International Journal of Basic & Clinical Pharmacology
Dafda A et al. Int J Basic Clin Pharmacol. 2025 Jan;14(1):50-54
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20243835

Original Research Article

Effectiveness and safety of daily versus alternate-day rosuvastatin dose in dyslipidemic patients: a prospective, randomized and open-label study

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Received: 10 October 2024
Accepted: 14 November 2024

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ABSTRACT

Background: Dyslipidemia is considered to be an important risk factor for development of atherosclerotic cardiovascular disease (ASCVD). Statins, also called HMG CoA reductase inhibitors are considered to the most effective lipid lowering agents. This study assessed the effectiveness and safety of daily versus alternate day dosing regimens of rosuvastatin in dyslipidemia patients.
Methods: This study was conducted for a period of 12 weeks. Study subjects comprised patients of either sex in age group 18-65 years diagnosed with dyslipidemia and a total of 90 subjects completed study who were randomly distributed to three groups, A (rosuvastatin 10 mg daily), B (rosuvastatin 10 mg on alternate days) and C (rosuvastatin 20 mg on alternate days).
Results: Rosuvastain significantly lowered total cholesterol, low density lipoprotein-cholesterol and triglycerides in all groups ($p<0.001$). High density lipoprotein-cholesterol increased, but non-significantly ($p>0.05$). Intergroup differences were not statistically significant. Group A reported slightly more adverse events than group B and group C.
Conclusions: Alternate-day rosuvastatin therapy showed effectiveness statistically similar to the daily dose therapy in dyslipidemic individuals. It also exhibited fewer side effects, suggesting it could be a feasible approach for managing dyslipidemia, providing a more economical and potentially safer alternative to daily administration.

Keywords: Dyslipidemia, Statins, Rosuvastatin, Lipid profile

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 Poulletier de la Salle, who identified solid cholesterol in gallstones. Dyslipidemia affects 15-30% of the Indian population, with higher prevalence in urban areas and among men.[1] Dyslipidemia is a primary risk factor for ASCVD. Other risk factors include sedentary lifestyle, excessive alcohol consumption, smoking, unhealthy diet, and certain medical conditions.[2] Dyslipidemia 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.

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]

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. 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.[6]

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

METHODS

This was a prospective, parallel group, randomized and open label study, conducted in a tertiary care hospital in Punjab, India.

The study included male and female dyslipidemia patients aged 18-65 from the medicine outpatient department. Based on prior data, a sample size of 90 was calculated, with a study power of 80% and an alpha error of 0.05. Patients were randomly assigned into three equal groups using computer software: one group received rosuvastatin 10 mg daily, another 10 mg on alternate days, and the third 20 mg on alternate days.

Male and female patients diagnosed with dyslipidemia, aged between 18 and 65 years, who were willing to participate and provided a written informed consent were included in the study. Patients who were unwilling to give consent, had a history of statin allergy, were currently using lipid-lowering agents, or had uncontrolled diabetes were excluded. Additionally, pregnant or lactating women, patients with rhabdomyolysis, and those taking drugs that interact with rosuvastatin, such as nicotinic acid, gemfibrozil, CYP3A4 inhibitors, HIV protease inhibitors, amlodipine, or amiodarone, were also excluded from the study.

A total of 97 participants were randomly assigned to three groups: Group A (n=32), group B (n=33), and group C (n=32) using a computer-generated randomization software to ensure random distribution. Seven participants (2 from groups A and C each, 3 from group B) dropped out due to non-compliance or adverse effects, leaving 90 patients who completed the study.

Group A received 10 mg of oral rosuvastatin daily, group B received 10 mg on alternate days, and group C received 20 mg on alternate days. After recording demographic information and medical history, patients' vitals and physical exams were documented at baseline. Blood samples were collected after overnight fasting for tests such as CBC, urine analysis, LFTs, and RFTs at baseline, 4, 8, and 12 weeks. Lipid profile was assessed at the start and after 12 weeks. All findings were recorded, and any adverse events were noted and addressed.

All patients gave a written informed consent after receiving a clear explanation of the study in an understandable language. The study followed good clinical practice guidelines and was approved by the institutional ethics committee at government medical college, Amritsar.

RESULTS

Demographic characteristics

All the three groups were statistically similar with respect to demographic and baseline characteristics. No significant difference ($p>0.05$) was found in the mean age of participants. The study included 40 males and 50 females. Among the participants, 1 was illiterate, 15 had primary education, 31 had secondary education, and 43 had college or higher education. Forty participants were unemployed, while 50 were employed. In terms of marital status, 5 were single, 79 were married, and 6 were widowed; none were divorced (Table 1).

