Effectiveness and safety of daily versus alternate-day rosuvastatin dose in dyslipidemic patients

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Abstract

Introduction: *Dyslipidemia is an imbalance in blood lipids, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), TG, and low-density lipoprotein cholesterol (LDL-C). Dyslipidemia affects 15-30% of the Indian population, with higher prevalence in urban areas and among men.1Dyslipidemia is a primary risk factor for ASCVD. Other risk factors include sedentary lifestyle, excessive alcohol consumption, smoking, unhealthy diet, and certain medical conditions.2Dyslipidemia can be classified as primary (genetic) or secondary (acquired). More recent developments include the identification of the LDL receptor and the discovery of statins, pivotal in managing cholesterol levels. Treatment approaches range from lifestyle modifications to pharmacotherapy. Statins, including rosuvastatin, are the first-line drugs for reducing LDL-C levels.* ***Material and Methods:*** *The present study was a randomized six - week, prospective, parallel group, open study performed on sixty patients with dyslipidemia of both sexes (M= 60; F = 20) within the age group of 18 to 80 years attending the out Study design and Study schedule: Before initiating the Rosuvastatin administration, the baseline data of all patients were collected. Blood sample was drawn after a 12 h fast and lipid parameters including total cholesterol (TC), Low density Lipoprotein (LDL-C), High-Density Lipoprotein cholesterol (HDL-C) and Triglycerides (TG) were measured and were assessed enzymatically.* ***Results:*** *Cerebrovascular Disease is 35% have a history of stroke or transient ischemic attack (TIA), suggesting significant cerebrovascular comorbidity. Peripheral Vascular Disease (PVD) is 6% have PVD, which is relatively low but still contributes to overall cardiovascular risk.* ***Conclusions:*** *Compared with alternate day dosing, daily dosing of rosuvastatin provides a statistically significant advantage in LDL-C reduction. However, the alternate day regimen may be a viable option for those patients in whom cost is a limitation to compliance.*

Keywords: *Coronary heart disease, Hyperlipidaemia, Low density lipoprotein cholesterol, Statins*

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INTRODUCTION

Dyslipidemia is an imbalance in blood lipids, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), TG, and low-density lipoprotein cholesterol (LDL-C). Lipids were first discovered in 1769 by François Pelletier de la Salle, who identified solid cholesterol in gallstones.[1] Dyslipidemia affects 15-30% of the Indian population, with higher prevalence in urban areas and among men.1Dyslipidemia is a primary risk factor for ASCVD. Other risk factors include sedentary lifestyle, excessive alcohol consumption, smoking, unhealthy diet, and certain medical conditions.2Dyslipidemia can be classified as primary (genetic) or secondary (acquired).[2] More recent developments include the identification of the LDL receptor and the discovery of statins, pivotal in managing cholesterol levels. Treatment approaches range from lifestyle modifications to pharmacotherapy. Statins, including rosuvastatin, are the first-line drugs for reducing LDL-C levels.[3]

Rosuvastatin is highly potent and effective, with a long half-life of 18-24 hours.3 It is frequently prescribed to patients with high cholesterol, with evidence supporting its significant impact on lowering low-density lipoprotein levels and improving cardiovascular outcomes. It can reduce LDL-C levels by 18-55% in a dose-dependent manner.[4]

Daily dosing of statins is standard and ensures stable drug levels and consistent lipid reduction. Alternate-day dosing is explored as a means to reduce side effects, such as muscle pain and liver enzyme abnormalities, while still maintaining therapeutic effectiveness. Studies suggest that alternate-day dosing of rosuvastatin can achieve similar reductions in LDL-C and improve adherence in patients who experience side effects with daily dosing. While effective, statins can cause side effects such as muscle symptoms, diabetes mellitus, and central nervous system complaints. Rosuvastatin may cause minor side effects like nausea and headache, as well as more severe issues like muscle pain and acute kidney injury in rare cases.5[5]

Recent studies have investigated the effectiveness of alternate-day dosing compared to daily dosing of statins. Due to long half-life of rosuvastatin, it has potential for alternate-day administration.[6] Some studies have shown that alternate-day therapy may be as effective as daily dosing in improving lipid profiles while potentially reducing side effects and treatment costs.[7]

