COMPARING HIGH INTENSITY WITH LOW INTENSITY STATINS IN ACHIEVING OPTIMAL LDL GOALS AMONG CORONARY ARTERY DISEASE PATIENTS IN SUBURBAN POPULATION IN SOUTH INDIA

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ABSTRACT

BACKGROUND

Patients with ischemic heart disease (IHD), including those with an acute coronary syndrome (ACS), should receive long-term, intensive lipid-lowering statin therapy. Target levels of low-density lipoprotein cholesterol (LDL-C) in patients with ACS are <70 mg/dl. Various studies have demonstrated that many high-risk patients do not achieve optimal LDL-C control in spite of being on adequate dose of lipid-lowering statin therapy. The aim of the present study was to analyse the control of LDL-C and high-density lipoprotein (HDL-C) levels after 12 weeks of statin therapy at different doses, in patients who had ACS and who underwent revascularization with or without a prior episode of ACS.

MATERIALS AND METHODS

This was a prospective cohort study. 100 consecutive cases diagnosed with ACS or those who underwent coronary intervention with or without prior ACS were enrolled. These patients were initiated on either atorvastatin (ATV; doses ranging from 10 mg to 80 mg) or rosuvastatin (RSV; 5 mg to 20 mg), according to initial LDL-C values at index point of contact. Continuous Variables are presented as mean ± SD and were compared using one-way ANOVA. Comparison of each class of patients according to the respective doses of statins and the degree of lowering of LDL-C after 12 weeks of treatment was done.

RESULTS

Majority of patients were male (80%). ATV40 demonstrated significant change in LDL-C, HDL-C and TC. ATV20 produced significant change in both LDL-C and TC, while ATV10 demonstrated significant change only in TC. Furthermore, only 69% of the people received high-dose of statin. More than 80% of the patients using high-dose stains (i.e., ATV40, ATV80 and RSV20) achieved optimal LDL-C control. In patients taking low-dose statin, more than 50% people did not achieve optimal LDL-C control.

CONCLUSION

Patients with CAD who were not receiving adequate dose of lipid lowering statin therapy, did not achieve optimal LDL-C control. Among these, patients treated with high-dose statins (ATV40, ATV80 and RSV20) achieved optimal LDL-C control and patients who received low-doses of statins did not acquire optimal LDL control and thus are further prone to adverse coronary events.

KEY WORDS

Acute Coronary Syndrome, Atorvastatin, High-Dose Statin, Rosuvastatin.

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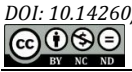

BACKGROUND

Unstable plaque in epicardial coronary arteries leads to acute coronary syndrome (ACS) and this in turn, results in clinical conditions extending from unstable angina to sudden cardiac death.[1] Statins are known as the agents with pleotropic effects and maximum lipid-lowering efficacy in patients with proven coronary artery disease.[2] Low-density lipoprotein cholesterol (LDL-C) in various studies have shown to be the chief risk determinant for coronary events and has a positive interrelation even for values within the normal range.[3] Evidence collated over the years demonstrates that statins can decrease the long-term

cardiovascular risk by reducing the elevated LDL-C, small-dense LDL-C, and C-reactive protein.[2] For very high risk patients, the present ESC/EAS guidelines (2016) for the treatment of dyslipidaemias advocates the LDL-C levels of<70 mg/dl (target goal).[4] In ACS patients, a meta-analysis validated the advantages of early intensive statin use in reducing the recurrent myocardial ischemia.[5] However, as a result of the safety concerns, intensive statin therapies not employed frequently.[6]Both atorvastatin and rosuvastatin are potent statins with varying pharmacologic characteristics. Evidence conveys that rosuvastatin produces greater decline in LDL-C and has a higher rate of accomplishing the therapeutic goals compared to other statins.[7]

Although there is abundant data analysing the efficacy of atorvastatin and rosuvastatin at different doses, in general, there is no analytical comparison of their lipid depleting effects in ACS patients.[8-12]

It has been demonstrated in numerous studies that many high risk patients do not attain desired LDL-C control in spite of being treated with intensive statin therapy.[13,14] Thus, the aim of the present study was to analyse the control of LDL-C and high-density lipoprotein (HDL-C) levels after 12 weeks of statin therapy at different doses, in patients who had ACS and those who underwent revascularization with or without a prior episode of ACS.

