



## Original Article

# Randomized controlled trial comparing the efficacy of daily and every other day atorvastatin therapy and its correlation with serum hydroxymethylglutaryl-CoA reductase enzyme levels in naïve dyslipidemic patients



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## ARTICLE INFO

## Article history:

Received 15 November 2017

Accepted 9 May 2018

Available online 26 May 2018

## Keywords:

Atorvastatin

Every other day atorvastatin

Dyslipidemia

Hydroxymethylglutaryl-CoA reductase enzyme

## ABSTRACT

**Objective:** Data regarding efficacy comparison of daily regimen (DR) versus every other day regimen (EODR) atorvastatin therapy is not validated by estimation of serum hydroxymethylglutaryl-CoA reductase (HMGR) levels and HMGR correlation with lipid indices.

**Methods:** In this randomized controlled trial, we compared the efficacy of DR versus EODR by measuring lipid indices and serum HMGR levels at baseline and after 12 weeks of 10 mg atorvastatin therapy. Primary endpoint was comparison of mean change in serum HMGR levels and lipid indices of both groups and their correlation with each other. Secondary endpoints were assessed by estimating serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and creatine kinase MM (CK-MM) levels and adverse drug reactions (ADRs).

**Results:** A total of 61 patients were enrolled of which 46 completed the study (24 in DR vs 22 in EODR group). The mean reduction in total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C) and non-high density lipoprotein-cholesterol (HDL-C) was significantly higher in DR group, whereas mean reduction in triglycerides (TG) and increase in HDL-C was similar in both the groups. Reduction in serum HMGR levels was comparable in both the groups (31.17% vs 28.19%). Change in serum HMGR levels correlated more with change in lipid indices of DR group. Also, safety parameters were similar between the two groups.

**Conclusion:** Both the regimens achieved therapeutic goals, however DR was found to be superior as it achieved greater reduction in TC and LDL-C. Further, these findings are substantiated by correlation of lipid indices with serum HMGR levels.

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## 1. Introduction

Cardiovascular diseases (CVD) are the most common cause of mortality and are responsible for about 31% of all deaths in the world.<sup>1</sup> In the developing countries, CVD related mortality is increasing and being encountered a decade earlier than developed countries.<sup>2</sup> Indian population has increased propensity of CVD risk factors viz. hypertension, diabetes mellitus, dyslipidemias, tobacco

use, obesity etc.<sup>3</sup> In addition, Indian population has lower high density lipoprotein-cholesterol (HDL-C), higher triglycerides (TG) and higher lipoprotein (a) levels as compared to the Western population which is associated with greater risk of development and progression of the atherosclerosis.<sup>4,5</sup> Early initiation of statins stabilizes the atherosclerotic plaque which in turn reduces the cardiovascular-related mortality.<sup>6,7</sup>

Statins are usually well tolerated by patients, but could be associated with adverse drug reactions (ADRs) including myalgia (190 per 100,000 patient years), myositis (5 per 100,000 patient years), rhabdomyolysis (1.6 per 100,000 patient years) and rise in serum liver enzymes i.e. aspartate aminotransferase (AST) and alanine aminotransferase (ALT).<sup>8,9</sup> Approximately 10–15% of dyslipidemic patients are intolerant to statins due to these adverse

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effects depriving them from pleiotropic benefits of statins.<sup>10</sup> Few researchers have studied every other day statin therapy (EODT) and found comparable clinical efficacy with daily statin therapy with reduced severity and frequency of associated adverse events.<sup>11–15</sup> The use of every other day statin may be justified for 3-Hydroxy-3-Methylglutaryl-CoA Reductase (HMGCR) inhibitors having longer half-life (>24 h) namely atorvastatin and rosuvastatin because of their active metabolites.<sup>16</sup> The benefits of every other day statin therapy claimed by studies available in the literature are not yet substantiated by extent of inhibition of serum HMGCR enzyme.<sup>11–15</sup> If the extent of inhibition of serum HMGCR enzyme is found to be similar in both daily and every other day atorvastatin therapy, every other day atorvastatin may be considered as alternative option to daily atorvastatin therapy especially for daily statin intolerant patients. Henceforth, the present study was undertaken to evaluate and compare the efficacy and safety of every other day atorvastatin with its standard daily regimen and investigated the correlation of alteration in lipid indices with serum HMGCR enzyme levels.