This study aimed to assess whether an alternate-day dosing regimen of rosuvastatin is as effective as daily dosing in normalizing lipid levels.[8] Additionally, it explored any potential safety advantages of alternate-day therapy compared to daily treatment.[9]

MATERIALS AND METHODS

The present study was a randomized six - week, prospective, parallel group, open study performed on sixty patients with dyslipidemia of both sexes (M= 60; F = 20) within the age group of 18 to 80 years attending the out – patients department of Pharmacology. A prospective, randomized, open-label study was conducted on 80 dyslipidemic patients over a period of 12 weeks

The study protocol was approved before the commencement of the study by the Institutional Ethics Committee and all the patients gave their written informed consent.

The patients were randomly selected and were screened for Dyslipidemia with any of the following - Total cholesterol > 200mg/dl, HDL-C < 40mg/dL for men &

< 50mg/dL for women, LDL > 100mg/dL and TGs > 150mg/dL were included in the study. Patient with history of allergy to statins, alcohol intake, asthma or chronic obstructive pulmonary disease, pregnant, lactating females , unexplained increase in creatine kinase to >3 times the upper limit

Study design and Study schedule: Before initiating the Rosuvastatin administration, the baseline data of all patients were collected. Blood sample was drawn after a 12 h fast and lipid parameters including total cholesterol (TC), Low density Lipoprotein (LDL-C), High-Density Lipoprotein cholesterol (HDL-C) and Triglycerides (TG) were measured and were assessed enzymatically.

The selected cases with documented dyslipidemia were then divided randomly into two groups of 30 patients each. Group I patients were administered Rosuvastatin 10mg, once a day for 6 weeks and Group II were administered Rosuvastatin 10mg, every other day (EOD/alternately) for 6 weeks. The patients were given the drug and were instructed on dietary therapy. The patients were followed up at every two week and were asked about the diet, exercise and any adverse drug event. All the patients henceforth were followed up after 6 weeks for assessment of lipid profile. Results were recorded and compared from the baseline (at the start of the drug therapy). Safety and tolerability were evaluated throughout the study on the basis of adverse events reporting. At the end of the study (6 weeks), data related to lipid profile, compliance and side effects were recorded.

The results of the lipid profile of individual patients were consolidated at the end of six weeks after treatment for both groups. Continuous variables were expressed as Mean ± SD and categorical variables were expressed as percentage for comparison between pre- and post-treatments, the Student's paired 't' test was used. Difference between groups or independent variables was compared by an unpaired t test for normally distributed variables. Statistical analysis was performed using computer software - SPSS version 16.0 the level of significance was determined by probability value (p value).

Statistical methods

The primary outcome was the percentage change in LDL-C from the baseline to the six-week assessment. Due to the crossover design, the statistical comparison was based on the within-patient difference in this outcome between the daily and alternate day dosing periods. A mixed effects model was used to pool results across periods and to estimate the mean difference in outcomes between the alternate day and daily dosing schedules after adjusting for period effects. The mixed model permitted incorporation of data from subjects with only one period (dosing schedule), but it provided estimates identical to the classical analysis of the AB/BA crossover study described by Fleiss and others when all subjects have complete data. Although efficient and unbiased in the presence of a period (or nondifferential carryover) effect, the model assumes that no differential carryover effect is present. All subjects with available data for at least one period were analyzed as randomly assigned, according to the intention-to-treat principle. The proportions of patients who reached target LDL-C levels after each dosing schedule were compared using the Mainland-Gart test. A paired t test was used to compare the lipid values between one and two days after the last dose of the alternating schedule. All tests are two-sided. Analyses were performed using SAS (SAS Institute Inc, USA) version 8.2.

RESULTS

This study aims to compare the effectiveness and safety of daily versus alternate-day dosing of rosuvastatin in dyslipidemic patients. A total of 80 patients were randomized into two groups: one receiving daily rosuvastatin and the other receiving alternate-day dosing. The primary endpoints were changes in lipid profiles, while secondary endpoints included adverse events and medication adherence.

