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Original Research Article

Evaluation of lipid lowering ability of atorvastatin and ezetimibe combination as compared with atorvastatin monotherapy

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ABSTRACT

Background: Many patients on statin therapy do not achieve recommended LDL cholesterol goals. They require either high dose statin regimen or combination of statins with other lipid modifying agents. Ezetimibe is a novel drug when added to statins, will provide additional reduction in LDL-C level.
Methods: Total 100 patients with CHD or hypertension and having serum LDL-C levels of ≥100 mg/dl were enrolled for the study and were randomly allocated to two groups. Baseline investigations done. Patients from Group I received Atorvastatin (10mg) per day orally and patients from group II received combination of Atorvastatin (10mg) and Ezetimibe (10mg) per day orally. Study treatment was started on the day of randomization and continued for 12 weeks and follow up visits were scheduled at 4, 8, and 12 weeks. During each follow up investigations repeated and patients were interviewed and examined for occurrence of any adverse effect.
Results: There was greater reduction in levels of LDL-C, Total cholesterol and serum triglycerides in patients treated with Atorvastatin plus Ezetimibe combination as compared to those patients treated with Atorvastatin alone. This difference in percentage reduction in LDL-C, Total cholesterol and serum triglycerides levels in two groups was highly significant at 4, 8 and 12 weeks ($p<0.01$).
Conclusions: Addition of Ezetimibe to Atorvastatin offers a very effective and well tolerated option for patients with CHD and hypertension having LDL-C levels of >100mg/dl as it significantly lowers the LDL-C along with total cholesterol and triglycerides.

Keywords: Hyperlipidemia, Lipoproteins, Low density lipoprotein cholesterol, Statins

INTRODUCTION

Coronary heart disease (CHD) is the leading cause of death in India and the leading cause of death worldwide.[1] Majority of patients of CVD have atherosclerosis and hyperlipidemia is a major cause of increased atherogenic risk.[2] Cholesterol contributes to the elevated lipid levels and recognition of hypercholesterolemia as a risk factor has led to the development of drugs that reduce cholesterol levels. statins are the most potent and commonly used drugs for treating hypercholesterolemia.[3] Lower dose regimens of statins are the most commonly prescribed regimens and each statin at a low recommended dose reduces LDL-C by 20-30%.[3,4] Even though statins are potent drugs, some patients require additional low density lipoprotein cholesterol (LDL-C) reduction beyond that achieved by lower dose statin regimens to attain the target levels recommended by the 'National cholesterol education program 2001 updated in 2004 Adult treatment panel III (NCEP 2004 ATP III).[6] These patients require either high dose statin regimen or combination therapy with statins and other lipid modifying agents.[4,5]

Statins at higher dose have been associated with increased incidence of hepatotoxicity and myalgias. Similarly combination therapy of statin with other lipid modifying agents (e.g. Fibric acid derivative, bile acid sequestrants and niacin) is often limited by an increased risk of side effects like intolerance, non-compliance, and drug interactions.[3,6,7] Ezetimibe is a novel drug that prevents the absorption of dietary and biliary cholesterol.

but is associated with compensatory increased cholesterol biosynthesis in the liver, whereas statins inhibit cholesterol production in the liver. Therefore, in combined therapy with these two classes of drugs would prove to be synergistic.[8-10] As mechanism of ezetimibe is different from that of statins, it provides additional reduction in LDL-C level, when given in combination with statins.[9]

Aims and objectives of the study were to compare the lipid lowering ability of atorvastatin and ezetimibe combination with atorvastatin monotherapy and to compare the adverse effect profile of atorvastatin and ezetimibe combination with atorvastatin monotherapy.

METHODS

This study was conducted at Medicine Department of a tertiary care hospital attached to Medical College.

Inclusion criteria

The patients with CHD and hypertension fulfilling following criteria were enrolled in the study.

Men and women ≥18 years of age with cardiovascular disease like coronary heart disease or hypertension, and having serum LDL-C levels of ≥100mg/dl.

Exclusion criteria

Whereas following patients were excluded from the study;

- Patients suffering from active or chronic hepatic disease.
- Patients with known coagulation disorder.
- Patients with impaired renal functions.

