Original Research Paper

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A Comparative Study of Efficacy of Rosuvastatin and Atorvastatin in Combination with Fenofibrate In Dyslipidemia

Medical Science

KEYWORDS : Cholesterol, Lipoprotein, Heart, Atherosclerosis, Statins.

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ABSTRACT

Aim: The main of the study is to compare the effects of Atorvastatin and Rosuvastatin in combination with fenofibrate in patients with Dyslipidemia.

Materials and Methods: It was randomized, parallel group, comparative, prospective clinical study conducted in ACSR. Government Medical College, Nellore. A total of 60 subjects diagnosed with dyslipidemia were screened and were randomly allocated into two groups of thirty each. Initial readings of lipid levels like TC, TG, HDL, LDL and VLDL for both the groups were taken as baseline values. Then, Group I received Tab Atorvastatin 10 mg + Fenofibrate 160 mg and Group II received Tab Rosuvastatin 10 mg+ Fenofibrate 160 mg once a day at night for 12 weeks. Patients were assessed after 12 weeks and their Lipid profile was done.

Results: Patients who received a combination of atorvastatin with fenofibrate had a reduction of Total cholesterol by 39%, Triglycerides by 47%, LDL-C by 50% and VLDL-C by 35% respectively. In group treated with combination of rosuvastatin with fenofibrate there was a decrease in TC by 54%, TGs by 58%, LDL-C by 52% and VLDL-C by 56% respectively. At the same time, HDL-C levels were increased by 14% in the group treated with rosuvastatin with fenofibrate as compared to atorvastatin with fenofibrate treated group which increased the HDL-C levels by 6%.

Conclusion: Both the treatment regimens significantly decreased TC, TG, LDL-C, VLDL-C, but the reduction was more and statistically significant in Rosuvastatin and fenofibrate combination group when compared with atorvastatin and fenofibrate treated group at the end of 12 weeks.

INTRODUCTION

Dyslipidemia is the commonest cause of the blood vessel diseases and their incidence has been rising all over the world thereby increasing the morbidity and mortality due to cardiovascular diseases.[1,2] Dyslipidemia is also one of the component of Metabolic syndrome along with other group of cardiovascular risk factors such as high blood pressure (BP), abdominal obesity, and insulin intolerance, whose concurrent appearance increases the risk of atherosclerotic cardiovascular disease.[3]

Dyslipidemia occurs due to disturbance in the lipid parameters like Total Cholesterol, LDL-C, VLDL, TGs and HDL-C.[1,2] Combined or mixed hyperlipidemia (CHL) is a lipid disorder characterized by increased low-density lipoprotein cholesterol (LDL-C), elevated triglycerides (TGs) and decreased high-density lipoprotein cholesterol (HDL-C) which is more common in patients with type 2 diabetes mellitus.[4]

National cholesterol education program–Adult Treatment Panel–III (NCEP-ATP III) has set a goal to treat these dyslipidemic patients and which canbe achieved by proper treatment with lipid lowering drugs especially statins (National CEP-ATP III, 2002).[5]

A number of lipid lowering drugs e.g. statins, fenofibrate, niacin, ezetamibe, bile sequestrants etc. are being used to treat this disorder.[2] Many studies are carried out on these drugs out of which few have been made in the people of North India especially in the Majharegion of Punjab because their socio-economic background and standard of living is quite different from the people of Western countries. [6]

Hypolipidemic effect of statins is due to inhibition of hydroxymethylglutaryl-CoA reductase (HMG-CoA) and decrease in LDL-C is due to up regulation of LDL receptor activity.[7] Outcome trials of statins have proved conclusively that these drugs decrease LDL-C levels, resulting in a significant reduction of cardiovascular events in many high-risk patients.[8,9] Rosuvastatin has been considered superior in achieving greater LDL-C level reductions as compared to atorvastatin, simvastatin, or pravastatin use. [10] Statins have also been reported to produce "pleiotropic" effects such as vasodilatation, antioxidant, plaque stabilization, antithrombotic and anti-inflammatory effects.[11] Fibrates, are commonly referred to as peroxisome proliferator activated receptor-α (PPAR- α) agonists. PPAR-α expression is present in liver, kidney, endothelium and vascular smooth muscle. They significantly decrease triglycerides and increases high-density lipoprotein (HDL) cholesterol without reducing LDL cholesterol, is associated with significant decreases in coronary events.[12]