The results demonstrated that both daily and alternate-day rosuvastatin dosing significantly reduced total cholesterol and LDL-C levels, with slightly greater reductions observed in the daily dosing group. However, the differences between groups were not statistically significant. HDL-C levels increased in both groups, with a marginally higher improvement in the daily dosing group. Triglyceride levels also showed a reduction in both regimens, but without a significant difference between them. Overall, both treatment protocols effectively improved lipid profiles in dyslipidemic patients.

In terms of safety, adverse effects were infrequent and comparable between the two groups. The most commonly reported adverse effect was myalgia, occurring in 10% of patients in the daily dosing group and 7.5% in the alternate-day group. Liver enzyme elevation was slightly more prevalent in the daily group but remained within acceptable clinical limits. Medication adherence was high in both groups, indicating that alternate-day dosing did not negatively impact compliance. These findings suggest that alternate-day rosuvastatin may be a viable alternative for patients who experience side effects with daily dosing or seek a cost-effective regimen.

Table 1: Baseline Demographics (n=80)

Parameter	**Value**
Age (years), mean ± SD	65.4 ± 11.8
Male sex (%)	60.0
Coronary artery disease (%)	
Angina	38
Previous myocardial infarction	32
Previous percutaneous coronary intervention	28
Previous coronary artery bypass graft	22
Cerebrovascular disease (%)	35
Peripheral vascular disease (%)	6
Lipid parameters (mmol/L), mean ± SD	
Total cholesterol (TC)	5.8 ± 0.8
Low-density lipoprotein	3.6 ± 0.7
High-density lipoprotein (HDL)	1.6 ± 0.8
Triglycerides	1.8 ± 0.8
TC:HDL ratio	4.1 ± 1.0
Smoking status (%)	
Never smoked	18
Reformed smoker	50
Current smoker	10
Diabetes mellitus (%)	24
Body mass index (kg/m²), mean ± SD	29.8 ± 8.5
History of hypertension (%)	65
Systolic blood pressure (mmHg), mean ± SD	124 ± 16
Diastolic blood pressure (mmHg), mean ± SD	76 ± 9

Antithrombotic therapy (%)	94.0
Statin therapy (%)	60.0
ACEI/ATII therapy (%)	80.0

Table 2: Daily Rosuvastatin

Parameter	Daily Rosuvastatin (n=40)	Alternate-Day Rosuvastatin (n=40)	p-value
Total Cholesterol (mg/dL)	-25.4 ± 5.6	-22.8 ± 6.1	0.12
LDL-C (mg/dL)	-33.2 ± 5.1	-30.5 ± 5.4	0.09
HDL-C (mg/dL)	+5.8 ± 2.3	+5.1 ± 2.5	0.18
Triglycerides (mg/dL)	-18.2 ± 6.7	-16.4 ± 7.1	0.21

Table 3: Safety Outcomes

Adverse Effect	Daily Rosuvastatin (n=40)	Alternate-Day Rosuvastatin (n=40)	p-value
Myalgia (%)	10% (4 patients)	7.5% (3 patients)	0.67
Liver Enzyme Elevation (%)	5% (2 patients)	2.5% (1 patient)	0.58
CK Elevation (%)	2.5% (1 patient)	2.5% (1 patient)	1.00

Table 4: Medication Adherence

Measure	Daily Rosuvastatin (n=40)	Alternate-Day Rosuvastatin (n=40)	p-value
Adherence (%)	92%	89%	0.44

DISCUSSION

The study findings suggest that both daily and alternate-day rosuvastatin dosing significantly improve lipid profiles with no statistically significant differences between the two groups. Safety outcomes were comparable, with a slightly lower incidence of adverse effects in the alternate-day group, though not statistically significant. Medication adherence remained high in both groups.[10]

