THE EFFECTS OF LOW-DOSE ROSUVASTATIN ALONE OR IN COMBINATION WITH FENOFIBRATE OR OMEGA 3 FATTY ACIDS IN MIXED DYSLIPIDEMIA

Cardiology

Sumit Kumar	MD, Associate Professor, Department of Medicine, Guru Gobind Singh Medical College and Hospital, Faridkot, India.
Suraj Kumar*	MD, DM Assistant Professor, Department of Cardiology, Government Medical College and Hospital, Chandigarh, India. *Corresponding Author
Sarabjit Singh	MD, Department of Medicine, District Hospital, Kartarpur.
Kirti	MD, Senior Resident, Department of Biochemistry, Guru Gobind Singh Medical College and Hospital, Faridkot, India.
Maninder Kansal	MD, Senior Resident, Department of Medicine, Government Medical College and Hospital, Chandigarh, India.

ABSTRACT

Objective: Mixed dyslipidemia is characterized by elevated cholesterol and triglycerides. Indians have high prevalence of this pattern. The aim of present study was to evaluate the effects of rosuvastatin and in combination with fenofibrate or omega-3-FAs on lipids and hsCRP.

Methods: This was an open-label randomized study. Patients were allocated to low-dose rosuvastatin(R), rosuvastatin plus fenofibrate (RF) or rosuvastatin plus omega-3-FA(RO). At 6-weeks and 12-weeks follow-up, lipid lowering effect and change in hsCRP was studied.

Results: The study involved 105 participants (M/F=68/37) with a mean age of 57±13 years. At end of 6 and 12-weeks, there was significant reduction in TC, LDL-C, TG and hsCRP in all treatment groups, but increase in HDL-C became significant at 12-weeks. Percentage reduction in TC was 21%vs17%vs23% at 6-weeks and 31%vs37%vs35% at 12-weeks in group R, RF and RO, respectively. At 12-weeks, reduction in LDL-C was 22% in R vs 45% in RF vs 18% in RO and increase in HDL-C was 3.8% in R vs 7.6% in RF vs 15.8% in RO. Percentage reduction in triglycerides was 18%vs31% vs30% at 6 weeks and 23%vs52%vs51% at 12-weeks.

Conclusion: The mixed dyslipidemic patients responded well in terms of significant reduction in TC, LDL-C, and improving HDL-C and inflammation across all study groups. However, combination of low-dose-rosuvastatin plus fenofibrate or omega-3-FAs had more potent effect in reducing triglycerides and also in percentage increase in HDL-C, when compared with rosuvastatin alone. Omega-3 FAs, therefore, seem to be an attractive alternative to fibrates in patients with mixed dyslipidemia.

KEYWORDS

Mixed dyslipidemia, Cholesterol, Triglycerides, Rosuvastatin, Fibrates, Omega-3-fatty acid.

INTRODUCTION

Coronary artery disease(CAD) has emerged as a leading cause of morbidity and mortality in modern times and its incidence is on the rise at a comparatively younger age, particularly in India.

Mixed dyslipidemia is a metabolic disorder characterized by elevated concentrations of both cholesterol and triglycerides. More specifically, these patients have elevated low density lipoprotein-cholesterol (LDL-C) and triglyceride (TG) levels, a preponderance of small, dense LDL particles, and reduced concentrations of high density lipoprotein-cholesterol (HDL-C). It is widely accepted that this dyslipidemia is associated with an increased risk of vascular events [1]. Indians have an unusually high prevalence in this pattern of dyslipidemia, when compared with Western populations [2]. The treatment of mixed dyslipidemia is a therapeutic challenge as monotherapy only partially correct all the underlying metabolic defects. hsCRP is also a widely used inflammatory biomarker that has also been studied as independent predictor of cardiovascular disease [3,4]. It has been suggested that the predictive value of hsCRP is incremental to the Framingham Risk Score [5].

Use of different lipid-lowering agents along with therapeutic lifestyle changes provides an effective way to reduce the ravages of CAD and other atherosclerotic vascular diseases. Although serum LDL-C is the primary target of lipid-lowering therapy, other parameters like HDL-C and triglycerides seem to be equally important, especially in indian population. It is well accepted that statins are the primary and more efficient method of reducing LDL-C levels even at low doses[6]. However, statins manifest minimal effects in raising HDL-C levels (5%–15%) and in decreasing TG levels (7%–30%)[7].