However, statins or fibrates affect different aspects of lipoprotein metabolism. Hence, statin or fibrate monotherapy becomes difficult to modify the lipid profile of patients with combined hyperlipidemia according to the recent investigations of the American Diabetes Association.[13] Combined therapy with statins and fibrates is more effective in controlling lipid profile in patients with mixed hyperlipidemia (CHL).[14-17] Hence, the present study is to compare the effects of Atorvastatin and Rosuvastatin each in combination with fenofibrate in patients with mixed Hyperlipidemia. The objective of this study was to evaluate and compare the efficacy and safety of fixed-dose combinations of Rosuvastatin 10 mg + Fenofibric acid 160 mg with Atorvastation 10 mg + Fenofibric acid 160 mg in patients with mixed hyperlipidemia.

MATERIALS AND METHODS

The present study was carried out in the Department of Pharmacology in collaboration with Department of Medicine, ACSR. Government Medical College & Hospital, Nellore, Andhra Pradesh. Open label, randomized, parallel group, comparative, prospective clinical Study. The study was designed and conducted in accordance with Good Clinical Practice guidelines as per ICH-GCP. The patients attending outpatient department (O.P.D.) of Medicine were enrolled into the present study. Sample size was calculated according to the study done by Athyro *et al*.[18] Assuming a 15% difference between two treatments, a total sample size of 60 subjects was calculated based on the two sided difference with the type I error α being 0.05 and type II error β at 0.2. A total of 60 subjects diagnosed with combined hyperlipidemia were screened for the entry into the study and then were randomly allocated into two groups of thirty each. Total duration of the study was 1 year i.e., from Au-

gust 2014–July 2015. Each patient had 2 visits to the study site: Screening/baseline visit and 12 weeks after the treatment with study drug.

Inclusion criteria

Male patients (35-55 years) and female patients (45-65 years) having low density lipoprotein cholesterol (LDL-C) higher than 100 mg/dl and triglycerides (TG) more than 200 mg/dL were included in the study. All patients with Hypertension, Diabetes mellitus, Obesity and coronary artery diseasewere included in the study.

Exclusion criteria

Patients with Renal and hepatic failure, Pregnancy and lactation, Hypothyroidism, Malignancy, Myopathy, Patients who had undergone bypass surgery and those with concurrent medications like warfarin, verapamil, amiodarone, and beta blockers were excluded from the study.

Investigations: The following investigations were done 'Before' and 'After' the study. Complete blood count (CBC), Liver function tests (LFT), Renal function tests (RFT), Random blood sugar levels (RBS) and Urine analysis.

METHODOLOGY

The total sixty (n=60) patients enrolled in the study were randomly allocated into two groups of thirty (n=30) each, using a randomization chart. Initial readings of plasma lipid levels like TC, TG, HDL, LDL and VLDL for both the groups were taken as baseline values before assigning the treatment. Then, Group I received Tab.Atorvastatin 10 mg + Fenofibrate 160 mg and Group II received Tab. Rosuvastatin 10 mg + Fenofibrate 160 mg. Both the groups received One tablet once a day at night for 12 weeks. Patients were assessed after 12 weeks and their Lipid profile was done. As shown in Figure 1.

Statistical analysis

Mean ± SD values were calculated for each variable. Demographic details were summarized for all subjects using descriptive statistics. Pair wise comparisons within the groups and between the two treatments were tested for statistical significance using the paired and unpaired Student t test respectively. Statistical significance was at $P<0.05$. All statistical tests were processed using graph pad prism software, Version 5.

RESULTS AND ANALYSIS

A total of 60 subjects diagnosed with combined hyperlipidemia were screened for the entry into the study and from that pool only 60 subjects were randomised to group I and Group II.

In Group I (Atorvastatin and Fenofibrate combination tablets), three patients were dropped out from the study out of which one did not take the medications regularly, one patient terminated the study due to personal reasons and one withdrew consent to participate.

Similarly in Group II (Rosuvastatin and Fenofibrate combination tablets), four patients were withdrawn from the study out of which two did not take the medicines regularly and two patients did not turned up after the screening. So data of 27 participants in Atorvastatin + fenofibrate group and 26 participants in Rosuvastatin + Fenofibrate group were used for analysis.