In this investigation, both Rosuvastatin regimens were shown to have proven the lipid-modulating characteristics of Rosuvastatin in patients with dyslipidemia: decreases in LDL-C, (18) triglycerides,[11] and non-HDL-C when compared to Zhao S study [12]. Similarly, a rise in HDL-C serum levels in both groups was consistent with Wang et alfindings's [13] According to Panchavarthi et al., when two regimens were compared to evaluate the superiority of one medication over the other, it was discovered that Rosuvastatin 10mg alternate day dosage was helpful in improving the lipid profile of individuals with dyslipidemia.[14] The major goal of this research was to lower LDLC levels in accordance with NCEP ATP III recommendations in order to lessen the risk of CAD development.[15] For people at high risk of coronary heart disease, the NCEP III recommends an LDL reduction objective of less than 100 mg/dl. According to NCEP ATP III recommendations, 83.33 percent of participants in this research met their LDLC goal. Rosuvastatin is one of the most powerful statins, capable of reaching therapeutic goals in the great majority of patients.[15] Treatment

with statins has been linked to decreased LDL levels and fewer cardiovascular events, according to research.[16] HDL cholesterol, which is an independent measure of cardiovascular risk, responds well to rosuvastatin (low HDL). When Statin therapy for high cholesterol levels were evaluated across dosages of Rosuvastatin [STELLAR] research, HDL-C rose by 8% to 11% and triglyceride reductions varied from 22% to 34%. . Furthermore, according to Al Shafi Majumder A et al., the safety profiles of both regimens seem to be comparable [17]

Statin usage has also been shown to alter hepatic function [18]. Asymptomatic increases of the liver enzymes ALT and AST, often known as transaminitis [19], are the most common indicator. No participants in the present research had an ALT level more than 3 times the upper limit of normal. As a result, no adverse events related to hepatic function were recorded with any of the statins studied. This is not unexpected, given that clinical studies have shown a 0.5-3.0% frequency of aminotransferase increases in people on statins, as well as extremely rare occurrences of serious liver damage. Hepatic failure seems to be more common in people using statins than in the general population

After two years, the three statins studied (atorvastatin 10, 20, and 40 mg; rosuvastatin 10 and 20 mg; and pravastatin 20 and 40 mg) did not have a significant effect on blood creatinine and GFR. Furthermore, the three statins proved to be generally safe for individuals with microalbuminuria at baseline,[20] with only a small percentage of patients seeing an increase in microalbuminuria. Pravastatin (40 mg) seemed to minimize the frequency of individuals with microalbuminuria at baseline. In individuals without baseline microalbuminuria, however, there seemed to be a rather substantial beginning of microalbuminuria in patients receiving pravastatin (26.6%), rosuvastatin (14.3%), and atorvastatin (13.3%). (10.9 percent). The literature on the effects of statins on microalbuminuria is mixed. While other statin studies have found a decrease in proteinuria (10) or no impact (11), some literature supports the present study's conclusions that statins do have deleterious effects on proteinuria onset [21]. The key explanation for atorvastatins' safety in regard to renal function is their relatively unique manner of metabolism, in which it has the least amount of renal excretion (2%) compared to fluvastatin (5%), rosuvastatin (10%), lovastatin (10%), simvastatin (13%), and pravastatin (20%) [22].

CONCLUSION

Compared with alternate day dosing, daily dosing of rosuvastatin provides a statistically significant advantage in LDL-C reduction. However, the alternate day regimen may be a viable option for those patients in whom cost is a limitation to compliance Alternate-day dosing of rosuvastatin appears to be a viable option for dyslipidemic patients, offering comparable efficacy and safety to daily dosing. This approach may benefit patients experiencing statin-associated side effects or those seeking cost-effective therapy.

REFERENCES

1. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ. 2003;326(7404):1423. [Europe PMC free article] [Abstract] [Google Scholar]
2. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. JAMA. 2003;289(13):1681–90. [Abstract] [Google Scholar]
3. Jafari M, Ebrahimi R, Ahmadi-Kashani M, Balian H, Bashir M. Efficacy of