## 2. Materials and methods

This was a randomized, open-label, controlled, per protocol analysis study on statin treatment naive dyslipidemic patients after the approval of Institutional Ethics Committee (IEC) for Human Research, Lady Hardinge Medical College and Associated Hospitals, New Delhi.

Dyslipidemic patients with 0–1 risk factor for CVD aged more than 18 years were prescribed hypolipidemic pharmacotherapy as per National Cholesterol Education Program (NCEP), Adult Treatment Panel (ATP) III Guidelines after obtaining their informed written consent to participate in the study.<sup>17</sup> The patients having ALT and AST levels >3 times of upper normal limit (UNL); creatine kinase MM isoenzyme (CK-MM) >10 times UNL; diagnosis of acute coronary syndrome within the last 3 months; history of alcohol intake (>60 ml/day for more than 6 months); concurrent use of other hypolipidemic drug(s), immune-suppressant agents and azoles; history of diabetes mellitus, hypertension, hypothyroidism, pregnancy, lactation, prior hypersensitivity and/or intolerance to any HMGCR inhibitors were excluded from the study.

The baseline clinical examination and biochemical investigations i.e. AST, ALT, lipid indices i.e. total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C), LDL-C, TG, non HDL-C and serum HMGCR & CK-MM levels were recorded for the study population. Using block randomization, patients were allocated to receive 10 mg atorvastatin either daily i.e. daily regimen (DR) group or every other day i.e. every other day regimen (EODR) group orally after dinner for a period of 12 weeks. Patients included in the study were explained dietary and lifestyle modifications and a written handout was given for the same.<sup>17</sup> At the end of study period i.e. 12 weeks, all the baseline biochemical investigations

were repeated and adverse drug events/reactions (if any) were documented as per definition and standards of Pharmacovigilance Program of India.<sup>18</sup> Change in the study parameters after 12 weeks of daily and every other day atorvastatin therapy were compared with their respective baseline values. Primary end point was the extent of inhibition of serum HMGCR levels in both the study regimens which were correlated with changes in lipid profile (TC, LDL-C, TG, HDL-C and non HDL-C) of patients in the respective groups. Secondary end points included mean change in serum liver enzymes (AST and ALT) levels, serum CK-MM levels and difference in reported ADR(s) between the two groups.

Lipid profile was estimated using Beckman Coulter AU-680/5800 auto-analyzer. The serum samples to estimate HMGCR and CK-MM were stored at –30° C till analysis. Serum HMGCR and CK-MM levels were estimated using BMASAY [Human HMGCR enzyme linked immunosorbent assay (ELISA)] kit and human CK-MM ELISA kit.

## 3. Statistical analysis

The data have been presented as Mean  $\pm$  SD and percentage and analyzed using SPSS-17 software. The comparison of lipid indices (TC, LDL-C, TG, HDL-C and non HDL-C), liver enzymes (AST and ALT), serum HMGCR and serum CK-MM levels at baseline and at the end of 12 weeks of therapy (within and in between the groups) was done by paired and unpaired student's *t*-test.

Paired student's *t*-test was used to compare within group and unpaired Student's *t*-test was used to compare in between the groups data of lipid indices (TC, LDL-C, TG, HDL-C and non HDL-C), liver enzymes (AST and ALT), serum HMGCR and serum CK-MM levels at baseline and at the end of 12 weeks of therapy.

Adverse drug reactions/events were compared using Chi square test with Yate's correction. Pearson's coefficient of correlation and regression was used to find the correlation between the lipid indices of the patients in both the regimens with mean serum HMGCR level. P-value less than 0.05 was considered as significant.

## 4. Results

Of a total of 61 patients enrolled, 46 patients completed the study. Age and gender distribution was similar in the two groups (DR: n = 24, mean age = 49.46  $\pm$  6.84 year, male: female = 13:11; EODR: n = 22, mean age = 47.73  $\pm$  9.09 year, male: female = 12:10). Mean weight and body mass index (BMI) of the patients were slightly increased (p value >0.05) after 12 weeks of the atorvastatin treatment from their respective baseline values in both the regimens.

