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An open-label prospective observational study to evaluate the efficacy and safety of alternate day versus daily dosing of atorvastatin in patients of dyslipidemia

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ABSTRACT

Background: Hypercholesterolemia is a main driver of atherosclerosis. Cholesterol-containing lipoproteins induce endothelial dysfunction and macrophage activation. Foam cell formation results from the uptake of cholesterol-containing lipoproteins by macrophages, it is an essential step in the initiation and progression of atherosclerosis. **Aims and Objectives:** To evaluate the efficacy and safety of alternate day versus daily dosing of atorvastatin in patients with dyslipidemia. **Materials and Methods:** This open-label, prospective, observational study was conducted on dyslipidemic patients who came into the medicine Outpatient Department of Dhanalakshmi Srinivasan Medical College and Hospital, Tamil Nadu. Approval for the study was taken from the Institutional Ethical Committee. The duration of the study was 3 months. The efficacy of atorvastatin was checked by noting their blood lipid profile status. **Results:** Out of 100 patients included in the study 79 completed the study whereas 21 patients were lost in follow-up, 42 patients were analyzed in daily dose (Group A), and 37 patients in alternate dose (Group B) of atorvastatin (20 mg). There was no statistically significant difference based on triglyceride, total cholesterol, low-density lipoprotein, and high-density lipoprotein levels both prior and post-treatment in both the groups. Adverse drug reactions (ADR) profile showed a statistically significant difference between both the groups after treatment by atorvastatin (P = 0.0001), with more ADRs noted in a daily dosing group. **Conclusion:** The results of this study show that alternate dosing of atorvastatin was better tolerated than daily dosing hence physicians can consider choosing an alternate day therapy to reduce pill burden on patients.

Key words: Dyslipidemia; Atorvastatin; Dosing pattern

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INTRODUCTION

Hyperlipidemia is the term used collectively for the raised level of cholesterol and triglycerides (TGs). An increased level of cholesterol is called hypercholesterolemia. The two major clinical sequelae of hyperlipidemias are acute pancreatitis and atherosclerosis.[1] Hypercholesterolemia is a main driver of atherosclerosis. Cholesterol-containing lipoproteins induce endothelial dysfunction and macrophage activation. Foam cell formation, which results from the uptake of cholesterol-containing lipoproteins by macrophages, is an essential step in the initiation and progression of atherosclerosis.[2] The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) can achieve relatively large reductions in plasma cholesterol levels.[3] This (statins) class of compounds are the most efficacious, most commonly used, and best tolerated hypolipidemic drugs.[4] In the myocardial

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ischemia reduction with aggressive cholesterol-lowering trial patients who had both diabetes and cardiovascular disease (CVD) were at very high risk for future CVD events, in terms of absolute risk reduction, this category of patient obtained the greatest benefit from statin therapy.[5] Several clinical trials have demonstrated that statins can ameliorate vascular atherosclerosis, and reduce cardiovascular-related morbidity and mortality, in patients with and without coronary artery disease (CAD) symptoms.[3] Statins are highly effective in lowering serum cholesterol concentrations and preventing ischemic heart disease.[6] There is a paradox in the meta-analysis of randomized trials showing that statins reduced the incidence of strokes by about 30%.[6] Statins are competitive inhibitors of the enzyme HMG-CoA reductase, which catalyzes an early, rate-limiting step in cholesterol biosynthesis. Because of their safety, efficacy, and tolerability, these cholesterol-lowering agents have become the drug of choice for raised low-density lipoprotein-cholesterol (LDL-C) in treating dyslipidemia.[7] Statins have efficacy in lowering cholesterol and reducing cardiovascular events but their cost is a major disadvantage. Atorvastatin is the most potent statin and has a long half-life. Therefore, atorvastatin given on alternate days may be reasonable and cost-effective, particularly in hypercholesterolemia patients.[8] Although atorvastatin induced smaller reductions in TG levels and a more modest increase in high-density lipoprotein (HDL)-cholesterol levels than either fenofibrate or nicotinic acid in patients with combined hyperlipidemia or hypertriglyceridemia, it produced larger reductions in total cholesterol (TC) and LDL-C.[9] Daily doses of atorvastatin (2.5–80 mg) produced a steady state maximum concentrations (1.95–252 μg/L) within 2–4 h after administration.[10] Atorvastatin has a much longer plasma t1/2 of 14–18 h and has additional antioxidant properties.[4] High percentage cost variation is seen with tablet atorvastatin 20 mg, where maximum to minimum price ranges from Rs. 17.00 to Rs. 2.56 per tablet/capsule.[11] Atorvastatin can be administered on alternate day and a cost reduction between 30% and 50% can be achieved.[12] Statins, like all other pharmacological treatments, inevitably have adverse effects. The major adverse effect associated with statin use is myopathy. Myopathy refers to a broad spectrum of muscle complaints, ranging from mild muscle soreness or weakness (myalgia) to life-threatening rhabdomyolysis. The risk of muscle adverse effects increases in proportion to statin dose and plasma concentrations.[13] The muscular system, hepatic function, and renal function have been documented to be affected by statin treatment.[13] Therefore by conducting this study we can evaluate how to minimize the adverse effects, drug interactions, pill burden, and cost effect on patients without compromising the efficacy by shifting them from daily to alternate-day dosing.

