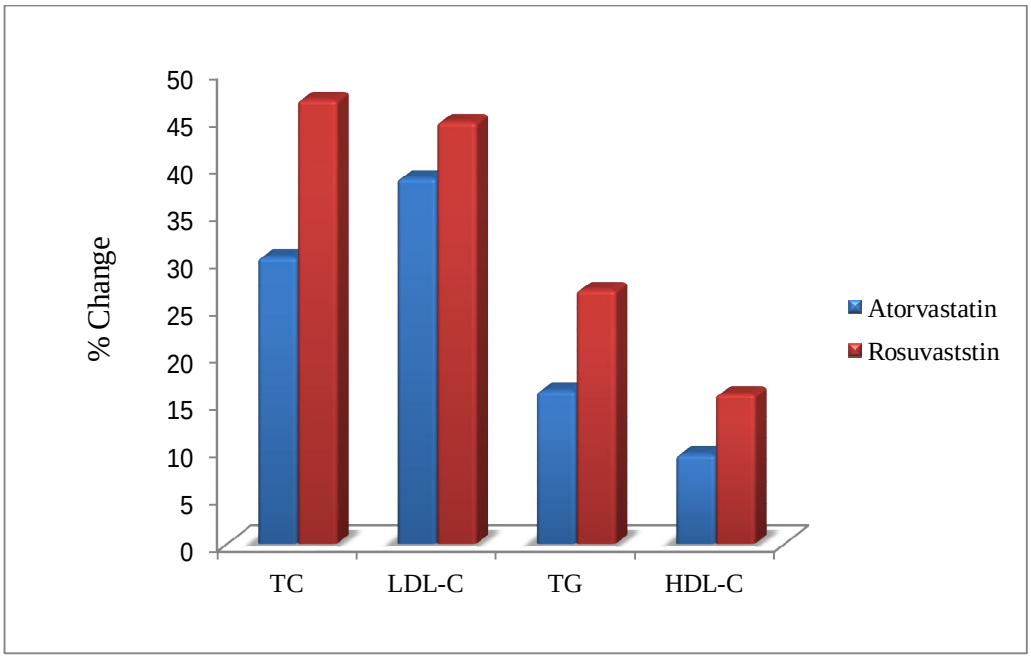

Figure 3: % Change in lipid profile from baseline to week 8

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