Total 100 patients were enrolled for the study, after obtaining their written informed consent, the patients were randomly allocated to two groups by chit method. Baseline investigations including Serum total cholesterol (Sr. total ch.), Serum LDL-C, Serum HDL-C, serum triglycerides (TG) levels, Serum Glutamate oxalate transaminase (SGOT), Serum Glutamate pyruvate transaminase (SGPT), Serum creatine phosphokinase (CPK) levels, Serum creatinine, Blood urea nitrogen (BUN) were done at the time of enrollment of patients (0 week).

Patients from Group I received Atorvastatin (10mg) per day orally and patients from group II received combination of Atorvastatin (10mg) and Ezetimibe (10mg) per day orally. All the patients also received other concurrently required medications such as, antihypertensive or antidiabetic drug etc. No patient used any other lipid lowering agent like bile acid sequestrants, fibrates or niacin.

Study treatment was started on the day of randomization and continued for 12 weeks and follow up visits were scheduled at 4, 8, and 12 weeks. During each follow up Sr. total ch., Sr. LDL-C, Sr. HDL-C, Sr. TG were estimated and they were interviewed and examined for occurrence of myalgia, jaundice or any other adverse effect. At 12 weeks CPK, SGOT, SGPT were repeated in all patients from both groups to check for the hepatotoxicity or myopathy that may be caused by statins.

Safety and efficacy end points

Efficacy measures

The primary efficacy end point was the mean percentage reduction in LDL-C concentration from baseline to final assessment. Along with it the secondary efficacy end points included the mean percentage change in Sr. T.G., Sr. total ch., Sr. HDL concentration from baseline to final assessment.

The percentage of patients who achieved NCEP ATP III target levels for LDL-C (≤100mg/dl and ≤70mg/dl) after 12 weeks of treatment was calculated and percentage of patients who achieved ≥30% reduction in LDL-C after 12 weeks of treatment was also calculated.

Safety and tolerability measures

At each visit patients were interviewed for occurrence of any adverse effect and physically examined during the study period. Safety and tolerability was also evaluated by reviewing results of laboratory tests at 12 weeks. Clinically significant laboratory abnormalities included elevations in levels of SGOT and SGPT to at least 3 times the upper limit of normal (ULN) and increase in levels of CPK ≥10 times ULN, in an asymptomatic patient. In symptomatic patient who had abdominal pain SGOT and SGPT were estimated when they were symptomatic.

Laboratory analytical methods

All analyses were conducted on fasting blood samples at Central Biochemistry Laboratory of the hospital.

Total cholesterol, HDL-C and triglycerides were measured using enzyme method and LDL-C was calculated using Friedewald equation [LDL-C=Total cholesterol-(TG/5)-HDL-C].

Table 1: Methods of estimation of serum lipid level.

Lipids	Method of estimation
Total cholesterol	Zak method/ (CHOD/PAP method)
Triglycerides	GPO/PAP method
HDL-C	PEG/CHOD-PAP method

Statistical analysis

Efficacy end points and safety end points in both treatment groups were analysed by 'z' test for difference between two population means and paired t-test. Patients who were lost to follow up were not included in the analysis. In analyses, p value <0.05 was considered statistically significant.

RESULTS

A total 100 patients were included in the study, 50 patients were allocated to Atorvastatin group and 50 patients to Atorvastatin and Ezetimibe combination group. During the study period one patient from Atorvastatin group and two patients from Atorvastatin and Ezetimibe group were lost to follow up and hence excluded from analysis. Thus 49 patients from Atorvastatin group and 48 patients from Atorvastatin plus Ezetimibe group were considered for analysis of data.

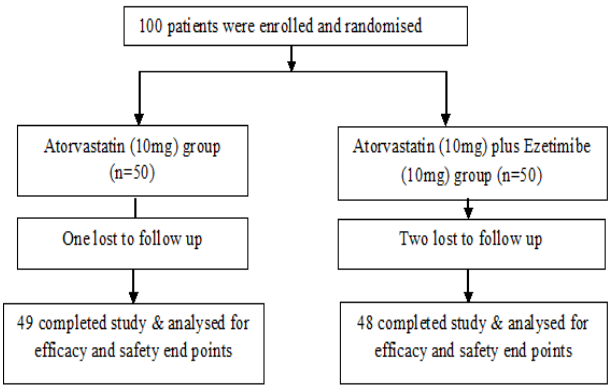

Figure 1: The study profile.