Fibric acid derivatives (fibrates) and omega-3 fatty acids represent ideal candidates for this kind of combination treatment. Fenofibrate belongs to a class of drugs that activate specific transcription factors known as peroxisome proliferator-activated receptors a (PPAR-a) [8]. These drugs reduce the concentration of plasma TG by 30–50% and raise the level of HDL-C by 2–20%. The effects of fenofibrate on HDL-C largely depend on baseline HDL-C levels. However, the elevated

risk for muscle side effects limits the widespread use of statin/fibrate combination. The omega-3 fatty acids mainly reduce TG concentration, but they also exert other anti-atherosclerotic properties [9]. Many trials have shown that moderate fish consumption lowers the risk of major cardiovascular events, such as myocardial infarction, sudden cardiac death, coronary artery disease, atrial fibrillation, and death in patients with heart failure [10]. Adding omega-3 fatty acids to statins reduces triglycerides to a greater extent than statin monotherapy [11]. It is currently unknown what would be the best treatment option for patients with mixed hyperlipidemia. The aim of this open-label randomized study was to compare the lipid lowering effect of low dose of rosuvastatin alone, low dose of rosuvastatin plus fenofibrate and low dose rosuvastatin plus omega-3 fatty acids treatment and also see the effect on hsCRP.

METHODS

Study design

Open-label randomized study. We followed a simple randomization method using a table of random numbers.

Study population

Patients attending the OPD of department of medicine of a tertiary care hospital were recruited for the study. Patients were considered eligible if they had serum total cholesterol (≥ 200 mg/dL) and triglycerides (≥ 200 mg/dL) at baseline. These targets were determined as per NCEP-ATP III guidelines. Patients with known coronary artery disease, recent myocardial infarction, peptic ulcer disease, pancreatitis, cholelithiasis, uncontrolled hypothyroidism, liver or renal dysfunction, very high triglyceride values (≥ 500 mg/dL), currently taking lipid-lowering drugs and hypersensitivity to study drugs were excluded for study.

Laboratory methods

Patients were allocated to rosuvastatin 10 mg (n = 35, group R), rosuvastatin 10 mg plus fenofibrate 160 mg (n = 35, group RF) or rosuvastatin 10 mg plus 1 gm of omega-3 fatty acid [each gram of the preparation contained approximately 180 mg of eicosapentaenoic acid (EPA) and 120 mg of docosahexaenoic acid (DHA)] (n = 35, group

RO) daily. Lipid profile and hsCRP was done at baseline and at 6-weeks and 12-weeks of follow-up, along with renal and liver function tests, creatinine kinase levels. All laboratory determinations were carried out after an overnight fast.

Study outcomes

At 6-weeks and 12-weeks follow-up, lipid lowering effect and change in hsCRP of three different regimens were studied.

Statistical analysis

Categorical variables were presented as numbers and percentage, continuous variables as mean $\pm$ standard deviation (SD) or median and 95% confidence interval (95% CI). Categorical variables were compared by chi-squared analysis. Continuous variables were tested for lack of normality by the Kolmogorov-Smirnov test. The paired samples t-test was used for assessing the effect of treatment in each group. Analysis of covariance (ANCOVA), adjusted for baseline values, was used for comparisons between treatment groups. A p-value of <0.05 was considered being statistically significant. All the data were recorded on Microsoft Excel database and statistical analysis was performed using SPSS software (version 23.0, SPSS Inc., Illinois, USA).

RESULTS

There were no differences in age between study groups. The baseline characteristics of patients are shown in Table I. Hypertension was

observed in 23 subjects, diabetes in 24 subjects, 3 were smokers and 5 subjects had a family history of coronary artery disease. The baseline concentrations of total cholesterol, serum triglycerides, LDL-C, and HDL-C as well as those of hsCRP were similar in the three study groups. The baseline values of serum lipids and effect of hypolipidemic treatment is shown in Table II.