In both DR and EODR group, the mean baseline levels of TC, LDL-C, non HDL-C and TG decreased while the HDL-C increased significantly (p < 0.0001) after 12 weeks of atorvastatin therapy (Table 1). On comparing the mean change in TC, LDL-C and non

**Table 1**

Showing mean of efficacy and safety parameters of the patients at baseline and at the end of 12 weeks (Mean  $\pm$  SD).

Parameters (Mean $\pm$ SD)	DR group			EODR group			
	Baseline	At the end of 12 weeks	p value	Baseline	At the end of 12 weeks	p value	
Lipid Indices (mg/dl)	TC	298.08 $\pm$ 24.64	217.33 $\pm$ 15.48	<0.0001	287.95 $\pm$ 25.70	214.67 $\pm$ 16.82	<0.0001
	LDL-C	213.72 $\pm$ 14.88	129.66 $\pm$ 9.51	<0.0001	213.48 $\pm$ 22.13	136.53 $\pm$ 11.07	<0.0001
	HDL-C	45.71 $\pm$ 11.11	52.54 $\pm$ 9.19	<0.0001	38.14 $\pm$ 8.59	46.67 $\pm$ 8.17	<0.0001
	TG	193.25 $\pm$ 56.07	175.67 $\pm$ 49.73	<0.0001	181.68 $\pm$ 50.41	157.33 $\pm$ 40.54	<0.0001
	Non HDL-C	252.38 $\pm$ 20.68	164.79 $\pm$ 12.32	<0.0001	249.82 $\pm$ 20.86	176.41 $\pm$ 16.67	0.0001
Serum HMG CoA reductase level (ng/dl)	15.36 $\pm$ 3.93	10.57 $\pm$ 1.70	<0.0001	14.81 $\pm$ 3.81	10.63 $\pm$ 2.61	0.0004	
Liver Enzymes (U/L)	ALT	52.13 $\pm$ 20.48	60.50 $\pm$ 21.61	0.01	55.14 $\pm$ 21.49	55.14 $\pm$ 21.49	0.18
	AST	54.50 $\pm$ 24.13	64.42 $\pm$ 23.70	0.009	54.72 $\pm$ 25.61	68.04 $\pm$ 24.22	0.008
Serum CK-MM (U/L)	28.39 $\pm$ 21.12	34.18 $\pm$ 54.69	0.65	28.43 $\pm$ 20.12	31.81 $\pm$ 17.29	0.56	

HDL-C levels in DR and EODR group, it was found that daily regimen was superior in reducing these values significantly ( $p < 0.0001$ ), whereas the comparison between mean change in the levels of TG and HDL-C were statistically insignificant (Table 2).

The baseline levels of serum HMGR in DR group and EODR group were similar (Table 1). These values at the end of 12 weeks of atorvastatin therapy were significantly reduced in both DR group and in EODR group. The percentage reduction was comparable in both the groups (31.17% vs 28.19%;  $p = 0.655$ ) (Table 2).

On analysis of the correlation between change in serum HMGR levels and change in lipid indices, we found that the correlation is better in DR group than EODR group for all the lipid indices. Also, correlation was significant for all the lipid indices in DR group but in EODR group, the correlation was significantly evident only for TC (Table 3).

On evaluating the safety parameters of both the regimens after 12 weeks of atorvastatin treatment, we found that the rise in mean ALT and AST levels was statistically significant in DR group whereas in EODR group, only mean AST levels were significantly raised (Table 1). Also, percentage change in AST and ALT did not significantly differ between DR and EODR group (Table 2). Serum CK-MM, a marker of muscular toxicity, did not significantly change within and in between the two groups (Tables 1 and 2). In addition, a total of 21 adverse drug reactions were reported in the DR group. Majority of these adverse drug reactions (ADRs) pertained to musculoskeletal system followed by neurological and gastrointestinal system. The frequency of the ADRs in EODR group was similar to DR group (Table 4).

