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Internal Medicine Section

Efficacy of Combination Therapy of Rosuvastatin and Ezetimibe vs Rosuvastatin Monotherapy on Lipid Profile of Patients with Coronary Artery Disease

SANDEEP JOSHI[1], RUBY SHARMA[2], HARBIR KAUR RAO[3], UDIT NARANG[4], NITIN GUPTA[5]

ABSTRACT

Introduction: Dyslipidaemia is one of the most important modifiable risk factor for the development of Coronary Artery Disease (CAD). Although, statins are established as first line lipid-lowering therapy, they may not be able to achieve treatment goals in significant number of patients. Combination therapy of statin with a non-statin drug like Ezetimibe is a therapeutic option.

Aim: To compare the efficacy and safety of Rosuvastatin/Ezetimibe combination therapy vs Rosuvastatin alone on the lipid profile of patients with CAD in Northern India.

Materials and Methods: This randomized prospective study was conducted on 80 patients of CAD presenting to Department of Medicine, Government Medical College, Patiala, Punjab, India. The patients were randomly divided into age and sex matched two groups of 40 each. After baseline investigations and lifestyle modifications, Group I was started on rosuvastatin 10 mg once daily, while Group II was started on rosuvastatin 10 mg+ezetimibe 10 mg daily. The fasting serum lipid profile was repeated initially after 12 weeks and then after 24 weeks. The two groups were observed for side effects which were noted.

Results: The combination therapy of rosuvastatin and ezetimibe resulted in significantly higher change in all lipid parameters (LDL-C, TC, TG, HDL-C) as compared to treatment with rosuvastatin alone. There was no difference in the adverse effects seen after treatment in the two groups.

Conclusion: Our study showed that combination therapy of ezetimibe with rosuvastatin can be used as an effective and safe therapy in high risk patients of CAD, especially in patients in whom statin monotherapy is not able to achieve the target lipid levels.

Keywords: Dyslipidaemia, Low density lipoprotein, Serum cholesterol, Statin

INTRODUCTION

Coronary artery disease is one of the leading causes of mortality worldwide [1]. In India, the epidemic of Cardiovascular Disorders (CVDs) is on increasing trend and a big economic burden [2]. Most large epidemiological studies including Framingham Heart Study have categorised Dyslipidaemia as one of the most important modifiable risk factor for the development of CAD [3]. Elevated serum cholesterol shows causal association with increased risk of CAD. It has been shown that reduction in serum cholesterol level is an effective therapeutic intervention which significantly reduces CAD incidence [4]. The risk benefit is more if lipid lowering therapy is started at a younger age in high risk groups [4]. Further, it has been established that elevated Low-Density Lipoprotein Cholesterol (LDL-C) values and decreased levels of High-Density Lipoprotein Cholesterol (HDL-C) are risk factors for CAD [3]. Reduction in LDL-C levels is established as a major therapeutic intervention for primary and secondary prevention in patients of cardiovascular diseases [5].

Most of the current guidelines recommend intensive and effective lipid lowering therapy in patients with CAD [6]. Statins (HMG CoA Reductase Inhibitors) are the first line treatment option in managing dyslipidaemias in patients having CVD [7]. Over the years many large studies have established their efficacy in reducing Serum Cholesterol/LDL-C levels and improving overall Cardiovascular morbidity/mortality [8-10]. Although, these agents result in significant reductions in LDL-C levels as monotherapy, but studies have proven that a large number of patients may not achieve therapeutic goals with statin therapy alone [11,12]. Combination therapy of statin with a non-statin drug is a therapeutic option in that category of patients.

Ezetimibe belongs to a class of drugs which selectively inhibit absorption of cholesterol (dietary and biliary) at the brush border of small intestine, resulting in reduction of overall delivery of cholesterol to the liver. This results in decrease in the cholesterol stores in liver and increases its clearance from the blood [13,14]. Combination therapy of ezetimibe (10 mg per day) with statin blocks both the synthesis and absorption of cholesterol, thereby having a synergistic effect on lipid metabolism. Higher doses of statins may result in musculoskeletal or hepatic side effects. Adding ezetimibe to statin therapy is an option for such patients. Clinical trials have shown that statin therapy in combination with ezetimibe result in higher reductions in LDL-C levels leading to more patients achieving the LDL-C targets than uptitrating the statin dose [15,16].