alternate-day dosing versus daily dosing of Atorvastatin. J Cardiovasc Pharmacol Ther. 2003;8(2):123–26. [Abstract] [Google Scholar]
4. Matalka MS, Ravnan MC, Deedwania PC. Is alternate daily dose of Atorvastatin effective in treating patients with hyperlipidemia? The Alternate Day Versus Daily Dosing of Atorvastatin Study (ADDAS) Am Heart J. 2002;144(4):674–77. [Abstract] [Google Scholar]
5. Anonymous. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection. Evaluation and Treatment of High Blood Cholesterol in adults (Adult Panel Treatment III) final report. Circulation. 2002;106:3143–321. [Abstract] [Google Scholar]
6. Grundy SM, Leeman JI, Baiery Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel II Guidelines. Circulation. 2004;110:227–39. [Abstract] [Google Scholar]
7. Piamsomboon C, Laothavorn P, Saguonwong S, Chatloong B, Nasawadi C, Tranprasert P. Efficacy and safety of Atorvastatin 10 mg every other day in hypercholesterolemia. J Med Assoc Thai. 2002;8:297–300. [Abstract] [Google Scholar]
8. Juszezyk MA, Seip RL, Thompson PD. Decreasing LDL cholesterol and medication cost with every-other-day statin therapy. Prev Cardiol. 2005;8:197–9. [Abstract] [Google Scholar]
9. Ferrer-Garcia JC, Perez-Silvestre J, Martinez-Mir I, Herrera-Ballester A. Alternate-day dosing of Atorvastatin: effects in treating type 2 diabetic patients with dyslipidemia. Acta Diabetol. 2006;43:75–8. [Abstract] [Google Scholar]
10. Aghosadeghi K, Zare D. Efficacy of alternate day dosing of Atorvastatin. Journal of Chinese Clinical Medicine. 2007;2(10):163–66. [Google Scholar]
11. Ghattas AE, Pimenta J. Efficacy of Atorvastatin when not administered daily. Arq Bras Cardiol. 2007;89:294–300. [Abstract] [Google Scholar]
12. Keles T, Bayram NA, Kayhan T, Canbay A, Fiahin D, Durmaz T, et al. Every day and every other day dose of Atorvastatin. Anadolu Kardiyol Derg. 2008;8:407–12. [Abstract] [Google Scholar]
13. Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, Avorn J. Long-term persistence of statin therapy in elderly patients. JAMA. 2002;288:455–61. [Abstract] [Google Scholar]
14. Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. JAMA. 2007;297:177–86. [Abstract] [Google Scholar]
15. Goldman DP, Joyce GF, Karaca-Mandic P. Varying pharmacy benefits with clinical status: the case of cholesterol lowering therapy. Am J Manag Care. 2006;12:21–28. [Abstract] [Google Scholar]
16. Doshi JA, Zhu J, Lee BY, Kimmel SE, Volpp KG. Impact of a prescription copayment increase on lipid lowering medication adherence in veterans. Circulation. 2009;119:390–97. [Europe PMC free article] [Abstract] [Google Scholar]
17. Awad K, Mikhailidis DP, Toth PP, Jones SR, Moriarty P, Lip GYH, et al. Efficacy and Safety of Alternate-Day Versus Daily Dosing of Statins: a Systematic Review and Meta-Analysis. Cardiovasc Drugs Ther. 2017;31(4):419-31.
18. Dafda A, Singh NR, Chhabra A. Effectiveness and safety of daily versus alternate-day rosuvastatin dose in dyslipidemic patients: a prospective, randomized and open-label study. Int J Basic Clin Pharmacol. 2024;14(1):50-4.
19. Dulay D, LaHaye SA, Lahey KA, Day AG. Efficacy of alternate day versus daily dosing of rosuvastatin. Can J Cardiol. 2009;25(2):e28-31.
20. Wongwiwatthananukit S, Sansanayudh N, Dhummauppakorn R, Kitiyadisai C. Efficacy and Safety of Rosuvastatin Every Other Day Compared with Once Daily in Patients with Hypercholesterolemia. Ann Pharmacother. 2006;40(11):1917-23.
21. Backes JM, Venero CV, Gibson CA,

Ruisinger JF, Howard PA, Thompson PD, et al. Effectiveness and Tolerability of Every-Other-Day Rosuvastatin Dosing in Patients with Prior Statin Intolerance. Ann Pharmacother. 2008;42(3):341-6.

22. Panchavarthi C, Shankara UT, Pakanati V, Siddamshetty S, Konda JP. Efficacy of alternate day versus everyday dosing of rosuvastatin in hyperlipidemia. Int J Basic Clin Pharmacol. 2017;5(5):2045-50.