Baseline characteristics

Both the groups were comparable as regards to age, sex distribution, clinical features, concurrent drug therapy as there was no statistically significant difference between the two groups when analysed by 'Z' test (p >0.05) (Table 2).

Baseline mean lipid values

Baseline mean lipid values of both the groups were comparable because when analysed by 'Z' test there was no significant difference between the two groups (p>0.05) (Table 3).

Efficacy of treatment with atorvastatin and atorvastatin plus ezetimibe combination

Efficacy of treatment was assessed by studying changes in lipid values in two groups.

Table 2: Baseline characteristics including age, sex, clinical features and concurrent drug therapy of both treatment groups.

Variables	Atorvastatin (10 mg) N=49	Atorvastatin (10 mg) plus ezetimibe (10mg) N=48	P value
Age (Mean)	54.44	52.64	>0.05
Sex distribution			
Male	26	24	>0.05
Female	23	24	>0.05
Clinical features			
CHD	30	32	> 0.05
HTN	26	23	>0.05
DM	9	10	>0.05
CVA	4	4	>0.05
AS	0	1	>0.05
Concurrent drug therapy			
Aspirin	34	37	>0.05
Clopidogrel	34	37	>0.05
Enalapril	22	20	>0.05
Atenelol	16	15	>0.05
Calcium channel blockers	3	2	>0.05
Oral antidiabetic drugs	9	10	>0.05

Table 3: Baseline mean lipid values in two treatment groups.

Baseline lipid values	Atorvastatin	Atorvastatin plus ezetimibe	P value
LDL-C	131	135	>0.05
Total cholesterol	196	193	>0.05
Triglycerides	118	116	>0.05
HDL-C	41	41	>0.05

Percentage reduction in LDL-C levels

Table 4: Percentage reduction in levels of LDL-C in both treatment groups.

Group	Atorvastatin	Atorvastatin plus ezetimibe	P value
4 weeks	6	16	<0.01
8 weeks	11	26	<0.01
12 weeks	27	44	<0.001

There was greater reduction in levels of LDL-C in patients treated with Atorvastatin plus Ezetimibe combination as compared to those patients treated with Atorvastatin alone. Average percentage reduction in levels of LDL-C in atorvastatin treated group was 6,11,27 at 4, 8 and 12 weeks respectively, while it was 16, 26 and 44 in atorvastatin plus Ezetimibe combination treated group. This difference in percentage reduction in LDL-C

levels in two groups was highly significant at 4, 8 and 12 weeks (p <0.01) (Table 4).

Table 5: Percentage of patients who achieved target levels of LDL-C ≤100mg/dl in the two groups.

Group	Atorvastatin	Atorvastatin plus ezetimibe	P value
4 weeks	4%(2/49)	31%(15/48)	<0.01
8 weeks	18%(9/49)	62%(30/48)	<0.001
12 weeks	30%(15/49)	100%(48/48)	<0.001

Proportion of patients reaching the target LDL-C levels

Percentage of patients who achieved target levels of LDL-C ≤100mg/dl.

Table 6 shows percentage of patients who achieved target levels of LDL-C ≤100mg/dl at 4 weeks, 8 weeks and 12 weeks. It was seen that significantly higher percentage of patients from Atorvastatin plus Ezetimibe group achieved the target level of ≤100mg/dl LDL-C as compared to Atorvastatin alone group at 4, 8 and 12 weeks (p value <0.01).

Table 6: Percentage of patients who achieved levels of LDL-C ≤70mg/dl.

Group	Atorvastatin	Atorvastatin plus ezetimibe	P value
4 weeks	0%(0/49)	0%(48/48)	-
8 weeks	0%(0/49)	0%(48/48)	-
12 weeks	0%(0/49)	16%(8/48)	<0.01

Percentage of patients who achieved target levels of LDL-C ≤70mg/dl.

None of the patients from either treatment group reached levels of LDL-C ≤ 70 mg/dl at 4 weeks and 8 week.

At 12 weeks, 16% of patients in Atorvastatin plus Ezetimibe group attained LDL-C levels of ≤70 mg/dl but no patient from Atorvastatin group could attain this level of ≤ 70 mg/ dl and this difference between the two groups was highly significant (p <0.01).