Efficacy assessment

Baseline parameters showed no significant differences. After 12 weeks of rosuvastatin treatment a statistically significant ($p<0.001$) reduction in TC levels was observed across all three groups, with group A showing a 21.04% decrease, group B a 15.51% reduction, and group C a 17.95% decrease compared to baseline. In contrast, HDL-C levels showed a marginal and non-significant ($p>0.05$) increase. LDL-C levels saw a statistically significant ($p<0.001$) decrease across all groups, with group A experiencing a 32.76% drop, group B a 26.04% decrease, and group C a 29.18% reduction. Additionally, TG levels also showed a statistically significant ($p<0.001$) decrease, with group A showing an 18.35% reduction, group B a 17.04% decrease, and group C a 17.64% decline. These changes on intergroup comparison were statistically non-significant ($p>0.05$) (Figure 1-3).

The study observed a non-statistically significant rise in liver enzymes (AST, ALT and alkaline phosphatase) from baseline to week 12.

Safety assessment

It was observed that the total number of adverse events reported by the patients in group A were 8 (5 had reported headache, 1 reported myalgia, 1 reported gastrointestinal disturbances and 1 reported uneasiness), that in group B were 4 (1 reported headache, 2 reported myalgia and 1 reported gastrointestinal disturbances), while in the group C, total number of adverse events reported were 4 (3 reported headache and 1 reported myalgia) (Table 2).

Table 1: Socio-demographic distribution in the study participants.

Demographic features		Group A, (n=30)	Group B, (n=30)	Group C, (n=30)	Total, (n=90)
Age (Mean±SD)		47.73±11.59	47.67±8.01	47.77±8.35	47.39±9.35
Sex	Male	12 (40%)	12 (40%)	16 (53.33%)	40 (44.44%)
	Female	18 (60%)	18 (60%)	14 (46.67%)	50 (55.56%)
Education	Illiterate	0 (0%)	0 (0%)	1 (3.34%)	1 (1.11%)
	Primary school	7 (23.33%)	4 (13.33%)	4 (13.33%)	15 (16.67%)
	Secondary school	9 (30%)	12 (40%)	10 (33.33%)	31 (34.44%)
	College and above	14 (46.67%)	14 (46.67%)	15 (50%)	43 (47.78%)
Occupation	Unemployed	13 (43.33%)	15 (50%)	12(40%)	40 (44.44%)
	Employed	17 (56.67%)	15 (50%)	18 (60%)	50 (55.56%)
Marital Status	Single	4 (13.33%)	1 (3.34%)	0 (0%)	5 (5.56%)
	Married	25 (83.34%)	27 (90%)	27 (90%)	79 (87.78%)
	Widow	1 (3.34%)	2 (6.67%)	3 (10%)	6 (6.67%)
	Divorced	0	0	0	0 (0%)

Table 2: Groupwise comparison of adverse effects at the end of week 12.

Adverse events	Group A, (n=32)	Group B, (n=33)	Group C, (n=32)	Total, (n=97)
No adverse events	24 (75%)	27 (81.81%)	26 (81.25%)	77 (79.38%)
Headache	5 (15.62%)	1 (3.03%)	3 (9.38%)	9 (9.27%)
Myalgia	1 (3.12%)	2 (6.06%)	1 (3.12%)	4 (4.12%)
Gastrointestinal disturbances	1 (3.12%)	1 (3.03%)	-	2 (2.06%)
Uneasiness	1 (3.12%)	-	-	1 (1.03%)

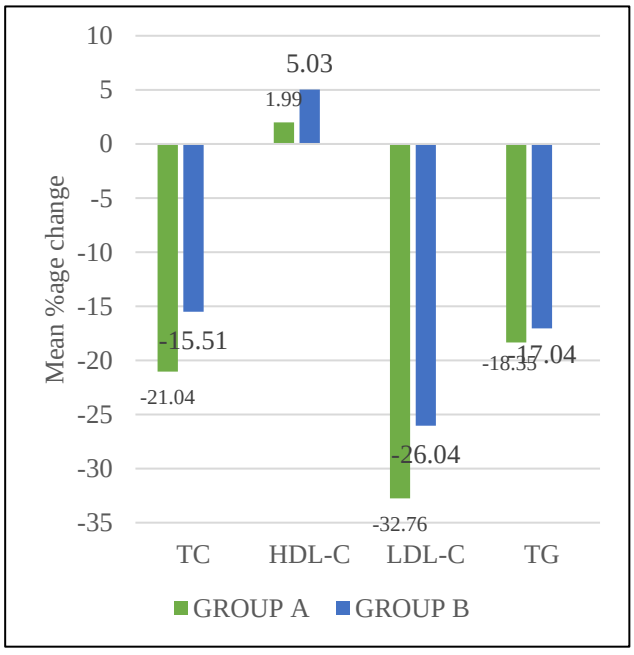

Figure 1: Comparative mean change in lipid profile from baseline to week 12 (group A versus B).