Aims and objectives

To evaluate the efficacy, safety, and tolerability of atorvastatin on reduction in total serum cholesterol, LDL-C, and TGs by giving alternate day versus daily dosing.

MATERIALS AND METHODS

This open-label, prospective, observational study was conducted on dyslipidemic patients who came to the outpatient department (OPD) of the Department of General Medicine, Dhanalakshmi Srinivasan Medical College and Hospital, Perambalur, Tamil Nadu. The duration of the study was 3 months (December 2018–February 2019). Ethical approval was obtained from the Institutional Ethics Committee (reference number: IECHS/DSMCH/180409/2018).

Sample size

A total of 100 subjects were recruited in our study, as this is a single hospital-centric and time-bound (3 months) study, therefore, all the patients diagnosed with dyslipidemia in accordance to exclusion and inclusion criteria that visited medicine OPD during the study duration constituted our sample size (reference for sample size – Ghia et al.,[7] Alternate day versus once-daily atorvastatin for primary prevention of [CHD] in Naïvï e Patients of Dyslipidemia). Out of 100 patients, 21 were lost in follow-up (sample size, n=100–21=79 patients). Patients were divided into two groups, Group A (daily dose, n=42) and Group B (alternate dose, n=37) using a simple randomization technique (based on odd and even numbers). The odd number of patients was included in Group A and an even number of patients in Group B.

Inclusion criteria

Patients of both genders (male and female), ages above 30 years and <80 years, the patient required to have dyslipidemia confirmed by a minimum of two plasma determinations, TC >200 mg/dL, LDL-C >135 mg/dL with or without hypertriglyceridemia.

Exclusion criteria

Patients aged <30 years and >80 years, with a history of hypersensitivity to statins, pregnancy, lactation, hypothyroidism, active liver disease and renal diseases, history of alcohol intake, epilepsy, long-term immunosuppressant intake, medication affecting lipoprotein metabolism, drugs associated with rhabdomyolysis, patient on fibrate therapy, patients with myocardial infarction and angioplasty, CAD with 3 months history, tuberculosis, blood disorder, patients with uncontrolled diabetes mellitus, patient with a serious illness such as cancer, human immunodeficiency virus, and patients on enzymes inducer drugs.

Baseline parameters were noted during the first hospital visit of the patient, thereafter follow-up was done at the end of the study, that is, at 3 months. The efficacy of atorvastatin was checked by noting their blood lipid profile status, that is, TC, LDL-C, HDL, and TGs. The safety profile of the atorvastatin-treated subjects was noted by the personal conversation with the patient. Data analysis was done using Statistical Package for the Social Sciences version 21.0, IBM, USA. The Student's *t*-test was applied to compare the mean values of quantitative variables while qualitative variables were analyzed using the Chi-square test.

