Research Article

A comparative evaluation of efficacy and safety of daily dosing versus alternate day dosing of Rosuvastatin for dyslipidemic patients

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ABSTRACT

Background: *Cardiovascular disease (CVD) is the most common contributor of morbidity and mortality in underdeveloped and developing countries and places a huge burden on the society in terms of health care resources and loss of productivity. Statins are the most popular hypolipidemic drug used to treat hyperlipidemia which is generally administered daily.*

Objectives: *The study was conducted to compare the percent change of LDL-C, TC, TG and HDL and compare the safety of Rosuvastatin in patients of dyslipidemia.*

Material and Methods: *Sixty patients were randomly divided into two groups: once daily group and Alternate day group of rosuvastatin 10mg for six weeks. The lipid profile was compared from the baseline and at end of six weeks.*

Results: *Baseline characters of both the groups were well balanced. LDL-C was reduced by 23.8 % in once-daily group and 26.05 % in alternate-day group, respectively. Changes were also recorded for the other lipid parameters (TC, TG, HDL). Such changes were found to be of no significant difference when compared between the two groups (p>0.05 NS)*

Conclusion: *Alternate day therapy is as effective as the once -daily dosing with rosuvastatin in Indian population in improving the lipid parameters in dyslipidemic patients.*

Keywords: *Rosuvastatin, dyslipidemia, alternate day regime, daily regime, lipid profile*

Introduction

Cardiovascular disease (CVD) is the most common contributor of morbidity and mortality in underdeveloped and developing countries and places a huge burden on the society in terms of health care resources and loss of productivity. [1]

Hyperlipidemias or dyslipidemias are one of the many modifiable risk factors contributing to the morbidity and mortality due to CHD. Many studies have established a relationship between the elevated levels of cholesterol mainly LDL-C in the development of CHD. Statins have become one of the most widely used therapeutic classes in clinical practice because of the cardiovascular benefits in lowering LDL-C significantly. Nowadays, statins seem to play a crucial role in modulating cardiovascular disorders such as ACS, not only by affecting lipids, but also by exerting a number of pleiotropic effects. [2, 3]

Rosuvastatin has been shown to reduce LDL-C in a dose dependent manner (dosage available 5-40mg) and has a similar safety profile to other available statins. However, the elimination half-life

(t1/2) of rosuvastatin is approximately 19 hours, its prolonged survival and HMGCoA reductase inhibition allows it to be administrated on an alternate basis or on every other day regimen (EOD). [4-5]

Though being well tolerated mild unwanted effects including myalgias, gastrointestinal disturbances, raised concentration of liver enzymes in plasma, insomnia and rash are among the most frequently reported adverse effects. Therefore statin treatment every other day may result in significant decrease in adverse effects. [6] So the aim of the study was to evaluate the efficacy and safety of daily dosing versus alternate day dosing of Rosuvastatin for percentage change in lipid profile in Haryana patients.

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= 33; F = 27) within the age group of 18 to 80 years attending the out – patients department of Medicine conducted from April 2011 to May 2012 at M.M.I.M.S.R., Mullana Ambala.

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 of normal, serum creatinine > 2.5mg/dL, alanine amino transferase (ALT) or aspartate amino-transferase (AST) values >3 times the upper limit of normal were excluded from the study.

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).

Results

Baseline characteristics

Baseline characteristics of patients with dyslipidemia receiving alternate-day dosing of rosuvastatin (n=30) or once-daily dosing of rosuvastatin (n=30) were summarized in Table 1. There were no differences regarding clinical characteristics between the two groups (>0.05 NS)

Table 1 Baseline characters of Group I & Group II

Characteristic	*Group 1*	*Group II*	*'p'*
Number of patients	30	30	
Age Range (years) Mean Age (years)	24 – 80 53.66 ± 13.40	27 – 80 50.16 ± 12.07	NS
Sex (Male / Female)	17 / 13	16 / 14	NS
TC (mg%)	237.57 ± 21.63	231.46 ± 23.39	NS
TG (mg%)	179.17 ± 114.59	191.74 ± 70.79	NS
LDL(mg%)	165.16 ± 36.32	153.62 ± 28.07	NS
HDL (mg%)	36.75 ± 14.95	39.49 ± 12.45	NS

Changes in the lipid profile:

As shown in Table 1, there were no differences of baseline parameters of lipid profile between the groups. Changes of lipid profile in detail including TC, LDL-C, HDL-C and TG at 6-weeks follow-up periods from baseline were presented in Table 2. There was a significant change in all the lipid parameters at the end of six weeks ($p<0.05$).