MATERIALS AND METHODS

This was a 12 week, a prospective cohort Study. It was designed to analyse the efficacy of atorvastatin and rosuvastatin at different doses in patients with ACS or those who had undergone coronary intervention with or without prior ACS. The pre-requisite at the time of enrolment was that patients should have an LDL-C level >70 mg/dl.

The study was performed at a hospital over a period of 24 weeks (From October 2016 to March 2017). Patients more than 18 years of age were enrolled in the study only after obtaining the approval of the Institutional Ethics Committee. Patients were explained about the study and written informed consent was obtained from them in their native language. A detailed history was taken, and clinical examination was performed. Blood samples were obtained for estimation of serum total cholesterol (TC) and HDL-C after fasting for 12 hours using Beckman Coulter AU5800 chemistry auto-analyser. Friedewald equation was used for calculation of LDL-C (LDL-C = total cholesterol - (HDL-C+ triglyceride/5). These biochemical parameters were estimated again at the end of 12 weeks.

A total of 100 consecutives cases were initiated on either atorvastatin (ATV) (10 mg to 80 mg) or rosuvastatin (RSV) (5 mg to 20 mg), according to initial LDL values, at an index point of contact. Comparison of each class of patients, according to their respective dose of statin and the percentage change in LDL-C after 12 weeks of treatment was done. Patients were excluded, if they had moderate or severe congestive heart failure, new-onset atrial fibrillation with an uncontrolled ventricular rate (100 beats/min), pulmonary oedema, complete heart block, sepsis, stroke or acute pericarditis within the preceding 4 weeks; women who were pregnant or breastfeeding; malignancy; active liver disease; malnutrition; hypothyroidism; and those taking oral contraceptives within the previous 3 months.

Statistical Analysis

Statistical analysis was done using the software SPSS version 21. Mean of Pre-test scores and Post-test scores for all the parameters were compared using Paired samples t-test. Cognitive gain was calculated as Post-test score minus Pre-test score. For all statistical evaluations, probability of value <0.05 was considered significant.

RESULTS

A total of 136 consecutive patients were screened, of which 100 patients were included and completed the study. Demographics and baseline biochemical parameters are described in Table 1. Overall, most patients were male (80 %). This points to higher incidence of dyslipidaemia in male patients. Distribution of patients in each group is described in Table 2. Doubling the doses of both the agents resulted in anticipated additional gain in terms of change in LDL-C, TC and HDL-C.

The influence of ascending doses of each statin on LDL-C levels is described in Table 3. The absence of additional benefit noticed at the highest dose of rosuvastatin was basically due to lower baseline LDL-C levels and probably indicates the higher possibility that they would acquire their target levels. Significant decline in LDL-C was observed with ATV20 (p = 0.028) and ATV40 (p = 0.0001) at the end of 12 weeks. The decline in LDL-C with ATV80 did not acquire the significance, but there was a tendency towards statistical significance (p = 0.068). At the end of treatment period, LDL-C decreased in all the groups except ATV10 and RSV5 (Table 4). After controlling for statin dose and baseline LDL-C level, multivariate analysis revealed increasing age (p = 0.038) as a predictor of accomplishing LDL-C goal of <70 mg/dl.

The influence of ascending dose of each statin on HDL-C levels is described in Table 3. Mean change in HDL-C over 12 weeks demonstrated that HDL-C increased to a significant extent with ATV40 (p = 0.024) (Table 3). At the end of treatment period, HDL-C was raised in all the groups except ATV10 (Table 4). The chance of reaching a HDL-C level > 40 mg/dl was more inpatients with lower baseline levels or those on higher doses of statin (Table 4).

The influence of ascending dose of each statin on TC levels is described in Table 3. Significant decline in TC was noticed with ATV10 (p = 0.039), ATV20 (p = 0.026) and ATV40 (p = 0.0001) at the end of 12 weeks. The decline in TC with ATV80 did not acquire the significance, but, there was a tendency towards statistical significance (p = 0.068). At the end of treatment period, TC cholesterol decreased in all the groups (Table 4).

On analysis, only 69% of the patients received high dose of statin. More than 80% of the patients using high dose statins i.e., ATV40 and ATV80 and RSV20 achieved optimal LDL-C control. In patients, taking lower dose of statin > 50% people did not attain optimal LDL-C control. Reduction in LDL-C in RSV20 is not significant as baseline LDL-C was near optimal level and these patients were already on statins.