RESULTS

Out of 100 patients included in the study, 79 completed the study whereas 21 patients were lost in follow-up because of various reasons such as some discontinuing the treatment in between due to the cost of medication, long duration of treatment, refusal to come for follow-up due to poor financial condition, investigation expenses during follow-up, some opted for some herbal/ayurvedic medication etc. A total of 79 patients were analyzed in which 42 patients were analyzed for the daily dose (Group A) and 37 patients for the alternate dose (Group B) of atorvastatin (20 mg). The mean age of patients in Group A (daily dose) was 49.9±12.6 years, whereas the mean age of patients in Group B (alternate dose) was 54.4±10.6 years. There were 48.8% male and 57.9% female in Group A, whereas 51.2% males and 42.1% females in Group B, respectively. In this study, 52.3% and 56.5% hypertensive and diabetic patients were present in Group A while 47.7% hypertensive and 43.5% diabetic patients were present in Group B, respectively as depicted in Table 1. There is no significant difference between the two groups based on demographic profile and history of diseases.

Table 2 shows, there was no significant difference between Group A (169.80±72.72 m/dL) and Group B (180.74±82.84 mg/dL) based on TG levels before the treatment and no significant difference was noted post-treatment in the groups as well. There was no significant difference in lipid profile parameters such as TC and LDL prior and post-treatment in both groups, respectively, HDL levels also showed no statistically significant difference both prior and post-treatment by atorvastatin in both the groups, although the greater increase in HDL levels was seen in patients receiving a daily dose of atorvastatin.

In this study, Table 3 depicts adverse effects of statin therapy such as muscle aches and epigastric distress were observed in 35.71% and 19.04% of patients in Group A (daily dosing) whereas only 2.70% and 0% of patients experienced muscle aches and epigastric distress in Group B (alternate dosing), respectively. Adverse drug reaction (ADR) profile showed a statistically significant difference between both the groups after treatment by atorvastatin (P=0.0001), with greater ADRs noted in the group receiving a daily dose of atorvastatin.

DISCUSSION

This study compared the efficacy and safety of atorvastatin 20 mg daily versus alternate-day dosing in the treatment of dyslipidemic patients. Our results showed that there was a reduction in lipid parameters (TC, LDL, and TG) in both groups, respectively, but this reduction was statistically insignificant when both the groups were compared with each other thus depicting that both daily and alternate dosing of atorvastatin are equally efficacious in treatment of dyslipidemia. Although adverse effects such as muscle aches and epigastric distress were observed more in patients receiving daily dosing.

Ghia et al.,[7] conducted a study to evaluate alternate day versus once-daily atorvastatin for primary prevention of (CHD) in patients with dyslipidemia. Atorvastatin 10 mg daily produced a significant reduction in TC, LDL, and very LDL as compared to atorvastatin 10 mg alternate day. The increase in the HDL level was also greater with a daily dose as compared to alternate day but these results were not statistically significant. Adverse events with alternate day therapy (n=4) were less as compared with daily treatment (n=10). Jafari et al.,[10] did a prospective, open-label, controlled clinical trial in 54 patients randomized to receive 10 mg atorvastatin daily, 10 mg atorvastatin alternate day, and 20 mg atorvastatin alternate day. Although all three regimens significantly reduced TC and LDL-C compared to baseline, the decrease was not statistically significant. All regimens were well tolerated and none of the patients had a significant elevation of liver enzymes or creatine kinase. They concluded that alternate-day atorvastatin is an efficacious and safe alternative to daily dosing.