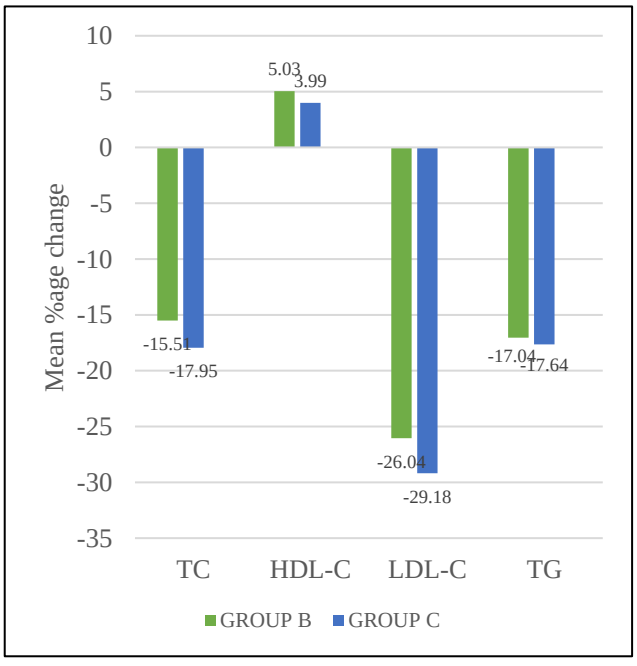

Figure 2: Comparative mean change in lipid profile from baseline to week 12 (group B versus C).

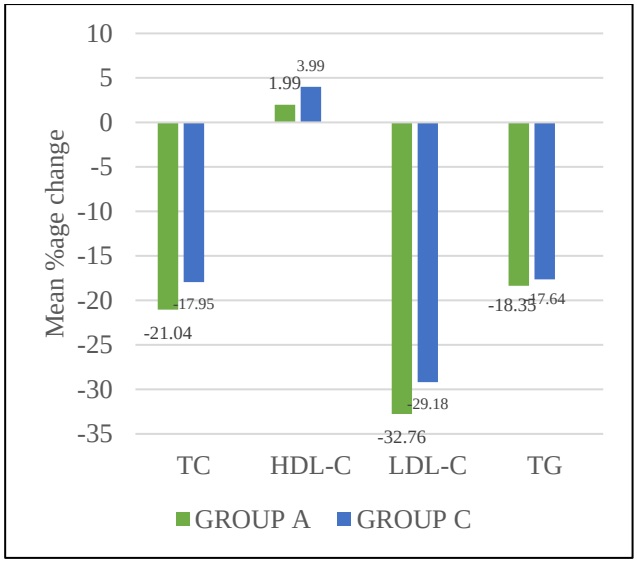

Figure 3: Comparative mean change in lipid profile from baseline to week 12 (group A versus C).

DISCUSSION

Dyslipidemia management involves lifestyle changes and sometimes medication to reduce cardiovascular risk. Statins, like rosuvastatin, are key drugs that lower cholesterol and LDL-C levels. Long half-life of rosuvastatin (20-30 hours) has led to an idea that alternate-day dosing may be as effective as and safer than daily dose.

This study compared the efficacy and safety of daily versus alternate-day rosuvastatin in 97 patients with dyslipidemia. Patients were divided into three groups: rgoup A (10 mg daily), group B (10 mg alternate days), and group C (20 mg alternate days) for 12 weeks. 7 patients dropped out due to adverse effects or non-compliance. The study design and dropout rate were similar to a previous study by Vasa et al.[7]

The mean age of patients across the three groups was similar, ranging from 47.67 to 47.77 years. Most participants were over 40 years old, suggesting late diagnosis of dyslipidemia. Most of the studies on dyslipidemia patients usually tend to enroll middle age groups with a few exceptions. There was a greater proportion of female participants (55.56%) than male participants (44.44%).[8] This is in contrast to a previous study by Vasa et al that comprised 26 men (62%) and 16 female participants.[7] Regarding marital status, 87.78% of patients were married, likely due to the higher age of enrolled subjects. Education levels varied among participants viz, 47.78% had college education or higher, 34.44% had secondary education, 16.67% had elementary education and 1.11% were illiterate. Additionally, 55.56% of the overall population was employed. The majority of participants in the research study conducted by Rosenson et al were employed, and their educational backgrounds varied.[9]

The three groups (A, B, and C) had comparable baseline lipid profiles, with mean levels of TC, LDL-C, and TG exceeding the optimal ranges, while mean HDL-C levels were within the optimal range.

