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Efficacy Of Alternate Day Versus Everyday Dosing Of RosuvastatinIn Hyperlipidemia.

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ABSTRACT

Hyperlipidemia is one of the common risk factors for cardiovascular disease. Statins are well established in treatment for lowering LDL-C, triglycerides, TC and improving HDL-C levels. Rosuvastatin is long acting and more efficacious than other statins in lesser dosages with good safety profile. In this prospective open label study, 42 patients with plasma LDL cholesterol of more than 130 mg/dl and total cholesterol more than 200 mg/dl were selected. After baseline tests they were randomly allocated to two groups. Oral 10 mg of rosuvastatin was given to group-A daily and group-B on alternative day for six weeks. Fasting plasma lipid profile was measured on 0 day, 4th and 6th week and serums ALT, AST were estimated in both the groups on 0 day, 6th week. Statistical analysis was done with Student paired t-test. There was significant reduction in total cholesterol, LDL-C, triglycerides and elevation of HDL after 4 weeks and 6weeks of the treatment in both the groups compared to baseline. The mean percentage change of TC-24%and 21.60%; LDL- 33.50% and 31%; HDL-19.89% and 17.09%; TG - 36.70%and 41.33%in once daily group and alternate day group respectively $p<0.0001$***. No significant elevation of the mean serum ALT and AST levels at any point of study. Rosuvastatin 10 mg on alternate days has similar efficacy in decreasing lipid levels and raising HDL levels compared to daily dose. The decrease in triglyceride levels was more significant than daily doses. Hence alternate day dosing of rosuvastatin may be an alternate regime and cost effective without a major decrease in therapeutic benefits and also decrease in adverse events in patients with hyperlipidemia.

Keywords: Rosuvastatin, Dyslipidemia, HMG-CoA reductase inhibitors, cost-effectiveness

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INTRO DUCTION

Hyperlipidemia is a major cause of Atherosclerosis and its associated conditions such as coronary heart disease, Ischemic cerebrovascular disease and peripheral vascular diseases. Cardiovascular disease (CVD) is one of the leading causes of the death in India [1]. The deaths due to CVD in India are more than 25% of all causes of mortality at present and are expected to contribute tomore than half of the cases of heart disease in the world within the next fifteen years [2]. It is also estimated that by 2030, over 23 million people will die from cardiovascular disease annually. Coronary artery disease caused over 18 million deaths in the world in 2005. Of these 8 million, 44% occurred in people under 60 years and 80% took place in low- and middle-income countries. Atherosclerosis of coronary vessels is the main pathognomonic mechanism responsible for CVD. Dyslipidemia is a major cardiovascular risk factor (others: hypertension, diabetes, smoking, etc.). WHO has drawn attention to the fact that coronary heart disease is our modern epidemic and has set a goal of reducing the global death rate from CAD by 2% a year up to 2015.Correction of dyslipidemia is an important intervention in primary prevention of CAD [3]. Hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins) are well established as treatment for improving dyslipidemia and reducing cardiovascular events. Overall, these agents have a remarkable safety profile [4-7]. Rosuvastatin besides being among the most prescribed Statins, has longer affect half-life of 20-30 hours, due to active metabolites [8]. Rosuvastatin being a drug with long half-life, this study proposes that by using alternate day doses of rosuvastatin a significant LDL-C reduction may still be achieved while reducing the total cost of treatment. Lowering serum cholesterol is cost effective inmany low- and middle-income countries [9]. The lower- and middle-income groups of Indian society are rapidly becoming major sufferers of CVD, causing loss of one quarter of days due to all non-communicable diseases and the economic burden of rosuvastatin therapymay be substantial for this large section of population [10]. Hence, the present study is undertaken to investigate the efficacy of rosuvastatin on alternate day versus daily dosing regimen in hyperlipidemic patients.