Rosuvastatin is a high potency statin which has been shown to have higher lipid lowering effect than other statins like simvastatin or atorvastatin [17]. The usefulness of statin-ezetimibe combination therapy in achieving lipid lowering targets is an area of active research. Especially, there is very limited data available on its use in the Indian population [18,19]. Therefore, this study was planned

to study and compare the efficacy and side effects of rosuvastatin/ezetimibe combination therapy vs rosuvastatin alone on the lipid profile of patients with CAD in Northern India.

MATERIALS AND METHODS

The present study was a randomized, prospective study conducted in the Department of Medicine at Government Medical College, Patiala. Eighty consecutive patients (47 males and 33 females) of CAD reporting to a single unit of Medicine Department were recruited.The study was done in 2007 to 2008 after approval from the Ethical Committee of the Institute. The total duration of the study was one year. CAD was diagnosed on the basis of clinical history and Electrocardiography (ECG) changes (ST depression/elevation, T wave inversion). Serum biochemical cardiac markers (CPK-MB, Troponin) were measured in patients who were admitted with new onset chest pain.

Inclusion and Exclusion Criteria

Patients more than 18 years of age and those who gave informed written consent were included in the study. Patients with renal disease, liver disease, history of seizures, pregnant or lactating females, were excluded from the study. Patients having history of drug allergy and those who were on some other medication known to have interaction with any of the two study drugs were also excluded. Those who were not willing or were unable to give written consent were also excluded from the study.

After verification of the patients for fulfilling the inclusion criteria and exclusion criteria, a detailed history of all the patients was taken and recorded as per a pre-designed performa. Complete clinical examination including vital signs, general and systemic examination was done. Details regarding presence of cardiovascular risk factors (Diabetes Mellitus, Hypertension, Smoking, Obesity, Sedentary lifestyle etc) were noted. All patients underwent routine investigations Haemoglobin (Hb), Random Blood Sugar (RBS), Renal Function Test (RFT), Liver Function Test (LFT), ECG and other investigations (cardiac biomarkers like CPK-MB and Troponins in patients presenting with chest pain) as required. Baseline fasting serum lipidogram was performed on each patient. Samples were taken after overnight fasting and serum was separated by centrifugation for 10 minutes. Total Cholesterol (TC), HDL-C and Total Triglycerides (TG) were measured by using appropriate testing kits. LDL-C was calculated by using Friedewald formula: LDL=TC-(TG/5+HDL-C). The patients of CAD were randomly allocated (1:1) using minimization method into two age and sex matched groups (groups I and II) of 40 patients each. Patients of both groups were advised to follow lifestyle modifications-quit smoking, regular exercise, avoid alcohol and take low fat diet. Adequate counselling regarding lifestyle modifications was given to all patients. Along with that, Group I was started on rosuvastatin 10 mg once daily, while Group II was started on rosuvastatin 10 mg+ezetimibe 10 mg daily. Total duration of study was 24 weeks. The regular treatment of CAD including antiplatelets (Aspirin, Clopidogrel), Beta-blockers, ACE inhibitors, Nitrates was continued as before. The patients were followed fortnightly and examined for any side effects of drugs and the same were noted down. The fasting serum lipid profile was repeated initially after 12 weeks and then after 24 weeks. The results of the two drugs on lipid profile were compared when used as monotherapy and in combination and evaluated. The patients were also observed for any side effects (gastrointestinal, musculoskeletal, liver function abnormalities) which were noted and analyzed statistically.

STATISTICAL ANALYSIS

The mean and standard deviation for different lipid parameters at baseline, 12 weeks and 24 weeks was calculated. Percentage change in lipid profile with treatment in both the groups was calculated. The data was analyzed statistically by using paired t-test and Analysis of variance (ANOVA) to compare the results and p-values were obtained. The statistical analysis was carried out with SPSS PC software version 13.0.

RESULTS

The [Table/Fig-1] shows the baseline demographic and clinical characteristics of the two study groups. The two groups were comparable with respect to age, sex, Body Mass Index (BMI) and any coexisting risk factors for CAD.