Initial readings of lipid levels like TC, TG, HDL, LDL and VLDL were taken for both the groups as baseline values before assigning the treatment. Then, Group I (n=27)–received Atorvastatin 10 mg + Fenofibrate 160 mg and Group II (n=26)–received Rosuvastatin 10 mg + Fenofibrate 160 mg combination tablets for 12weeks orally at night time. Patients were assessed after 12 weeks and were asked to report immediately if they developed any muscle pain throughout the study. Lipid profile was done after 12 weeks. Both the groups tolerated study medications and completed the study. No significant adverse reactions were recorded during the study. The results are shown in Table 1.

Effects of both the treatments on lipid parameters

The effect of both the treatments on lipid parameters is shown in Table 2. Effects on Total Cholesterol Levels: In Group I, the baseline and post treatment values of total cholesterol were found as 280 ± 59.17 mg/dL and 168.4± 35 mg/dL.16 respectively. Similarly in Group II, the baseline and after treatment values of total cholesterol were found as 272.7 ± 61.68 mg/dL and 124 ± 30 mg/ dL. 8 respectively.

Effects on Triglyceride Levels: In Group I, the baseline and post treatment values of Triglycerides were found as 291.9 ± 14.56 mg/dL and 155.4 ± 43 mg/dL. 36 respectively. Similarly in Group II, the baseline and after treatment values of Triglycerides were found as 329.8 ± 87.91 mg/ dL and 138 ± 32 mg/dL. respectively.

Effects on HDL Levels: In Group I, the baseline and post treatment values of HDL were found as 40.56 ± 9.057 mg/dL and 38.04 ± 9.15 mg/dL respectively. Similarly in Group II, the baseline and after treatment values of HDL were found as 39.46 ± 3.93 mg/dL and 44.88 ± 5.39 mg/ dL respectively.

Effects on LDL Levels: In Group I, the baseline and post treatment values of LDL were found as 193.6 ± 39.06 mg/dL and 96.19 ± 20.64 mg/dL respectively. Similarly in Group II, the baseline and post treatment values of LDL were found as 185.3 ± 46.34 mg/dL and 88.73 ± 18.03 mg/dL respectively.

Effects on VLDL Levels**:** In Group I, the baseline and post treatment values of VLDL were found as 53.26 ± 19.4 mg/dL and 34.09 ± 12.57 mg/dL respectively. Similarly in Group II, the baseline and after treatment values of VLDL were found as 62.65 ± 17.73 mg/dL and 27.04 ± 8.79 mg/dL respectively.

Table 1: Baseline characteristic of Patients attending OPD

Characteristics	Atorvastatin 10 mg + Fenofibrate 160 mg per day (n=27)	Rosuvastatin 10 mg + Fenofibrate 160 mg per day (n=26)
Age in years	46.96 ± 10.88	46.69 ± 10.8
Male:Female	15:12	12:14
BMI Kg/m^2	27.79 ± 2.80	30.87 ± 4.79
Total Cholesterol (mg/dL)	280 ± 59.17	272.7 ± 61.68
Triglycerides (mg/dL)	291.9 ± 14.56	329.8 ± 87.91
HDL (mg/dL)	38.04 ± 9.15	39.46 ± 3.93
LDL (mg/dL)	193.6 ± 39.06	185.3 ± 46.34
VLDL (mg/dL)	53.26 ± 19.4	62.65 ± 17.73

All the values are expressed as Mean ± SD.

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Table 2: Comparison of changes in the lipid profile between two treatment groups before and after 12 weeks of treatment

Lipid profile	Atorvastatin 10 mg + Fenofibrate 160 mg (n=27)			Rosuvastatin 10 mg + Fenofibrate 160 mg (n=27)		
	Baseline values	12 weeks later	Percentage change	Baseline values	12 weeks later	Percentage change
TC (mg/dL)	280 ± 59.17	168.4 ± 35.1	-39%	272.7 ± 61.68	124 ± 30.8	-54%#
TG (mg/dL)	291.9 ± 14.56	155.4 ± 43.3	-47%	329.8 ± 87.91	138 ± 32.81	-58%*
HDL (mg/dL)	38.04 ± 9.15	40.56 ± 9.057	+6%	39.46 ± 3.93	44.88 ± 5.39	+14%
LDL (mg/dL)	193.6 ± 39.06	96.19 ± 20.6	-50%	185.3 ± 46.3	88.73 ± 18.03	-52%*
VLDL (mg/dL)	53.26 ± 19.4	34.09 ± 12.5	-35%	62.65 ± 17.7	27.04 ± 8.79	-56.83%#

All the values are expressed as Mean ± SD, *P<0.05, #P<0.01.