When an intergroup comparison was made in the two study groups, there

was no significant difference (p>0.05 NS) noted at baseline and at six weeks (Table 3)

The percentage reduction at 6 weeks in mean LDL-C was reduced by 23.8 % in once-daily group and 26.05 % in alternate-day group, respectively. There was a reduction of 15.89 % and 18.98 % in the total cholesterol and 9.80 and 9.40 of triglycerides in Group I and Group II. There was an increase of 13.52% and 10.88 % in HDL for both groups. Such changes were found to be of no significant difference when compared between the two groups (p>0.05 NS)

Rosuvastatin was well tolerated over six week's duration; the main adverse events that were experienced by the patients in either groups were that of gastrointestinal symptoms (nausea, diarrhea and constipation) and insomnia. No patient discontinued the study during the study period due to the adverse effect.

Table 2 -Comparison of Lipid Profile at Baseline and at 6 weeks in both the groups

Parameter (mg%)	*Mean ± SD Group I*		*'p'*	*Mean ± SD Group II*		
	At Baseline	**At 6 weeks**		**At Baseline**	**At 6 weeks**	**'p'**
TC	237.57 ± 21.63	199.81 ± 21.06	< 0.05	231.46 ± 23.39	192.14 ± 20.96	<0.05
TG	179.17 ± 114.59	161.50 ± 108.88	< 0.05	191.74 ± 70.79	173.71 ± 60.60	<0.05
LDL	165.16 ± 36.32	125.78 ± 33.19	< 0.05	153.62 ± 28.07	113.60 ± 25.80	<0.05
HDL	36.75 ± 14.95	41.72 ± 16.27	< 0.05	39.49 ± 12.45	43.79 ± 12.38	<0.05

Table 3 Inter group comparison of Lipid Profile at Baseline and at 6 weeks

Parameter (mg%)	*Mean ± SD Baseline*		*'p'*	*Mean ± SD At 6 Weeks*		
	Group I	**Group II**		**Group I**	**Group II**	**'p'**
TC	237.57 ± 21.63	231.46 ± 23.39	>0.05	199.81 ± 21.06	192.14 ± 20.96	>0.05
TG	179.17 ± 114.59	191.74 ± 70.79	> 0.05	161.50 ± 108.8	173.71 ± 60.60	>0.05
LDL	165.16 ± 36.32	153.62 ± 28.07	>0.05	125.78 ± 33.19	113.60 ± 25.80	>0.05
HDL	36.75 ± 14.95	39.49 ± 12.45	>0.05	41.72 ± 16.27	43.79 ± 12.38	>0.05

Discussion

In the present prospective, randomized, comparative six week clinical trial using two regimens of Rosuvastatin we found that both the regimens were effective in improving the various parameters of atherogenic lipid profile.

When we compared the two regimens amongst themselves to determine the superiority of one therapy regime over the other; we found that both the therapies are equally effective in improving the lipid characteristics of the patients with dyslipidemias. Moreover the safety profiles of both the therapies appear to be similar. Consequently our study demonstrates that both, the daily day dosing as well as the alternate day dosing have similar safety and efficacy profile with its use in dyslipidemic patients.

LDL-C is a well-established risk factor for cardiovascular disease, and there is considerable evidence that lowering LDL-C reduces the risk of both cardiovascular events and mortality. [7-8] The real clinical benefits of statins are due to their LDL-C lowering effects and this benefit has been observed in clinical trials. Rosuvastatin has been approved for use at doses of 5 – 40 mg to reduce LDL-C and improve HDL and other parameters in dyslipidemic patients. [4-5] However, we choose Rosuvastatin to perform the present study for Indian patients because Rosuvastatin is a suitable drug for alternate-day application due to longer half-lives (18–20 h). Their prolonged survival and HMG-CoA reductase inhibition allows Rosuvastatin to be dosed every other day, but this possibility is unknown to many clinicians. [9]