Percentage of patients who achieved ≥30% reduction in target levels of LDL-C.

None of the patient from either treatment group achieved ≥30% reduction in levels of LDL-C at 4 weeks.

At 8 and 12 weeks also, no patient from Atorvastatin group achieved ≥30% reduction in levels of LDL-C. However 30% and 94% of patients achieved ≥30% reduction in LDL-C at 8 and 12 weeks respectively in Atorvastatin plus Ezetimibe combination group. This difference in two groups at 8 and 12 weeks was highly significant (p <0.001).

Table 7: Percentage of patients achieving ≥30% reduction in levels of LDL-C in two groups.

Group	Atorvastatin	Atorvastatin plus ezetimibe	P value
4 weeks	0%(0/49)	0%(48/48)	-
8 weeks	0%(0/49)	30%(14/48)	<0.001
12 weeks	0%(0/49)	94%(45/48)	<0.001

Percentage reduction in levels of total cholesterol and sr. triglycerides in the two treatment groups

There was greater reduction in the levels of total cholesterol and sr. triglycerides in Atorvastatin plus Ezetimibe combination group as compared with Atorvastatin alone group. This difference in percentage reduction in total cholesterol in two groups was highly significant at 4, 8 and 12 weeks (p<0.01).

Table 8: Percentage reduction in levels of total cholesterol and sr. triglycerides in the two treatment groups.

Lipid levels	Total cholesterol			Sr. triglycerides		
Groups	**Atorvastatin**	**Atorvastatin plus ezetimibe**	**P value**	**Atorvastatin**	**Atorvastatin plus ezetimibe**	**P value**
4 weeks	5	12	<0.01	6	15	<0.01
8 weeks	10	18	<0.01	11	21	<0.01
12weeks	14	25	<0.01	14	26	<0.01

Changes in mean values of HDL-C

At 4 weeks both therapies did not change mean levels of HDL-C. At 8 weeks both therapies led to slight rise in level of HDL-C which is statistically non significant, whereas at 12 weeks Atorvastatin plus Ezetimibe combination therapy led to statistically significant rise in levels of HDL-C.

Safety and tolerability measures

There was no occurrence of any serious adverse event in any patients during this study. Minor adverse effects in form of nausea, headache, bodyache or abdominal pain were encountered in both groups. These adverse events were mild and self limiting, hence did not require discontinuation of the study drugs.

Table 9: Changes in mean values of HDL-C in these two treatment groups.

Groups	Atorvastatin	Atorvastatin plus ezetimibe	P value
Baseline	41	41	-
4 weeks	41	41	-
8 weeks	43	43	-
12 weeks	43	44	>0.05

Table 10: Incidence of adverse effects in both treatment groups.

Adverse effects	Atorvastatin group (N=49)		Atorvastatin plus ezetimibe group (N=48)		P Value
	No. of patients	%	No. of patients	%	
Nausea	3	6%	4	8%	>0.05
Headache	1	2%	2	4%	>0.05
Bodyache	3	6%	1	2%	>0.05
Abdominal pain	2	4%	1	2%	>0.05

Table 10 gives the comparative data regarding the percentage of patients who reported a particular adverse effect like nausea, headache, bodyache or abdominal pain in the two treatment groups. There was no statistically significant difference in the incidence of these adverse effects in two treatment groups (p >0.05).

Although a total of three patients from both the groups experienced abdominal pain, their SGOT and SGPT levels were within normal range ruling out the likelihood of liver dysfunction. At 12 weeks there was elevations of hepatic enzymes in two patients in Atorvastatin group and three patients in Atorvastatin plus Ezetimibe group but it was clinically not significant as these enzymes were below three times of upper normal limit and these patients were asymptomatic. During this study no patient from either group showed clinical signs of liver dysfunction like jaundice.

All patients from both treatment groups had renal function within normal limits at 12 weeks. No musculoskeletal adverse effects like myalgia, rhabdomyolysis was encountered and no patient from either group had an increase in Sr. CPK levels at 12 weeks.