Variable	Rosuvastatin Group	Combination Therapy Group
Age (years)	59.78±11.12	60.33±9.83
Gender		
Males. no. (%)	25 (62.5%)	22 (55%)
Females. no. (%)	15 (37.5%)	18 (45%)
BMI (kg/m^2)	29.5±5.1	29.7±4.8
Coexisting CAD Risk Factors		
Hypertension	18 (45%)	17 (42.5%)
Diabetes Mellitus	9 (22.5%)	11 (27.5%)
Smoking	9 (22.5%)	7 (17.5%)
Sedentary Life Style	6 (15%)	8 (20%)
Obesity	8 (20%)	9 (22.5%)
Blood Pressure		
SBP	145.10±24.74	142.50±24.13
DBP	87.50±10.39	87.00±10.27
S. Creatinine (mg%)	1.11±0.32	1.16±0.39

[Table/Fig-1]: Showing baseline demographic and clinical characteristics of the two groups:
SBP: Systolic Blood Pressure
DBP: Diastolic Blood Pressure

Variable	Baseline (Mean±SD)	After 12 weeks therapy			After 24 weeks therapy		
		Mean±SD	% Change	p-value	Mean±SD	% Change	p-value
TC	237.50± 25.67	168.57± 18.23	-28.91	p<0.01	160.52± 14.20	-32.16	p<0.01
TG	225.75± 32.65	184.13± 28.57	-18.39	p<0.01	176.13± 26.54	-21.88	p<0.01
LDL-C	153.38± 24.78	90.38± 17.91	-41.13	p<0.01	83.15± 14.03	-45.54	p<0.01
HDL-C	39.38± 3.17	41.38± 3.35	5.09	p<0.01	42.15± 3.34	7.08	p<0.01

[Table/Fig-2]: Showing changes in lipid parameters at 12 and 24 weeks of Rosuvastatin therapy (Group I).
(p<0.01 at both 12 weeks and 24 weeks for all parameters. Data analysed by paired t-test).
TC: Total Cholesterol, TG: Total Triglycerides

[Table/Fig-2,3] show the baseline lipid parameters and change in their levels after 12 weeks and 24 weeks of therapy in Group I (Rosuvastatin) and Group II (Combination Therapy) respectively. Rosuvastatin (10 mg/d) in Group I significantly reduced TC (28.91%), TG (18.39%) and LDL-C (41.13%) and increased HDL-C by 5.09% after 12 weeks of therapy. It also significantly reduced TC (32.16%), TG (21.88%) and LDL-C (45.54%) and increased HDL-C by 7.08% after 24 weeks. Similarly, rosuvastatin (10 mg/d)+ezetimibe (10 mg/d) in Group II reduced TC (38.98%), TG (26.29%) and LDL-C (53.65%) and increased HDL-C by 7.73% after 12 weeks of therapy. It reduced TC (41.92%), TG (30.68%) and LDL-C (57.39%) and increased HDL-C by 9.56% after 24 weeks.

The incidence of side effects with treatment in both the groups after different intervals of therapy is shown in [Table/Fig-4]. Common side effects seen were headache, musculoskeletal symptoms and gastrointestinal effects. As shown in the table, there was no significant difference in the incidence of side effects at both 12 and 24 weeks of treatment in the two groups.

Variable	Baseline (Mean±SD)	After 12 weeks therapy			After 24 weeks therapy		
		Mean±SD	% Change	p-value	Mean±SD	% Change	p-value
TC	247.13± 26.77	150.00± 11.43	-38.98	p<0.01	142.75± 10.79	-41.92	p<0.01
TG	218.88± 39.99	152.13± 22.61	-26.29	p<0.01	143.38± 22.83	-30.68	p<0.01
LDL-C	162.68± 23.13	76.80± 10.10	-53.65	p<0.01	70.58± 8.97	-57.39	p<0.01
HDL-C	39.73± 2.56	42.78± 2.74	7.73	p<0.01	43.50± 2.70	9.56	p<0.01

[Table/Fig-3]: Showing changes in lipid parameters at 12 and 24 weeks of combination therapy (Group II).
(p<0.01 at both 12 weeks and 24 weeks for all parameters. Data analysed by paired t-test)

Group	Duration	Headache	Musculoskeletal side effects	Gastrointestinal side effects	Deranged LFT's
I	12 weeks	3	1	2	-
	24 weeks	4	2	3	-
II	12 weeks	3	2	2	-
	24 weeks	5	3	3	-

[Table/Fig-4]: Showing comparison of incidence of side effects in both groups at different intervals of therapy.