Table I. Baseline demographic characteristics of all study participants

Characteristic	Group R (n=35)	Group RF (n=35)	Group RO (n=35)	p-value
Age (years)	57.8 $\pm$ 15.5	56.5 $\pm$ 13.8	56.8 $\pm$ 14.5	NS
Males/Females	22/13	25/10	21/14	NS
Diabetes (%)	20	25.7	22.9	NS
Hypertension (%)	20	17.1	28.6	NS
Smokers (%)	5.7	2.9	0	NS
Familial H/O CAD (%)	2.9	5.7	5.7	NS
Total Cholesterol (mg/dL)	261.5 $\pm$ 58.5	294.8 $\pm$ 93.8	263 $\pm$ 58	NS
Triglycerides (mg/dL)	349 $\pm$ 149	360.5 $\pm$ 160	355 $\pm$ 150	NS
LDL-C (mg/dL)	150.5 $\pm$ 66.5	184.4 $\pm$ 69.6	150.5 $\pm$ 66.5	NS
HDL-C (mg/dL)	39 $\pm$ 9	39.5 $\pm$ 9.5	39.35 $\pm$ 9.4	NS
hsCRP (mg/L)	2.7 $\pm$ 0.9	2.7 $\pm$ 1.2	2.7 $\pm$ 0.9	NS

All values are presented as Mean $\pm$ SD or number (%).

Table II. Serum Metabolic Parameters at Baseline, after 6-weeks and 12-weeks of drug therapy.

	Baseline	6 weeks	% change	12 weeks	% change
Total Cholesterol					
Group R	261.5 $\pm$ 58.5	205.5 $\pm$ 59.5	- 21.41	179.5 $\pm$ 48.5	- 31.36
Group RF	294.8 $\pm$ 93.8	244.5 $\pm$ 82.5	- 17.06	185.5 $\pm$ 69.5	- 37.08
Group RO	263.0 $\pm$ 58	202.5 $\pm$ 57.5	- 23	170.5 $\pm$ 43.5	- 35.17
Triglycerides					
Group R	349 $\pm$ 149	283.5 $\pm$ 135.5	- 18.77	268 $\pm$ 118	- 23.21
Group RF	360.5 $\pm$ 160	247.4 $\pm$ 83	- 31.37	170.5 $\pm$ 59.5	- 52.7
Group RO	355 $\pm$ 150	248 $\pm$ 95	- 30.14	172.5 $\pm$ 42.5	- 51.41
LDL-C					
Group R	150.5 $\pm$ 66.5	125 $\pm$ 48	- 16.94	117 $\pm$ 40	- 22.26
Group RF	184.4 $\pm$ 69.6	133.5 $\pm$ 67.5	- 27.6	100.5 $\pm$ 56.5	- 45.5
Group RO	150.5 $\pm$ 66.6	139.5 $\pm$ 66.5	- 7.31	123 $\pm$ 53	- 18.27
HDL-C					
Group R	39 $\pm$ 9	39.5 $\pm$ 7.5	1.28	40.5 $\pm$ 9.5	3.85
Group RF	39.5 $\pm$ 9.5	41.6 $\pm$ 8.4	5.32	42.5 $\pm$ 8	7.59
Group RO	39.35 $\pm$ 9.4	42.5 $\pm$ 6.5	8.01	45.55 $\pm$ 7.45	15.76
hsCRP					
Group R	2.7 $\pm$ 0.9	2.45 $\pm$ 0.65	- 9.26	2.16 $\pm$ 0.47	- 20
Group RF	2.7 $\pm$ 1.2	2.4 $\pm$ 0.7	- 11.11	2.1 $\pm$ 0.4	- 22.22
Group RO	2.7 $\pm$ 0.9	2.3 $\pm$ 0.6	- 14.81	2.15 $\pm$ 0.45	- 20.37

Values are expressed as mean $\pm$ SD

At the end of the 6-weeks and 12-weeks treatment period, there was a significant reduction in total serum cholesterol levels in all treatment groups ($p < 0.001$ compared with baseline values). More specifically at 12-weeks, total serum cholesterol was reduced by 31% in group R, by 37% in group RF and by 35% in group RO (Figure 1).