METHODS

The study was done in Departments of Pharmacology and General medicine of Government Medical College & Hospital, Namakkal, Tamil Nadu, India in the year 2022. Rosuvastatin 10 mg with brand name CRESTOR of Astrazenica company was used in this study. In this prospective open label study 45 patients of age group between 30-60 years of both sexes were enrolled according to the inclusion criteria (Age group 30-60 years, both sex, patient with LDL more than 130 mg/dl, total cholesterol more than 200 mg/dl, hypertension, CAD, sedentary and low physical activity persons, persons on executive jobs, physical laborers) and exclusion criteria (NIDDM, hypothyroidism, smokers, patient on concurrent administration of immune suppressants - steroids, azole antifungals and protease inhibitors, patient on diuretic therapy, patient on other anti-cholesterol drugs (Gemfibrozil, FenoFibrate), H/O Statin intake in last 3 months, Patient reported to non- adherence to any lipid lowering agents in the past. Significant hypertriglyceridemia more than 400 mg/dl,history of prior sensitivity to statins, pregnancy and lactation, myalgia and liver dysfunction). Prior to participation in the study voluntary informed consent was obtained from all participants in prescribed format. After baseline investigations, patients who has plasma LDL >130 mg/dl and total cholesterol >200 mg/dl are considered in the study. Patients were randomly divided into groups A and B following odd-even method. Group A treated with daily doses of rosuvastatin (odd no. patients) and group B treated with alternate day 10 mg rosuvastatin (even no. patients) for six weeks at night after dinner. All participants were advised appropriate diet regimens based on NCEP step-II diet. Patients were counselled about the probable adverse effects of rosuvastatin including those on the hepatic and musculoskeletal system. The participant was asked to contact us if he experienced any muscle pain/cramps, malaise, pale stool or dark urine. For patients who complaints above symptoms were asked to stop the medication and LFT were done.42 patients had completed the study for 6 weeks. Three patients were dropped out. The reasons were one patient with allergic rash, one patient with gastric upset and one patient with insomnia. All the patients belong to low and middle economic group. Fasting plasma lipid profile was measured on 0-day, 4th and 6th week and serums ALT, AST were estimated in both the groups on 0 day and 6th week.

RESULTS

Values were expressed as Mean ± SD. Statistical difference in mean was analysed using student paired and unpaired t test. P value less than 0.05 was considered as significant.

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Gender distribution

A total of 42 patients participated in the study and consist of 15 females (36%) and 27 males (64%). All the patients belonged to lower and middle socio-economic status. Distribution of patients shows in the age group of 31-40 years were 36%; 41-50 years were 38% and 51-60 years were 26%. There was no significant difference in baseline parametersof lipid profile between the two groups. (>0.05) (Table 1).

Table 1: Baseline characteristics of patients with dyslipidemia receiving daily dosing rosuvastatin (n =21) and alternate day dosing of rosuvastatin (n = 21).

Baseline characteristics	Group A	Group B
Number of patients	21	21
Age range (in years)	30-60	30-60
Sex (male/female)	14/7	13/8
TC (mg/dl)	258.57±40.21	238.91±22.84
LDL	182.35±33.29	164.32±17.67
HDL	40.17±6.49	40.95±7.01
TG	214.17±69.00	224.00±77.54
VLDL	42.82±14.74	41.36±14.31
TC/HDL	6.44±1.37	5.97±1.22
LDL/HDL	4.61±1.07	4.10±0.92

The results of the study demonstrated that the lipid levels varied from zero to 6th week in each test group significantly but they did not vary much when compared tween the two test groups showing both the therapiesare similar in efficacy (Table 2).

Table 2: Changes in the lipid profile in the daily rosuvastatin, group - A and alternate day rosuvastatin group - B(Mean ± SD) and student paired t test.

Parameter		Mean ± SD			P Value
	Groups	At '0' weeks	At '4' weeks	At '6' weeks	0 week versus '6' weeks
TC	Group A	258.57±40.21	220±29.61	196.53±22.56	t=13.5; P<0.0001***
	Group B	238.91±22.84	209.55±15.55	187.29±12.58	t=9.425; P<0.0001***
LDL	Group A	182.35± 33.29	148.43±28.21	121.32±21.07	t=14.17; P<0.0001***
	Group B	164.32± 17.67	135.27±13.43	113.38±10.62	t=10.20; P<0.0001***
HDL	Group A	40.17± 6.49	45.43±7.26	48.16 ± 6.84	t=6.12; P<0.0001***
	Group B	40.95± 7.01	45.41±6.56	47.95 ± 6.26	t=5.982; P<0.0001***
Triglycerides	Group A	214.17±69.00	152.44±37.98	135.58±27.91	t=6.152; P<0.0001***
	Group B	224.00±77.54	151.50±40.73	131.43±26.32	t=6.261; P<0.0001***
VLDL	Group A	42.82±14.74	30.29±7.42	27.00± 5.41	t=5.75; P<0.0001***
	Group B	41.36±14.31	29.95±8.01	26.71±5.93	t=5.588; P<0.0001***
TC/HDL	Group A	6.44±1.37	4.96±0.77	4.14±0.58	t=11.10; P<0.0001***
	Group B	5.97±1.22	4.72±0.85	3.97±0.58	t=9.237; P<0.0001***
LDL/HDL	Group A	4.61±1.07	3.30±0.68	2.56±0.48	t=11.29; P<0.0001***
	Group B	4.10±0.92	3.05±0.63	2.51±0.45	t=9.324; P<0.0001***

Table 3: Changes in serum alanine transaminase andaspartate transaminase levels in the study group.