DISCUSSION

Statins are the first line treatment option to treat dyslipidaemias, especially in high risk CAD patients. Using higher doses of high potency statins is one option in these patients. In studies evaluating uptitration of statin dosage, it was found that, although starting doses of statins could reduce LDL-C by 20-30%, doubling the dose result in only 5-6 % additional reduction. There is also an increased risk of adverse effects with higher doses. Another approach is to use some non-statin drugs like ezetimibe as an add-on therapy.

Previous studies have evaluated the effect of using statin-ezetimibe combination therapy on lipid profile in different groups of patients [20-24]. In a study including 769 patients of primary hypercholesterolemia, it was shown that by adding ezetimibe to the Statin therapy, significant reductions in LDL-C, TG and TC levels and increase in HDL-C level can be achieved. Also, 71.5% patients in combination group were able to achieve LDL-C target level as compared to only 18.9% in Statin-placebo group [20]. Similarly, in the Ezetimibe Add-on to Statin for Effectiveness (EASE) trial, the combination therapy reduced the LDL-C level by an additional 25.8 % in the total population [21]. A pooled analysis of over 21,000 subjects from 27 clinical trials showed that the statin-Ezetimibe combination had significant favourable effects than statin monotherapy across a diverse population of patients [25].

In this study, we evaluated the efficacy and safety of rosuvastatin-ezetimibe combination as compared to rosuvastatin alone. The effect on lipid profile was calculated after 12 weeks and 24 weeks of therapy. Our results showed that there was significantly higher percentage reductions in LDL-C (53.65 vs 41.13), TGs (26.29 vs 18.39) and TC (38.98 vs 28.91) and higher elevation in HDL-C (9.56 vs 7.08) in Group II (rosuvastatin+ezetimibe) as compared to Group I (rosuvastatin alone) after 12 weeks (p<0.01). Similarly, after 24 weeks of therapy, there was significantly higher reductions in LDL-C (57.39 vs 45.54), TGs (30.68 vs 21.88) and TC (41.92 vs 32.16) and higher elevation in HDL-C (7.73 vs 5.09) in Group II as compared to Group I (p<0.01).

Our study showed that after 24 weeks of therapy, the combination therapy resulted in an additional 11.8% reduction in LDL-C levels as compared to rosuvastatin monotherapy (57.39% vs 45.54%, p<0.01). Similarly, significant incremental changes were seen in other lipid parameters like TGs, TC and HDL-C. Our findings were consistent with the findings of other similar studies evaluating the efficacy of rosuvastatin-ezetimibe combination [26-32]. In a single blind, placebo-controlled study to evaluate the pharmacodynamic effects and safety of the rosuvastatin and ezetimibe coadministration, it was shown that after two weeks of therapy, rosuvastatin-ezetimibe combination resulted in an incremental change of -16.4% in LDL-C levels as compared to rosuvastatin alone (61.4% vs 44.9%). This incremental change is comparable to increasing the dose of statin alone therapy three times [26]. The EXPLORER study investigated the efficacy and safety of higher dose of rosuvastatin (40 mg) alone or in combination with ezetimibe 10 mg in high risk patients of coronary heart disease. 94% of patients on rosuvastatin/ezetimibe therapy achieved LDL-C goal as compared 79.1% of patients on rosuvastatin alone therapy at six weeks. Also, the combination therapy reduced LDL-C significantly more than rosuvastatin alone (-69.8% vs -57.1%, p <0.001). This showed that addition of ezetimibe can have additional benefit over and above the maximum statin alone therapy [27]. In a recent prospective randomized study on 51 patients over a duration of 6 months, LDL-C level was significantly reduced in the rosuvastatin-ezetimibe combination group (-55.8%) versus that in the monotherapy group (-36.8%) [30].

In addition to their synergistic effect in lipid lowering and achieving LDL-C targets, recent evidence using intravascular ultrasonography has shown that rosuvastatin-ezetimibe combination therapy also results in significant reduction in coronary atherosclerotic plaques in comparison to statin alone therapy. Further they also decrease high sensitivity C-Reactive Protein (hs-CRP) and inflammatory cytokines and improves the plaque stability [30,31].