Matalka et al.,[14] conducted a 6 weeks double-blind, placebo-controlled study on 35 hypercholesterolemia patients. Twenty-six patients completed the study and it was found that alternate-day atorvastatin produced a reduction in LDL-C that was comparable to daily administration of atorvastatin. Besides this, the alternate-day therapy was less expensive. It was also observed that patients on alternate-day therapy paid 34% less than daily therapy patients annually. In this study, the patients in both study groups did not experience myalgia, elevation of creatinine kinase levels, or hepatotoxicity. Keleş et al.[15] conducted a study in which a 20 mg atorvastatin alternate-day treatment group showed a 36.1% reduction in LDL-cholesterol levels by the end of 1st month of treatment (P=0.05). The LDL-C

Table 1: Baseline parameters in both the groups

Parameters	Group A (n=42), n (%)	Group B (n=37), n (%)	P
Age (years), mean±SD	49.9±12.6	54.4±10.6	0.0923
Male	20 (48.8)	21 (51.2)	0.4173
Female	22 (57.9)	16 (42.1)	
Hypertension	23 (52.3)	21 (47.7)	0.7512
Diabetes	13 (56.5)	10 (43.5)	

SD: Standard deviation

Table 2: Lipid profile parameters in both the groups

Lipid profile parameters (mg/dL)	Group A (mean±SD)	Group B (mean±SD)	P
TG			
Pre	169.80±72.72	180.74±82.84	0.5337
Post	122.19±16.00	136.78±54.38	0.1009
TC			
Pre	205.14±43.53	212.48±56.23	0.5159
Post	161.95±16.35	158.70±24.06	0.4803
LDL			
Pre	114.63±36.75	127.77±40.73	0.1358
Post	87.30±9.48	85.40±18.30	0.5573
HDL			
Pre	47.04±5.86	45.37±6.23	0.2235
Post	63.54±6.08	57.48±10.16	0.0017

HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TG: Triglyceride, TC: Total cholesterol, SD: Standard deviation

Table 3: ADR profile of both the groups

ADR profile	Group A (n=42), n (%)	Group B (n=37), n (%)	P
Muscle aches	15 (35.71)	1 (2.70)	0.0001
Epigastric distress	8 (19.04)	0	

ADR: Adverse drug reaction

levels of the group receiving 20 mg of atorvastatin every day (daily) were reduced by 41% by the end of 1 month (P<0.01). At the end of 3 months, the difference between the changes in all lipid parameters of the groups was found to be statistically insignificant, hence showing that alternate-day and daily dosing regimens both are equally efficacious.

Pramanik et al.[16] conducted a study among 40 dyslipidemic patients out of which 38 completed the study. Both atorvastatin daily dosing and alternate dosing treatment regimens significantly reduced LDL-C and TC compared to baseline. There was no statistically significant difference between the two groups in terms of reduction of plasma LDL-C and TC at 6 and 12 weeks of treatment. Both regimens were well tolerated. Awad et al.[17] conducted a metanalysis including 12 randomized controlled trials and one quasi-randomized controlled trial, (n=1023 patients). Pooled analysis revealed no statistically significant difference between alternate-day and daily regimens of atorvastatin and rosuvastatin in terms of change in LDL-C and TG (P>0.05). Daily regimens of atorvastatin and rosuvastatin were superior to alternate-day regimes in terms of change in TC. The alternate-day therapy was less expensive. The patients in Group A receiving daily dose experienced more side effects than Group B who received alternate day dosing.

Limitations of the study

Small sample size, quiet significant number of patients lost in follow up and short study duration are limitations of this study.

CONCLUSION

The results of this study show that the atorvastatin alternate dose regimen was better tolerated as compared to the daily dose regimen while efficacy remained the same in both groups. Hence, the physician may consider choosing an alternate day therapy in patients of dyslipidemia without compromising on efficacy as this regimen will not only reduce adverse effects and drug interactions but pill burden/cost effect will also be minimized.

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Authors' Contributions:
GM – Concept and design of the study, manuscript preparation, and revision, data collection, statistical analysis; **SS –** Data analysis, statistical analysis, manuscript preparation, and revision; **PS –** Data analysis and statistical analysis; **VG -** Manuscript preparation, manuscript revision, data analysis **PVA –** Data collection and data analysis.

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