Figure 1. Effect of hypolipidemic treatment on serum lipid concentrations at 12-weeks.

There were also significant reductions seen in the plasma levels of LDL-C in all study groups, both at 6-weeks and 12-weeks. The reduction in LDL-C was more at 12-weeks as compared 6-weeks ($p <$

0.01 at 6-weeks and $p < 0.001$ at 12-weeks). There was also a significant reduction in serum triglycerides, both at 6-weeks and 12-weeks in all treatment groups ($p < 0.05$ at 6-weeks in all three groups and in Group R at 12 weeks, $p < 0.001$ in Group RF and RO at 12 weeks).

The increase in HDL-C levels was seen not significant at 6-weeks in all three treatment groups ($p > 0.05$), but became significant at 12-weeks ($p < 0.05$). The percentage increase in serum HDL-C was more in Group RF and RO, as compared to Group R (3.89% in group R vs 7.59% and 15.76% in group RF and RO respectively).

Also, in all treatment groups there was a significant reduction in serum hsCRP levels ($p < 0.001$ at both 6-weeks and 12-weeks in all treatment groups). The percentage reductions in serum hsCRP at 12-weeks was 20% in group R, 22% in group RF and 20.37% in group RO.

The prevalence of adverse effects, in general was low. In group RF, 2 patients complained of gastrointestinal tract disturbances in the form of dyspepsia, and 5 patients had myalgia. No patients showed an increase in aminotransferase and creatine kinase (CK) levels. Comparing the incidence of side effects between the three groups, the incidence of myalgias were significantly more in group RF, as compared to R or RO. None of the patients had to stop treatment because of adverse effects.

DISCUSSION

In this open-label randomized study, we studied the effects of low doses of rosuvastatin (Group R) versus its combination with fenofibrate (Group RF) or omega-3 fatty acids (Group RO) on mixed dyslipidemia.

In the present study after treatment with rosuvastatin and fenofibrate (Group RF), there was a statistically significant increase in HDL-C and decrease in serum cholesterol, triglycerides, LDL-C, and hsCRP levels at the end of 12 weeks. In previous randomized controlled studies [12,13] using fenofibrate and low dose rosuvastatin, similar findings were observed as in the present study.

The treatment group consisting of subjects receiving rosuvastatin and omega fatty acids (Group RO), showed that after treatment for 12 weeks there was a statistically significant fall in serum total cholesterol, triglycerides, LDL-C, and hsCRP. In a study by Contacos[14], using pravastatin and omega-3 fatty acids, after 6 weeks there was a decrease in total cholesterol by 27%, LDL-C by 23%, triglycerides by 42%, whereas in the group given pravastatin and placebo, fall in triglyceride was by 19%. Similar findings are observed in the present study when comparing group RO and group R. In another conducted by Chan[15], atorvastatin 40mg and omega-3 fatty acids combination for 6 weeks showed fall in triglycerides by 40%, total cholesterol by 38%, VLDL-C by 47% and LDL-C by 47%. These findings are higher than those observed at 6 weeks in the present study, which may be because of higher doses used in above study. Japan EPA Lipid Intervention Study [16] was first one the large-scale trial evaluating clinical outcomes with the use of statin and omega-3 fatty acid combination therapy. This trial showed a statistically significant 19% decrease in major cardiac end points and this benefit appeared to be independent of any changes in lipids. In another recent study, The Reduction of Cardiovascular Events with Icosapent Ethyl Intervention Trial (REDUCE-IT),[17] in which of icosapent ethyl, a prescription, highly purified ethyl ester of EPA was used, showed a significant reduction in clinical events, including cardiovascular death in study group when compared to placebo at a mean follow-up of 4.9 years.

In group receiving rosuvastatin alone, no significant difference was observed from group RF and RO in decrease in the levels of total cholesterol, LDL-C, hsCRP and increase in level of HDL-C but fall in triglyceride levels was significantly more in group RF and RO. Thus addition of fenofibrate and omega-3 fatty acids cause a significant fall in triglycerides as compared to rosuvastatin alone.