In our study, both rosuvastatin-ezetimibe combination and rosuvastatin alone therapy were well tolerated. No significant difference was found in the two groups with regard to incidence of adverse effects. Common side effects seen were headache, musculoskeletal symptoms and gastrointestinal effects. There was no derangement in LFT in either group. Previous studies also showed that the combination of Rosuvastatin with ezetimibe was safe and well tolerated [19, 20].

LIMITATION

Our study had a limitation that it was restricted to the efficacy of combination therapy on the lipid profile of the patients. Patient outcomes including cardiovascular morbidity and mortality were not evaluated in our study. Another limitation could be the smaller sample size in our study. Further larger studies are warranted to evaluate the effect of rosuvastatin-ezetimibe combination on lipid profile and cardiovascular outcomes in CAD patients.

CONCLUSION

To conclude, combination of rosuvastatin with ezetimibe can be used as an effective and safe therapy in high risk patients of CAD, especially in patients in whom statin monotherapy is not able to achieve the target lipid levels.

REFERENCES

[1] Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet. 2006;367(9524):1747-57.
[2] Gupta R, Mohan I, Narula J. Trends in Coronary Heart Disease Epidemiology in India. Ann Glob Health. 2016;82(2):307-15.
[3] Dawber TR, Kannel WB. The Framingham study: An epidemiological approach to coronary heart disease. Circulation. 1966;34(4):553-55.
[4] Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? BMJ. 1994;308(6925):367-72.
[5] National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). 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) final report. Circulation. 2002;106:3143-421.