Sr. No.	Parameters	Cohort (n = 100)
1	Mean Age (yrs)	58.41 ± 10.57
2	Male Gender (%)	80 %
3	Total Cholesterol (TC) (mg/dl)	161.95 ± 40.84
4	Low Density Lipoprotein Cholesterol (LDL-C) (mg/dl) High Density Lipoprotein	125.46 ± 112.29
5	cholesterol (HDL-C) (mg/dl)	38.60 ± 10.87

Table 1. Demographics and Baseline Biochemical Parameters

Data is expressed as mean ±SD or as percentages

Statin	Gender		Total (n = 100)
	Male	Female	
ATV10	11	2	13
ATV20	12	4	16
ATV40	37	12	49
ATV80	4	0	4
RSV5	3	0	3
RSV10	8	1	9
RSV20	5	1	6

Table 2. Distribution of Patients (N = 100) In Each Treatment Group

Data expressed as absolute numbers

Sr. No.	Parameters	Statins and their Doses	Baseline (mg/dl)	12 Weeks (mg/dl)	p value
1	Total Cholesterol (TC)	ATV10	173.92 ± 58.45	152.69 ± 34.89	<0.05
		ATV20	156.50 ± 45.67	139.94 ± 37.88	<0.05
		ATV40	159.27 ± 36.90	125.06 ± 26.87	<0.05
		ATV80	195.50 ± 12.77	133.25 ± 11.64	>0.05
		RSV5	145.33 ± 19.63	136.67 ± 31.01	>0.05
		RSV10	176.67 ± 38.24	162.44 ± 30.15	>0.05
		RSV20	136.83 ± 12.07	123.33 ± 22.26	>0.05
2	Low-Density Lipoprotein Cholesterol (LDL-C)	ATV10	106.23 ± 42.88	109.46 ± 34.06	>0.05
		ATV20	109.50 ± 34.51	98.88 ± 26.37	<0.05
		ATV40	137.08 ± 155.38	93.04 ± 20.37	<0.05
		ATV80	177.25 ± 16.19	96.00 ± 2.83	>0.05
		RSV5	111.33 ± 27.15	114.00 ± 26.46	>0.05
		RSV10	125.11 ± 36.34	118.89 ± 30.63	>0.05
		RSV20	87.83 ± 17.21	84.17 ± 8.99	>0.05
3	High-Density Lipoprotein Cholesterol (HDL-C)	ATV10	41.46 ± 12.25	41.00 ± 8.45	>0.05
		ATV20	38.13 ± 12.24	39.81 ± 7.37	>0.05
		ATV40	38.04 ± 11.17	39.53 ± 7.78	<0.05
		ATV80	33.50 ± 9.00	37.00 ± 12.06	>0.05
		RSV5	37.00 ± 3.46	38.00 ± 6.96	>0.05
		RSV10	41.56 ± 10.67	42.00 ± 7.81	>0.05
		RSV20	38.00 ± 5.79	38.50 ± 6.25	>0.05

Table 3. Within Group Analysis of Different Treatment Groups at The End of Treatment

Values expressed as mean ± SD; within group analysis done by One-way ANOVA; $p < 0.05$ is considered as statistically significant; ATV – Atorvastatin; RSV – Rosuvastatin

Parameters	Statins	Mean Change (mg/dl)	% Change
Total Cholesterol (TC)	ATV10	- 21.2	- 12.13
	ATV20	- 16.6	- 10.61
	ATV40	- 34.2	- 21.47
	ATV80	- 62.2	- 31.82
	RSV5	- 8.6	- 5.92
	RSV10	- 14.3	- 8.09
	RSV20	- 13.5	- 9.87
Low-Density Lipoprotein Cholesterol (LDL-C)	ATV10	3.3	3.11
High-Density Lipoprotein Cholesterol (HDL-C)	ATV20	- 10.6	- 9.68
	ATV40	- 44.1	- 32.17
	ATV80	- 81.3	- 45.85
	RSV5	2.7	2.43
	RSV10	- 6.2	- 4.96
	RSV20	- 3.6	- 4.10
	ATV10	- 0.5	- 1.20
	ATV20	1.7	4.46
	ATV40	1.5	3.95
	ATV80	3.5	10.45
	RSV5	1	2.70
	RSV10	0.4	0.96
	RSV20	0.5	1.32

Table 4. Mean and Percentage Change in Biochemical Parameters at The End Of 12 Weeks