Fenofibrate has small or minimal effects on LDL-C levels, which depends on baseline TG levels. [6] These data imply that a combination of a statin and a fibrate may have additional benefits, especially in patients with mixed dyslipidemia. Combining fenofibrate with a statin appeared to be safe and effective in several short-term studies. [18-23] The combination of fenofibrate with a statin, along with better improvements in lipid profile, has been shown to induce a marked increase in the ratio of large to small LDL subspecies compared with statin monotherapy. [24,25]

Omega-3 fatty acids have also been shown to have beneficial effects on endothelial function [26], cytokine secretion [27,28] and decrease arrhythmias in various human and animal studies [29]. The combination of statins with omega-3 fatty acids may have beneficial effects besides their effects on lipids. This combination may also exert antithrombotic and anti-inflammatory effects. Patients, with mixed dyslipidemia, have an increased tendency to develop thrombosis. In particular, hypertriglyceridemia may cause abnormal coagulation and fibrinolytic pathways.

We believe that the most important limitations of our study are its open-label design and the small number of participants, and there was no long-term follow-up. Impact on clinical endpoints and major adverse cardiovascular events was not seen, so it is not possible to comment on whether the benefit of adding fibrates or omega fatty acids on lipid levels would contribute to improvement in outcome as well. We also didn't study the food habits of the subjects, which is again a potential limitation as certain food habits like fish-eating can have an impact on lipids.

CONCLUSIONS

The mixed dyslipidemic patients responded well in terms of significant reduction in TC, LDL-C, and improving HDL-C and inflammation

across all study groups. However, combination of low-dose-rosuvastatin plus fenofibrate or omega-3-FAs had more potent effect in reducing triglycerides and also in percentage increase in HDL-C, when compared with rosuvastatin alone. Omega-3 FAs, therefore, seem to be an attractive alternative to fibrates in patients with mixed dyslipidemia. Larger, prospective clinical trials with a double-blind design are needed to delineate whether these differences in biochemical efficiency can be translated into significant differences in clinical efficiency and more specifically in the ability of various regimens to reduce cardiovascular morbidity and mortality in patients with mixed dyslipidemia.