[6] Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, et al. Cholesterol Treatment Trialists' CTT Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376(9753):1670-81.
[7] Stein EA. The power of statins: aggressive lipid lowering. Clin Cardiol. 2003;26(4 Suppl 3):III25-31.
[8] LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. JAMA. 1999;282(24):2340-46.
[9] Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ. 2003;326(7404):1423.
[10] Heart Protection Study Collaborative Group. Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20,536 high-risk individuals: a randomised controlled trial. Lancet. 2011;378(9808):2013-20.
[11] Kotseva K, Wood D, De Backer G, De Bacquer D, Pyörälä K, Keil U; EUROASPIRE Study Group. EUROASPIRE III: a survey on the lifestyle, risk factors and use of cardioprotective drug therapies in coronary patients from 22 European countries. Eur J Cardiovasc Prev Rehabil. 2009;16(2):121-37.
[12] Frolkis JP, Pearce GL, Nambi V, Minor S, Sprecher DL. Statins do not meet expectations for lowering low density lipoprotein cholesterol levels when used in clinical practice. Am J Med. 2002;113(8):625-29.
[13] Lipka LJ. Ezetimibe: a first-in-class, novel cholesterol absorption inhibitor. Cardiovasc Drug Rev. 2003;21(4):293-312.
[14] Nutescu EA, Shapiro NL. Ezetimibe: a selective cholesterol absorption inhibitor. Pharmacotherapy. 2003;23(11):1463-74.
[15] Feldman T, Koren M, Insull W Jr, McKenney J, Schrott H, Lewin A, et al. Treatment of high-risk patients with ezetimibe plus simvastatin co-administration versus simvastatin alone to attain National Cholesterol Education Program Adult Treatment Panel III low-density lipoprotein cholesterol goals. Am J Cardiol. 2004;93(12):1481-86.
[16] Conard SE, Bays HE, Leiter LA, Bird SR, Rubino J, Lowe RS, et al. Efficacy and safety of ezetimibe added on to atorvastatin (20 mg) versus uptitration of atorvastatin (to 40 mg) in hypercholesterolemic patients at moderately high risk for coronary heart disease. Am J Cardiol. 2008;102(11):1489-94.
[17] Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller E, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). Am J Cardiol. 2003;92(2):152-60.
[18] Siddiqi SS, Misbahuddin, Ahmad F, Rahman SZ, Khan AU. Dyslipidemic drugs in metabolic syndrome. Indian J Endocrinol Metab. 2013;17(3):472-79.
[19] Padhy BM, Yadav R, Gupta YK. Hypolipidaemic and anti-inflammatory effects of fixed dose combination of atorvastatin plus ezetimibe in Indian patients with dyslipidaemia. Singapore Med J. 2013;54(2):90-95.
[20] Gagné C, Bays HE, Weiss SR, Mata P, Quinto K, Melino M, et al. Ezetimibe Study Group. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. Am J Cardiol. 2002;90(10):1084-91.
[21] Pearson TA, Denke MA, McBride PE, Battisti WP, Brady WE, Palmisano J. A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic patients: the ezetimibe add-on to statin for effectiveness (EASE) trial. Mayo Clin Proc. 2005;80(5):587-95.
[22] Bissonnette S, Habib R, Sampalis F, Boukas S, Sampalis JS; Ezetrol Add-On Investigators. Efficacy and tolerability of ezetimibe 10 mg/day coadministered with statins in patients with primary hypercholesterolemia who do not achieve target LDL-C while on statin monotherapy: A Canadian, multicentre, prospective study--the Ezetrol Add-On Study. Can J Cardiol. 2006;22(12):1035-44.
[23] Denke M, Pearson T, McBride P, Gazzara RA, Brady WE, Tershakovec AM. Ezetimibe added to ongoing statin therapy improves LDL-C goal attainment and lipid profile in patients with diabetes or metabolic syndrome. Diab Vasc Dis Res. 2006;3(2):93-102.
[24] Okada K, Kimura K, Iwahashi N, Endo T, Himeno H, Fukui K, et al. Clinical usefulness of additional treatment with ezetimibe in patients with coronary artery disease on statin therapy. - From the viewpoint of cholesterol metabolism. Circ J. 2011;75(10):2496-504.
[25] Morrone D, Weintraub WS, Toth PP, Hanson ME, Lowe RS, Lin J, et al. Lipid-altering efficacy of ezetimibe plus statin and statin monotherapy and identification of factors associated with treatment response: a pooled analysis of over 21,000 subjects from 27 clinical trials. Atherosclerosis. 2012;223(2):251-61.
[26] Kosoglou T, Statkevich P, Yang B, Suresh R, Zhu Y, Boutros T, et al.Pharmacodynamic interaction between ezetimibe and rosuvastatin. Curr Med Res Opin. 2004;20(8):1185-95.
[27] Ballantyne CM, Weiss R, Moccetti T, Vogt A, Eber B, Sosef F, et al; EXPLORER Study Investigators. Efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe in patients at high risk of cardiovascular disease (results from the EXPLORERstudy). Am J Cardiol. 2007;99(5):673-80.
[28] Stein EA, Ose L, Retterstøl K, Tonstad S, Schleman M, Harris S, et al. Further reduction of low-density lipoprotein cholesterol and C-reactive protein with the addition of ezetimibe to maximum-dose rosuvastatin in patients with severe hypercholesterolemia. J Clin Lipidol. 2007;1(4):280-86.
[29] Torimoto K, Okada Y, Mori H, Hajime M, Tanaka K, Kurozumi A, et al. Efficacy of combination of Ezetimibe 10 mg and rosuvastatin 2.5 mg versus rosuvastatin 5 mg monotherapy for hypercholesterolemia in patients with type 2 diabetes. Lipids Health Dis. 2013;12:137.
[30] Masuda J, Tanigawa T, Yamada T, Nishimura Y, Sasou T, Nakata T, et al. Effect of combination therapy of ezetimibe and rosuvastatin on regression of coronary atherosclerosis in patients with coronary artery disease. Int Heart J. 2015;56(3):278-85.
[31] Wang X, Zhao X, Li L, Yao H, Jiang Y, Zhang J. Effects of Combination of Ezetimibe and Rosuvastatin on Coronary Artery Plaque in Patients with Coronary Heart Disease. Heart Lung Circ. 2016;25(5):459-65.
[32] Kim KJ, Kim SH, Yoon YW, Rha SW, Hong SJ, Kwak CH, et al. Effect of fixed-dose combinations of ezetimibe plus rosuvastatin in patients with primary hypercholesterolemia: MRS-ROZE (Multicenter Randomized Study of ROsuvastatin and eZEtimibe). Cardiovasc Ther. 2016;34(5):371-82.

PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Medicine, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala, Haryana, India.
2. Assistant Professor, Department of Physiology, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala, Haryana, India.
3. Professor, Department of Medicine, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala, Haryana, India.
4. Associate Professor, Department of Medicine, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala, Haryana, India.
5. Assistant Professor, Department of Medicine, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala, Haryana, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Sandeep Joshi,
78, Ekta Vihar, Street No. 3, Ambala Cantt-133001, Haryana, India.
E-mail: sandeepj134@gmail.com

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