## 5. Discussion

Reduction in serum LDL-C, non HDL-C and TG with elevation in serum HDL-C is a cornerstone in the treatment of dyslipidemia. Conventional daily regimen of statin is well established for treating dyslipidemia by inhibiting HMGR, the rate limiting enzyme in the synthesis of cholesterol.<sup>16</sup> The use of every other day statins viz. atorvastatin is advocated due to its longer duration of action (24–30 h) despite its  $t_{1/2}$  of 7 h as its ortho- and parahydroxylated metabolites also have lipid lowering effect.<sup>16</sup>

In our study, 12 weeks of atorvastatin therapy in both the regimens was significantly effective in lowering TC, TG, LDL-C & non HDL-C and increasing HDL-C (Table 1). However, efficacy benefit on TC and LDL-C with DR was significantly higher (Table 2). Similarly, a study reported higher reduction in mean percentage of LDL-C with daily than with every other day atorvastatin regimen after 6 weeks of therapy.<sup>15</sup> Also, in a prospective, randomized trial on CVD patients reported insignificantly higher mean reduction in TC with daily than every other day atorvastatin (31.6% vs 28.3%) after 3 months of therapy.<sup>14</sup> On the contrary, Jafari et al. reported no statistical difference between daily and every other day atorvastatin therapy in

**Table 3**

Showing the correlation between change in serum HMG CoA reductase level and various lipid indices after 12 weeks of atorvastatin therapy.

Group	Parameter	r value	p value
<b>Daily Regimen group</b>	TC	0.68	<0.01
	LDL-C	0.52	<0.01
	HDL-C	-0.39	0.03
	TG	0.48	<0.01
	Non HDL-C	0.52	<0.01
<b>Every Other Day Regimen group</b>	TC	0.40	0.04
	LDL-C	0.34	0.07
	HDL-C	-0.09	0.35
	TG	0.26	0.14
	Non HDL-C	0.35	0.14

**Table 4**

Comparison of reported ADR's to atorvastatin treatment in daily regimen and every other day regimen group at the end of study duration (12 weeks).

ADR involving Organ system	No. of patients, n (%)		p value
	DR group	EODR group	
Musculoskeletal	4 (16.67%)	3 (13.64%)	0.77
GIT	2 (8.33%)	0 (0%)	0.53
Neurological	2 (8.33%)	4 (18.18%)	0.54
Others	1 (4.17%)	1 (4.54%)	0.95

terms of reduction in TC and LDL-C levels after 6 weeks of treatment.<sup>12</sup> Since the action of atorvastatin is dose dependent,<sup>16</sup> the doubling of dose per week in DR group vs EODR group may provide an explanation for these findings in our study.

Assessment of non-HDL-C provides a measure of cholesterol present in atherogenic particles.<sup>19</sup> A meta-analysis reported positive relationship between reduction in non-HDL-C and decrease in CVD risk.<sup>19</sup> Our study pioneered to report significant ( $p < 0.0001$ ) reduction in non HDL-C in both daily and alternate day atorvastatin regimen (Table 1). Dyslipidemia treatment guidelines of Lipid association of India recommended non-HDL-C as a co-primary target and ATP III of the US NCEP recommended it as a secondary target of therapy in persons with triglycerides  $\geq 200$  mg/dl.<sup>20,17</sup> In clinical practice, the role of non-HDL-C should be considered as a vital target of dyslipidemic therapy to prevent CVD.

Further, both the groups showed significant lipid lowering efficacy in terms of mean percentage inhibition of serum HMGR levels in DR (31.17%) and EODR (28.19%) group which was matching between the two groups (Table 2). Moreover, serum HMGR levels in both the groups, positively correlated with TC, LDL-C, non HDL-C, TG and negatively correlated with HDL-C. However, this correlation was more apparent in DR group. No study in the literature is available to compare this finding. It appears that this lower correlation in EODR group could be due to poor adherence with alternate day therapy. Missing a single dose in DR group leads

**Table 2**

Comparison of mean change in lipid profile (TC, LDL-C, HDL-C, TG, and non HDL-C), Liver enzymes (ALT and AST) and serum HMGR & CK-MM in DR and EODR regimen groups.