REFERENCES

- Durrington P., 2003. Dyslipidaemia. *Lancet*. 362, 717-731. 10.1016/S0140-6736(03)14234-1.
- Joshi SR., 2000. Hypertriglyceridemia - The Indian Context, in: *API Medicine Update*. India, pp. 298.
- Ridker PM., 2005. C-reactive protein, inflammation, and cardiovascular disease: clinical update. *Tex Heart Inst J*. 32, 384-386.
- Danesh J, Wheeler JG, Hirschfield GM, et al., 2004. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med*. 350, 1387-1397.
- Bassuk SS, Rifai N, Ridker PM., 2004. High-sensitivity C-reactive protein: clinical importance. *Curr Probl Cardiol*. 29, 439-493.
- Bruckert E, De Gennes JL, Malbecq W, et al., 1995. Comparison of the efficacy of simvastatin and standard fibrate therapy in the treatment of primary hypercholesterolemia and combined hyperlipidemia. *Clin Cardiol*. 18, 621-629.
- Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III), 2001. *JAMA*. 285, 2486-2497.
- Elisaf M., 2002. Effects of fibrates on serum metabolic parameters. *Curr Med Res Opin*. 18, 269-276.
- Lavie CJ, Milani RV, Mehra MR, et al., 2009. Omega-3 polyunsaturated fatty acids and cardiovascular diseases. *J Am Coll Cardiol*. 54, 585-594.
- Gazi I, Liberopoulos EN, Saougos VG, et al., 2006. Beneficial effects of omega-3 fatty acids: the current evidence. *Hellenic J Cardiol*. 47, 223-231.
- Davidson MH, Stein EA, Bays HE, et al., 2007. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/dl to simvastatin 40 mg/dl in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. *Clin Ther*. 29, 1354-1367.
- Jones PH, Davidson MH, Goldberg AC, et al., 2009. Efficacy and safety Of fenofibric acid in combination with a statin in patients with mixed Dyslipidemia: pooled analysis of three phase III, 12-week, randomized, Controlled studies. *J Clin Lipidol*. 3, 125-137.
- Klosiewicz, Latoszek L, Respondek W, et al., 2003. Efficacy and safety of combined statin - fenofibrate therapy compared with monotherapy in patients with mixed hyperlipidemia and high risk Of coronary heart disease. *Pol Merkuriusz Lek*. 15, 42-46.
- Contacos C, Barter PJ, Sullivan DR., 1993. Effects of Pravastatin and Omega 3 fatty acids on plasma lipids and lipoproteins in patients with combined hyperlipidemia. *Arterioscler Thromb*. 1, 1755-1762.
- Chan DC, Watts GF, Barrett PHR, et al., 2002. Regulatory effects of HMG CoA reductase inhibitors and Fish oils on apolipoprotein B-100 kinase in insulin resistant obese male subjects with dyslipidemia. *Diabetes*. 5, 2377-1386.
- Yokoyama M., Origasa H., Matsuzaki M., et al., 2007. Effects of icosapentaenoic acid on major coronary events in hypercholesterolemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet*. 369, 1090-1098.
- Bhatt DL, Steg PG, Miller M, et al., 2019. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 380, 11-22.
- Grundy SM, Vega GL, Yuan Z, et al., 2005. Effectiveness and tolerability of simvastatin plus fenofibrate for combined hyperlipidemia (the SAFARI trial). *Am J Cardiol*. 95, 462-468.
- Ellen RL, McPherson R., 1998. Long-term efficacy and safety of fenofibrate and a statin in the treatment of combined hyperlipidemia. *Am J Cardiol*. 81, B60-B65.
- Athyros VG, Papageorgiou AA, Athyrou VV, et al., 2002. Atorvastatin and micronized fenofibrate alone and in combination in type 2 diabetes with combined hyperlipidemia. *Diabetes Care*. 25, 1198-1202.
- Kiortsis DN, Millionis H, Bairaktari E, et al., 2000. Efficacy of combination of atorvastatin and micronized fenofibrate in the treatment of severe mixed hyperlipidemia. *Eur J Clin Pharmacol*. 56, 631-635.
- Liamis G, Kakafika A, Bairaktari E, et al., 2002. Combined treatment with fibrates and small doses of atorvastatin in patients with mixed hyperlipidemia. *Curr Med Res Opin*. 18, 125-128.
- Derosa G, Cicero AE, Bertone G, et al., 2004. Comparison of fluvastatin + fenofibrate combination therapy and fluvastatin monotherapy in the treatment of combined hyperlipidemia, type 2 diabetes mellitus, and coronary heart disease: A 12-month, randomized, double-blind, controlled trial. *Clin Ther*. 26, 1599-1607.
- Vega GL, Ma PT, Cater NB, et al., 2003. Effects of adding fenofibrate (200 mg/day) to simvastatin (10 mg/day) in patients with combined hyperlipidemia and metabolic syndrome. *Am J Cardiol*. 91, 956-960.
- May HT, Anderson JL, Pearson RR, et al., 2008. Comparison of effects of simvastatin alone versus fenofibrate alone versus simvastatin plus fenofibrate on lipoprotein subparticle profiles in diabetic patients with mixed dyslipidemia (from the Diabetes and Combined Lipid Therapy Regimen study). *Am J Cardiol*. 101, 486-489.
- Chin JPF, Gust AP, Nestel PJ, et al., 1993. Fish oils dose- dependently inhibit vasoconstriction of forearm resistance vessels in humans. *Hypertension*. 21, 22-28.
- Bauman KH, Hessel F, Larass I et al., 1999. Omega-3, omega-6 and omega-9 unsaturated fatty acids and growth factor and cytokine gene expression in unstimulated and stimulated monocytes. A randomised volunteer study. *Arterioscler Thromb Vasc Biol*. 19, 59-66.
- De Caterina R, Cybulsky MI, Clinton SK et al., 1995. The omega-3 fatty acids and endothelial leukocyte adhesion molecules. *Prostaglandins Leukot Essent Fatty Acids*. 52, 191-195.
- Leaf A., 1995. Omega-3 fatty acids and prevention of ventricular fibrillation. *Prostaglandins Leukot Essent Fatty Acids*. 52, 197-198.