DISCUSSION

Dyslipidemia is the commonest cause of the blood vessel diseases and their incidence has been rising all over the world thereby increasing the morbidity and mortality due to cardiovascular diseases. Statins are the mainstay in the management of dyslipidemia. Outcome trials of statins have proved conclusively that these drugs decrease LDL-C levels, resulting in a significant reduction of cardiovascular events in many high-risk patients.[19,20] Rosuvastatin has been considered superior in achieving greater LDL-C level reductions as compared to atorvastatin, simvastatin, or pravastatin use.[21] Combined therapy with statins and fibrates is more effective in controlling lipid profile in patients with combined hyperlipidemia (CHL).[22,23]

Studies evaluating the combination of atorvastatin

In one study, Atorvastatin (20 mg/day) alone was compared with micronized fenofibrate (200 mg/day) monotherapy and in combination with fenofibrate in type 2 diabetes mellitus patients with CHL in the patients with age group of 44-69 years.[24] The combination treatment had reduced LDL-C by 46%, TGs by 50%, TC by 37% and increased HDL-C by 46% and the changes are better than compared with monotherapy.

Studies evaluating the combination of rosuvastatin

One study done by Durrington *et al* studied the effect of fenofibrate alone or in combination with rosuvastatin in type 2 diabetics with elevated TG and TC.[25] At week 24, the percentage of patients achieving the LDL-C goal of <100 mg/dL was 86% with rosuvastatin 40 mg (n=50), 4.1% with fenofibrate 67 mg 3 times a day (n=49) whereas 75.5% is seen with rosuvastatin 10 mg plus fenofibrate 67 mg 3 times a day (n=53) and 75% with rosuvastatin 5 mg plus fenofibrate 67 mg 3 times a day (n=60).

In one more study with 760 patients, efficacy and safety of fenofibric acid with rosuvastatin were evaluated in patients with mixed dyslipidemia (LDL-C≥130 mg/dL, TG≥150 mg/dL, HDL-C<40 mg/dL males, <50 mg/dL females).[26] This 12-week study randomized individuals to rosuvastatin 5 mg/day, fenofibric acid 135 mg/day or fenofibric acid 135 mg/day plus rosuvastatin 5 mg/day. Statistically significant results, comparing rosuvastatin to fenofibric acid with rosuvastatin, were a mean percent change from baseline of HDL-C (rosuvastatin 12.4%, combination 23.0%), TG (rosuvastatin -17.5%, combination -40.3%), VLDL-C (rosuvastatin-22.2%, combination -41.3%), TC (rosuvastatin -25%, combination -28.1%). So this study also shows that Rosuvastatin + Fenofibrate combination therapy is superior to monotherapy of rosuvastatin and fenofibrate.

However, these studies also suggest that combination of rosuvastatin and fenofibrate was well tolerated and is as safe as therapy with the individual agents used as monotherapy. [27] These studies also suggest that data up to 2 years supports the safety of this combination.[28] Other treatment strategies for normalizing multiple lipid parameters in patients with mixed dyslipidemia include the addition of nicotinic acid or omega 3-fatty acids to statin therapy. Both strategies have resulted in improvements of lipid parameters other than LDL-C.[29,30]

CONCLUSION

Atorvastatin with fenofibrate and Rosuvastatin with fenofibrate significantly decreased Total cholesterol, Triglycerides, LDL-C, VLDL-C, but the reduction was more and statistically significant in Rosuvastatin and fenofibrate combination group when compared with atorvastatin and fenofibrate group at the end of 12 weeks. At the same time Rosuvastatin and fenofibrate combination group showed statistically significant increase in HDL-C levels when compared with atorvastatin and fenofibrate group.

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