Parameters (Mean $\pm$ SD)	Mean of change in parameters in (% change)			
	DR group	EODR group	p value	
Lipid Indices (mg/dl)	TC	80.75 $\pm$ 12.06 (-27.01%)	65.09 $\pm$ 9.72 (-22.58%)	<0.0001
	LDL-C	84.06 $\pm$ 10.25 (-39.28%)	69.39 $\pm$ 10.24 (-32.57%)	<0.0001
	HDL-C	6.83 $\pm$ 5.10 (+17.37%)	8.32 $\pm$ 5.16 (+23.15%)	0.33
	TG	17.58 $\pm$ 8.91 (-8.86%)	20.77 $\pm$ 14.07 (-11.07%)	0.36
	Non HDL-C	87.58 $\pm$ 11.00 (-34.64%)	73.41 $\pm$ 10.52 (-29.38%)	<0.0001
Serum HMG CoA reductase level (ng/ml)	4.79 $\pm$ 3.62 (-31.17%)	4.25 $\pm$ 4.29 (-28.19%)	0.65	
Liver enzymes (U/L)	ALT	8.38 $\pm$ 14.79 (+24.21%)	5.05 $\pm$ 17.21 (+13.83%)	0.48
	AST	9.92 $\pm$ 17.09 (+29.22 %)	13.77 $\pm$ 21.90 (+41.43%)	0.51
Serum CK-MM (U/L)	5.79 $\pm$ 61.41 (+16.94%)	3.38 $\pm$ 26.33 (+10.61%)	0.87	

to gap of 48 h between the next atorvastatin doses, whereas in EODR group this duration will be at least of 72 h. However, it is reported that the serum levels of HMGCR enzyme achieved a plateau beyond the compliance of 60% to statin therapy.<sup>21</sup> In view of this, it is hypothesized that good compliance with every other day regimen of atorvastatin may achieve desired HMGCR enzyme inhibition and provide benefits comparable to that of daily regimen. This aspect was not evaluated in our study and need further studies with appropriate design.

Statins are usually well tolerated by the patients but muscle and liver toxicity may lead to discontinuation of the therapy. In our study, slight rise in liver transaminases i.e. ALT and AST was present in both the treatment groups but the levels were not high enough to modify the therapy.<sup>22</sup> Previous studies have shown similar asymptomatic rise in liver transaminases (ALT and AST) levels with atorvastatin therapy.<sup>9,23</sup> It has been postulated that changes in the lipid components of the hepatocyte membrane increase its permeability resulted in increased liver transaminases.<sup>23</sup> Statin induced myalgia and myositis is a distressing condition which affects the compliance and the outcome of the therapy. In our study, myalgia was more frequently reported in DR group than EODR group (Table 4). The rise in CK-MM was also more in daily group than EODR group (Table 2). However, these findings are not statistically significant to advocate alternate day therapy in statin intolerant patients. On the contrary, few previous studies have reported no difference in number of adverse events between daily and every other day atorvastatin treatment.<sup>11,12</sup> Hence larger studies are needed in this direction to support or refute this finding.

The limitations of our study were small sample size, open label study design, high dropout rate (lost to follow-up) and dose of atorvastatin per week in EODR group was half of DR group which makes comparison of these two regimens difficult, especially the safety outcomes. Therefore, we recommend a study with double dose every other day as compared to daily dose.

It is concluded that both daily and every other day atorvastatin regimen for a period of 12 weeks achieved the therapeutic goals i.e. reduction in TC, LDL-C, non HDL-C, TG and serum HMGCR and increase in HDL-C with respect to their baselines. However, these benefits were more with daily atorvastatin therapy. Alteration of lipid indices better correlated with reduction of serum HMGCR levels in patients on daily therapy. Safety parameters i.e. AST, ALT, CK-MM and ADRs did not differ significantly between the two groups. Large randomized controlled trials are advocated to further substantiate the merits of every other day atorvastatin therapy.

### Conflict of interest

None.

### Funding

All the authors declare no financial relationships with any organizations that might have an interest in the submitted work

and no other relationships or activities that could appear to have influenced the submitted work.

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