In our study we found that when Rosuvastatin was used daily for six weeks, there was a significant reduction of 23% in the LDL levels. In a similar study conducted by Marias et al. [10] also demonstrated a 19 % reduction of LDL-C with the use of Rouvastatin. In another Indian study performed by Jayaram et al. [11] administration of Rosuvastatin 10mg daily for six weeks resulted in 41% mean reduction of LDL-C level as compared to the baseline. Another study from China showed that LDL –C decreased by 37% after daily dosing which showed greater percentage of reduction from our trial. Another trial by Teramoto et al. [12] reported a reduction of 42-52% in LDL-C level at daily administration of Rosuvastatin. In the same pipeline, Deedwania et al. [13] also found a significant decrease of 45% LDL-C with daily dosing of Rosuvastatin. Farnier et al. [14] reported that six week therapy of Rosuvastatin on daily dosing resulted in 16% reduction in LDL-C in high risk patients. The difference in the reduction in LDL levels from the baseline was significantly higher in the previous studies than our study. This could possibly be attributed to differences in the patient profile as well as due to regional and cultural differences.

When Rosuvastatin was used as alternate day regime (EOD), the percent reduction in LDL –C levels at six weeks were 26% when compared to the baseline values. Li at el. [15] in a similar study found out reduction of 36% in LDL –C in alternate day group with the administration of Rouvastatin for six weeks. In a study Juszczyk et al. [16] concluded a significant reduction of LDL –C to the extent of 43% with 10mg dose of Rosuvastatin. Use of Rosuvastatin on every other day therapy led to 40% reduction in LDL –C levels at six weeks in a study conducted by Dulay et al. [17] In the same tune, a study by Bakes et al. [5] demonstrated an improvement of 34% in the LDL-C levels at six weeks. Joy et al. [18] also showed a difference of 37% in the LDL-C levels at six weeks with the use of 10 mg Rosuvastatin. The difference between our study and that demonstrated by Dulay et al. [17] and others could have resulted due to a difference in the dosage strength. Dulay et al. [17] used 20mg of Rosuvastatin on every other day regimen which was just double the dose used in our Indian study.

When we compare the daily day therapy with every other day therapy of 10mg Rosuvastatin, there was no significant difference in the LDL –C lowering capability with the use of either regimen. There was a similar percent reduction of LDL-C with the use of either therapy. This demonstrates that both the therapies are equally efficacious in providing improvement in the LDL-C in dyslipidemic patients. In a study conducted by Li et al. [15] no significant difference in the decrease in LDL-C was observed with daily dosing when compared to alternate day dosing of 10 mg Rosuvastatin for six weeks. This suggests that our trial have similar impact on the LDL-C level as demonstrated by the study of Li et al. Similar results were shown by the study conducted by Wongwiwatthananukit et al. [19] who concluded that the LDL-C reduced 48% and 39% with daily day dosing and alternate day dosing of Rosuvastatin 10 mg therapy, respectively. However Dulay et al. [17] found a significant absolute reduction of 7% of LDL-C when daily day dosing was as compared to alternate day dosing. The difference of the observations in our study and that of Dulay et al. [17] could be related to the ethnic differences of the two countries. The patients of study

were primarily from rural background in our study whose compliance to the drug therapy could possibly influence the results. The previous done studies was conducted in a population who had better awareness of health care system and could have had a better drug compliance resulting in significant impact on the lipid improving effect with daily dosing as compared with every other day dosing of Rosuvastatin 10mg.

Dyslipidemia including hypercholesterolemia and low HDL-C are the major causes of atherogenic risk and both genetic and lifestyle contributes to dyslipidemia. In patients with low HDL-C and average LDL-C appropriate drug therapy reduced CHD endpoint events by 20-30%. Hence it is important to include low HDL-C patients in the management guidelines of dyslipidemia. [20]

In our study the administration of Rosuvastatin 10mg on daily basis lead to significant increase of HDL –C levels by 13% when compared to baseline and at six weeks. A study conducted by Farnier et al. [14] by use of daily dosage of Rosuvastatin 10mg for six weeks concluded an increment of 3 % only which is less than what was observed in our study. The difference can be attributed to the variable response related to ethnicity. In our patients who received alternate day drug therapy with Rosuvastatin 10 mg showed 11% improvements in HDL-C levels at six weeks. Marias et al. [10] also showed an increment of 5% with the use of Rosuvastatin for six weeks. Another study carried out by Juszczyk et al. [16] similar to that of ours, showed improvements of 11 % with the use of Rosuvastatin which were in tune with our study. There was a 5% increase in HDL-C levels in a study conducted by Li et al. [15] at six weeks therapy with Rosuvastatin 10mg on an alternate day basis. Bakes et al. [5] conducted a study which showed only 1.7% increase in HDL-C levels by using Rosuvastatin. The difference between our study and their study mainly would have resulted due to dose difference. They used 5.6mg Rosuvastatin which was almost half of the dose used in our study. However when we compared the Group I and Group II with each other in respect to HDL-C elevating capacity, we could not record any significant difference among the two groups. The findings of Li et al. [15] also did not observe any significant difference between the daily and alternate day study groups of Rosuvastatin 10mg.