Data expressed as mean or percentage; ATV – Atorvastatin; RSV – Rosuvastatin

DISCUSSION

The present study analysed the relative efficacy of atorvastatin and rosuvastatin over the dose range in Indian patients and thus, presented an opportunity to distinguish the percentage change in lipid levels determined by doubling the dose of statins. The conclusion that the greatest gain is derived at the highest dose of statins is uniform with the observation that the greatest impact on clinical events [15,16] and on the advancement of atherosclerosis[17, 18]is observed at these doses. Overall, high dose ATV (20-80 mg) and RSV (20 mg) were effective in decreasing LDL-C levels after 12 weeks of treatment. Various studies have established that in real-world scenario, only 67% of dyslipidemic patients reach their desired LDL-C level goals.[19] These studies highlight the distinction of practicing high intensity statins therapy in very high-risk patients to warrant them to acquire the target LDL-C level.

With respect to other components of the lipid profile, overall decline in TC was greater with ATV as compared to RSV, while rise in HDL-C was relatively equal (maximum with ATV80) across all the treatment groups, except ATV10.

Thapa R et al.[12] compared RSV5 with ATV10 and demonstrated significant change in LDL-C, TC, and HDL-C with both at the end of 3rd and 6th months. Similarly,

percentage change in LDL-C, TC, and HDL-C with RSV5 was – 48.69%, - 35.01%, and + 25.56% respectively, while that with ATV10 was - 43.85%, - 34.94%, and + 8.71% respectively. All these observations are contradictory to our findings, except significant decline in TC with ATV10.

Park JS et al.[8] Demonstrated significant change in LDL-C and TC on treatment with both RSV10 and ATV10 for a period of 6 weeks. Moreover, ATV10 demonstrated significant change in HDL-C. Percentage change in LDL-C, TC and HDL-C with RSV10 was – 48%, - 35% and – 1%, respectively, while that with ATV10 was – 40%, - 30% and – 4% respectively. Only significant decline in TC and percentage decrease in HDL-C levels with ATV10 is in accordance with our study.

Lee CW et al.[9]compared RSV10 and ATV20 in 350 cases and reported significant change in LDL-C, HDL-C and TC with both at the end of treatment period. Percentage change in LDL-C, TC and HDL-C with RSV10 was – 49%, - 31% and + 20%, respectively, while that with ATV20 was – 47%, - 29% and + 19% respectively. However, the present study demonstrated similar trend with respect to percentage change in biochemical parameters in both the groups, but the intensity of percentage change was relatively less.

Khurana S et al.[11]compared RSV20 and ATV40 in 100 patients and demonstrated significant change in LDL-C, HDL-C and TC with both at the end of 4 weeks. Percentage change in LDL-C, TC and HDL-C with RSV20 was – 39.16%, - 28.36% and -0.68% respectively, while that with ATV40 was – 37.06%, - 26.40% and – 0.78% respectively. Percentage change in LDL-C and TC with both the treatments demonstrated similar trend but percentage change in HDL-C was opposite to that of our findings.

Pitt Bet al.[10] Reported significant change in LDL-C, HDL-C and TC on treatment with both RSV20 and ATV80 for a period of 12 weeks. Percentage change in LDL-C, TC and HDL-C with RSV20 was – 42%, - 28.6% and + 9.7%, respectively, while that with ATV80 was – 42.7%, - 30.9% and + 5.6% respectively. With ATV80, percentage change in LDL-C and TC were similar, while in HDL-C was more in the present study. RSV20 demonstrated trend which was similar to our study, although magnitude of change was relatively large.

It was an observational study and thus, has its own limitations. Limitations of the study includes small sample size, significant difference in the baseline biochemical parameters among different groups, rosuvastatin 40 mg was not compared, and using low-dose statins in very high-risk patients.

Unwillingness to use the higher doses of statin may be correlated by some to the perception of a relatively small additional decline in LDL-C levels. It is apparent from this study that the use of high-dose statin leads to greatest proportion of patients acquiring treatment goals of all components of lipid profile. he significance of attaining target goals has evolved as a basic component of guidelines for management of dyslipidaemia, thus additionally emphasizing the distinction of the present findings.

CONCLUSION

This study demonstrates that over all, patients on high dose atorvastatin and rosuvastatin achieve optimal levels of LDL-C and TC. Moreover, it was observed that atorvastatin raised the HDL-C to a greater extent as compared to rosuvastatin. Additional studies analysing statins across different doses in Indian patients, not acquiring their treatment goals with low-dose statins, are needed.

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