Timeline		Group-B	Group-A	P value
ALT	Baseline	27.97±1.180	28.42±1.302	0.7997 (NS)
	6th week	27.89±1.190	28.42±1.312	0.7672 (NS)
AST	Baseline	31.68±1.313	32.82±1.278	0.5386(NS)
	6th week	32.085±1.218	32.29±1.311	0.8951 (NS)

The estimation of liver enzymes-serum ALT, AST at end of 6th week in group A and group B have shown that thereis no significant rise in the levels and were within normal limits (Table 3).

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DISCUSSION

Hyperlipidemia is a major cause of atherosclerosis and its associated conditions such as coronary heart disease, ischemic cerebrovascular disease and peripheral vascular diseases. Statins are well established in treatment for lowering LDL-C, triglycerides, TC and improving HDL-C levels. Rosuvastatin is the most potent of the available statins, leading to both the greatest LDL-C lowering and HDL-C rising effects. Rosuvastatin also produced greater reductions in total cholesterol and non-HDL-C and produced similar or greater reduction in triglycerides compared to other Statins [11]. Hence the rosuvastatin has been selected for the present study. In the present study the efficacy of rosuvastatin was compared by administering daily versus alternate day oral dosing. The patients were randomly divided into two groups, group A (daily dose) and group B (alternate day dose). In both the groups rosuvastatin 10 mg was given orally. Serum lipid profile was analysed at 0-day, 4th week, and 6th week. Liver enzymes ALT, AST were analysed at 0 day and 6th week. The variations in base lineparameters between the two test groups was non- significant ($p>0.05$). The results of the study demonstrated that the cholesterol levels varied from zero to 6th week in each test group significantly but they did not vary much when compared between the two test groups showing both the therapies are similar in efficacy. According to the previous study done by Wongwiwatthananukit S et al the reduction of LDL-C in once daily regimen was 48% and 39% reduction seen in alternate regimen after 8 weeks. In supporting the above study, the present study of 6 weeks duration has achieved percentage decrease in LDL-C was 33.5% in daily regimen and 31% in alternate day regimen. It shows alternate day regimen is similar in efficacy and also attained nearly the same percentage of reduction in 6 weeks duration.[12]The differences in reduction of percentage compared tothe previous study could be due to the differences in culture, socioeconomic background, lifestyle and food habits of the participants enrolled in the study. There is highly significant reduction in all the lipid parameters like total cholesterol, LDL-C, triglycerides, VLDL levels and highly significant raise in HDL levels after six weeks of the treatment period in both group A and group B showing p value <0.0001***.When compared between the two groups the alternate day therapy of rosuvastatin 10 mg is similar in efficacy compared to daily dose of rosuvastatin. The study also hasachieved more reduction in triglyceride levels in group B than group A. Hypertriglyceridemia when associated with high LDL-C significantly increases the risk of coronary heart disease. In our study alternate day dosing reduced more TG levels than daily dosing. Hence it is highly beneficial and could be a better option for patients with hypertriglyceridemia. In India therapy with rosuvastatin in WHO recommended dose may cost between rs. 400.00 - rs. 800.00 per month. The lower- and middle-income groups of Indian society are rapidly becoming major sufferers of CVD, causing loss of one quarter of days due to all non- communicable diseases and the economic burden of rosuvastatin therapy may be substantial for this large section of population. Rosuvastatin being a drug with long half-life, this study proposes that by using alternate day doses of rosuvastatin a significant LDL-C reduction, increase in HDL levels and more reduction in TG levels may still be achieved while reducing the total cost of treatment.[9]In present study 10 mg tablet rosuvastatin had a cost of rs.25.90/- per tablet. Therefore, the cost of daily rosuvastatin for 6 weeks is rs. 1087.80 (yearly daily dosing expenses 9453.50/-) accounting for mean reduction of LDL-C of 33.50%. The cost of treatment with alternate day rosuvastatin for 6 weeks is 543.90/- (yearly alternate day dosing expense 4713.80/-) accounting for mean reduction of LDL-C of 31%. Projecting the above data to yearly expenses the cost of treatment with daily dose rosuvastatin is rs. 282/- perpercentage reduction of LDL-C per year compared to Rs.152/- per percentage reduction of LDL-C per year with the alternate therapy. This amounts to savings of Rs.130/- per percentage reduction of LDL-C per year with alternate day rosuvastatin therapy over the daily treatment regimen. ADR`s with rosuvastatin are minimal compared to the other statins [12]. By choosing alternate day regimen, not only there is reduction in cost, the ADR`s with rosuvastatin are sub minimized compared to daily regimen. Previous study done by Backes JM et al, on statins intolerance, the present study supports their study, stating that alternate day therapy of rosuvastatin is beneficial for people who cannot tolerate daily dosing on chronic use and achieve the same benefits of significant decrease in lipoproteins, while avoiding common adverse effects, which may be seen in daily dosing regimen. Another study by Clearfield MB et al, who had done the study with rosuvastatin in high risk patients with diabetes and CAD shown once daily regimen of rosuvastatin is effective with decrease in reduction of LDL-C about 44.6% with incidence of adverse reactions about 27.5%. Though in the present study diabetes patients are not included still it proves alternate day regimen of rosuvastatin with nil incidence of adverse events may be a better choice in patients who cannot tolerate daily regimen with hyperlipidemia [13]. The results show that rosuvastatin 10 mg alternate day dosing has equal efficacy compare to daily dosing achieving the same benefits without any side effects and also cost effective.