Lowering total serum cholesterol levels is an ideal strategy for reducing the burden of cardiovascular disease. Deaths due to cardiovascular causes are attributable to a few modifiable risk factors, most importantly high blood pressure, smoking and high total serum cholesterol. [21]

In our patients, we observe a significant reduction of TC with 10 mg Rosuvastatin in Group I and Group II at six weeks when they are compared from the baseline values. However, when the two groups are compared in regard to their beneficial effects i.e. reduction in total cholesterol, there is no significant difference between the two groups.

In our study with daily day therapy of 10 mg Rosuvastatin, we observed a 15 % reduction of TC from baseline at six weeks. Our study nearly mirrored the percent reduction of TC carried out by Marias et al. [10] who demonstrated a reduction of 17 % of TC at the end of six weeks of administration of Rosuvastatin. In a similar study conducted by Farnier et al. [14] there was 10 % reduction of TC with the use of 10 mg Rosuvastatin daily for six weeks. In another study with administration of Rosuvastatin 10 mg on

daily basis for six weeks, Jayaram et al. [11] showed a 30% reduction of TC which is much higher than that observed in our study. This difference may be attributed to the difference in the responses of the patients of different ethnic origins.

In our study when Rosuvastatin was administered on an alternate day basis we observed 19% reduction in TC levels from baseline values. Juszczyk et al. [16] also reported 18% reduction with the use of 10mg Rosuvastatin with every other day treatment. However no statistical significant difference is observed when the two groups are compared for the reduction of TC at six weeks. One similar study which compared daily day therapy with alternate day therapy of Rosuvastatin also could not find any difference in the efficacy to reduce total cholesterol between the two study groups.

It is unclear whether hypertriglyceridemia is an independent risk factor for developing atherothrombotic CVD. Moderately elevated triglyceride levels are of concern because they often occur as part of the metabolic syndrome, which includes insulin resistance, obesity, hypertension low HDL-C levels, a procoagulant state and substantially increased risk of CVD. [20]

In our study the use of either once daily dosing or alternate day dosing of Rosuvastatin 10 mg resulted in a similar percentage reduction of 9 % in Triglycerides at six weeks from baseline. Our study had nearly same percent reduction as that reported by Marias et al. [10] They reported 8% reduction of TG at the end of six week administration of Rosuvastatin. Farnier et al. [14] reported 5% reduction of TG with the use of Rosuvastatin 10mg with daily dosing. Teramoto et al. [12] also showed a 16% reduction of TG with the use of Rosuvastatin daily. In another conflicting Indian study, use of similar dose of Rosuvastatin daily led to 20% reduction of TG at six weeks.

Similar contrasting reports were seen with alternate day regime of Rosuvastatin. Bakes et al. [5] reported a reduction of 19% after administering 5 mg of Rosuvastatin on alternate day treatment regimen. However use of 10mg Rosuvastatin alternately by Juszczyk et al. [16] resulted in 20% reduction in TG levels which is in tune with the percent change of TG in our study.

Though being well tolerated mild unwanted effects including myalgias, gastrointestinal disturbances, raised concentration of liver enzymes in plasma, insomnia and rash are among the most frequently reported adverse effects. The patients experience GI disturbances like abdominal pain, headache, nausea, diarrhoea, dry mouth, constipation and flatulence. [22]

In our study we compared most common ADR of Rosuvastatin- GI disturbance and Insomnia. There occurred a very low incidence of adverse effects which are comparable among the two study groups. So considering the results of ADRs it reflects the safety profile of the drug Rosuvastatin.

Therefore, the present study concluded that alternate day dosing of Rosuvastatin 10 mg showed significant reductions in TC, LDL-C, TG and elevation in HDL-C levels similar to that of daily day dosing of Rosuvastatin 10 mg. It was well tolerated by all patients hence indicated a good safety profile. The study suggested that alternate day therapy may be beneficial not only in improving the lipid profile but also reducing the adverse effects due to use of statins in the health care system.

In clinical practice, this improved effectiveness and safety in lipid profile for dyslipidemic patients could be translated into an advantage in achieving and maintaining the lipid targets.

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