After 12 weeks of treatment, all three groups showed a significant decrease (p=0.001) in TC, LDL-C, and TG levels from baseline, while HDL-C levels slightly increased, but not significantly (p>0.05). This is consistent with previous studies, such as Harivenkatesh et al which found significant reductions in TC, LDL-C, and TG, and increases in HDL-C with atorvastatin and fenofibrate treatment.[10] Similarly, Panchavarthi et al observed significant reductions in TC, LDL-C, and TG and increases in HDL-C with rosuvastatin treatment, but no significant differences between daily and alternate-day dosing.[11]

A comparison of the changes in lipid levels across the three study groups revealed no significant differences (p>0.05) between groups A and B, B and C, or A and C, in terms of TC, LDL-C, HDL-C, and TG levels. This suggests that all three regimens (daily and alternate-day dosing of rosuvastatin) had equivalent effects in reducing TC, LDL-C, and TG levels over 12 weeks. Additionally, the study found that a lower dose of rosuvastatin (10 mg every alternate day) may be as effective as a higher dose (20 mg every alternate day) for moderately elevated lipid levels.

This finding is consistent with previous studies, such as those by Dulay et al, Wongwiwatthananukit et al and Vasa et al which also found similar reductions in lipid levels with daily and alternate-day dosing of rosuvastatin.[12,13] However, unlike these studies, our study did not find a significant increase in HDL-C levels with statin treatment.

During the treatment course, no major adverse effects were reported in any of groups. However, minor adverse events were observed across all groups. In group A, which received rosuvastatin 10 mg daily, 25% of patients (8 out of 32) experienced adverse events, primarily headaches, with isolated cases of myalgia, gastrointestinal discomfort, and uneasiness. Group B, receiving alternate-day treatment of rosuvastatin 10 mg, saw adverse events in 12.12% of patients (4 out of 33), including headache, gastrointestinal disturbance, and myalgia. In group C, which received rosuvastatin 20 mg on alternate days, 13.33% of patients (4 out of 30) reported adverse events, predominantly headaches and 1 case of myalgia.

These findings suggest a marginally higher incidence of minor adverse effects in the daily dose group compared to the alternate-day dose groups. This trend aligns with previous studies, such as the one conducted by Ghia et al on atorvastatin, which reported more adverse events in the daily dose group than the alternate-day group.[14] Similarly, a study by Wongwiwatthananukit et al in Thailand found both daily and alternate-day rosuvastatin regimens to be well-tolerated, with minor adverse effects like headaches, myalgia, and gastrointestinal issues being most common.[13]

Baker et al study in 2008 on patients with previous statin intolerance also reported fewer adverse events, particularly muscle-related side effects, with alternate-day rosuvastatin administration compared to daily dose. These findings collectively suggest that alternate-day statin regimens may offer a slightly improved safety profile compared to daily dosing, while maintaining efficacy in managing dyslipidemia.[15]

Our study largely conforms to the previous data in literature with respect to effectiveness and safety profile of daily versus alternate day dose regimen of rosuvastatin, a commonly prescribed HMG CoA reductase inhibitor, in patients with dyslipidemia. Alternate day therapy seems to have a slight edge in terms of safety profile. Alternate day therapy with higher dose (20 mg every other day vs 10 mg every other day) did not provide any added benefit in terms of effectiveness in the moderately raised lipid levels in our study. Patients with statin intolerance may find the alternate-day dose to be a feasible choice as it seemingly has a comparable effectiveness to that of daily dosing with a slight edge in terms of safety.

CONCLUSION

Alternate-day dose of rosuvastatin achieved a reduction in the atherogenic lipid levels statistically comparable to a daily dose in patients with dyslipidemia. It also had a marginally lower incidence of adverse effects. Alternate-day dose therapy of rosuvastatin, thus, seems a viable option for dyslipidemia offering a more cost-effective and safer alternative to daily dose. These findings support the flexibility in rosuvastatin dosing schedules, which could enhance patient adherence and overall treatment outcomes in clinical practice. The study was a limited academic project delimited to a single health centre catering to a couple of districts of Punjab. Larger studies covering a broader population base and including higher dose range may provide better insight in terms of rosuvastatin effectiveness and safety.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: 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 2025;14:50-4.