However, further extensive long-term studies with larger sample size including patients associated with other comorbid conditions are recommended.

CONCLUSION

The results of the present study indicate that treatment with alternate day dose of rosuvastatin is comparably effective when compared to currently practicing daily dose rosuvastatin therapy. Rosuvastatin 10 mg alternate day versus daily dosing has equal efficacy in treating hyperlipidemia. Alternate day regimen is more-safe in patients who cannot tolerate daily dosing. Alternate day dosing is more cost effective. It is also more efficacious in reducing triglycerides.

REFERENCES

[1] Mukherjee AK. Prediction of coronary heart disease using risk factor categories. J Indian Med Assoc 1995;93;312-5.

[2] Gupta R, Joshi P, Mohan V, Reddy KS, Yousuf S. Epidemiology and causation of coronary heart disease and stroke in India. Heart 2008;94;16-26.

[3] Lloyd Johns DM, O`Donnell CJ, D`Agostino RB,Massaro J, Silbershatz H, Wilson PW. Applicability of cholesterol lowering primary prevention trials to a general population. The Framingham Heart study.Arch intern Med 2001;161;949-54.

[4] Williams D, Feely J. Pharmacokinetic- pharmacodynamic drug interaction with HMG CoA reductase inhibitors. Clin Pharmacokinet 2002;41;343-70.

[5] Ghirlanda G, Oradie A, Manto A, Lippa S, Uccioli L, Caputo S, et al. Evidence of plasma CoQ 10 loweringeffect by HMG CoA reductase inhibitors; a double-blind placebo- controlled study. J clin Pharmacol1993;33;226-9.

[6] Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C. Efficacy and safety of cholesterol lowering treatment. Prospective meta- analysis of data from 90056 participants in 14 randomised trials of statins. Lancet 2005;366;1267- 78.

[7] Bersot PT. Drug therapy for hypercholesterolemia and dyslipidemia. In Bruton LL, editor. Goodman and Gillman manual of pharmacology and Therapeutics. 12th edition New York; McGraw- Hill; 2010:893.

[8] Lennernas H. Clinical pharmacokinetics of atorvostatin. Clin Pharmocokinet 2003;42;1141-60.

[9] WHO collobarating centre for drug statistic and methodology. ATC classification index with DDDs; 2011.

[10] Park K. Epidemiology of chronic non communicable diseases and conditions, In; Park K, editor. Parks textbook of preventive and social medicine. 20th ed. Jabalpur. Bhanot; 2009:316.

[11] Bakes JM, Venoro CV, Gibson CA, Ruisinger JF, Howard PA, Thompson PD, et al. Effectiveness and tolerability of every other day rosuvastatin in patient with prior statin intolerance. Ann Pharmacother 2008;2(3):341-6.

[12] Wongwiwatthananukit S, Sansanayudh N, Dhummauppakorn R, Kitiyadisai C. The efficacy and safety of rosuvastatin every other day compared with once daily in patient with hypercholesterolemia. The Annals of Pharmacotherapy 2006;40(11):1917-23.

[13] Clearfield MB, Amerena J, Bassand JP, Hernández García HR, Miller SS, Sosef FF, et al. Comparison of efficacy and safety of rosuvastatin 10 mg and Atorvastatin 20 mg in high-risk patients with hypercholesterolemia. Prospective study to evaluate the use of low doses of the statins atorvastatin and rosuvastatin (PULSAR). Trials 2006; 7:35.