DISCUSSION

Cardioprotective effect of statins is not only due to cholesterol reduction, it is beyond LDL-C reduction.[11-15] Many pleiotropic effects of statin are demonstrated by different studies.[12,13,16] Although statins have proven efficacy, some of the patients needs higher dose of statin or combination of statin with other lipid lowering agent. Use of other lipid lowering agents is often limited by an increased risk of side effects like intolerance, non-compliance, and drug interactions. Ezetimibe inhibits cholesterol absorptionby inhibiting the transport protein NPC1L1. The actions of ezetimibe are complementary to those of statins.

In the present study, lipid lowering ability and tolerability of Atorvastatin plus Ezetimibe combination therapy was compared with that of Atorvastatin alone in patients with CHD and hypertension.

We included the patients with CHD or hypertension as lipid lowering is recommended (LDL ≤70mg /dl in very high risk and LDL-C ≤100mg/dl in high risk patients) according to NCEP ATP III guidelines.[6] Patients enrolled in the study received either Atorvastatin (10 mg) or a fixed dose combination of Atorvastatin plus Ezetimibe (10mg+10mg).[8]

The rationale for combining Atorvastatin and Ezetimibe is that these drugs have different mechanism of action and possibly have additive effect in lowering LDL-C levels. Atorvastatin in dose of 10mg achieves approximately 30% reduction in LDL-C and Ezetimibe when used as monotherapy lowers LDL-C levels by 1520%.[3,8]

In our study at the end of 12 weeks we found that that co-administration of Ezetimibe with Atorvastatin caused a significantly greater reduction in LDL-C as compared with Atorvastatin alone. Co-administration of Ezetimibe with Atorvastatin provided 44% reduction in LDC-C, which is much greater than 27% reduction achieved with Atorvastatin alone. This difference in percentage reduction between the two groups, was statistically highly significant (p<0.01).**

In addition, more patients in the combination group of Atorvastatin plus Ezetimibe achieved the target levels of LDL-C ≤100mg/dl goal (as defined by the NCEP ATP III guidelines).[6] In our study LDL-C was above ATP III target of 100 mg/dl at the baseline in all the patients. At 12 weeks the ATP III target of ≤100mg/dl was achieved in 100% (48/48) of patients receiving combination therapy as opposed to 30 % (15/49) with Atorvastatin monotherapy. The difference between the two treatment groups in the percentage of patients achieveing ATP III LDL-C target was very highly significant. In our study 16% of patients from Atorvastatin plus Ezetimibe group reached the target goal of LDL-C ≤70mg/dl while none of the patients from Atorvastatin monotherapy group achieved the same (as defined by the NCEP ATP III guidelines).[6] The results of our study showed that 94% of the patients from Atorvastatin plus Ezetimibe combination group achieved a percentage reduction of ≥30% in LDL-C whereas no patient from Atorvastatin monotherapy group achieved a reduction of ≥30%. whereas more intensive regimens as reported by Cannon et al lower LDL-C by 45 to 50 % and CVD events by as much as 50%.[11] However in our study we have evaluated how many patients achieved ≥30% reduction in LDL-C

as NCEP ATP III guidelines stipulate a figure of ≥30% reduction in LDL-C in patients of CHD.

In addition to the LDL-C lowering effects, combination therapy also produced favourable effects on other lipid related variables including significant reduction in total cholesterol and triglycerides when compared with Atorvastatin monotherapy.

In our study, at the end of 12 weeks percentage reduction in total cholesterol was 25% with combination therapy and 14% with Atorvastatin alone.

At the end of 12 weeks combination therapy with Atorvastatin and Ezetimibe produced a significant rise in levels of HDL-C when compared with baseline levels however Atorvastatin monotherapy after 12 weeks resulted in a slight rise in the levels of HDL-C which was statistically not significant. When the increase in HDL-C levels at 12 weeks in both groups was compared, the difference was statistically not significant.

The safety and tolerability elicited by both drugs in present study were consistent with previous studies. The combination of Ezetimibe plus Atorvastatin was well tolerated, with an overall safety profile similar to that of Atorvastatin alone. The most commonly noted adverse events were nausea, headache and abdominal pain. The adverse events were mild and none of the patients from either group discontinued the study drugs because of it. All elevations in hepatic enzymes were asymptomatic and no hepatitis or jaundice was observed in any of the patients. No case of rhabdomyolysis was encountered and none of the patients from either group had elevated CPK levels suggestive of increased risk of myopathy.

Cardioprotective effect of statins is not only due to cholesterol reduction, it is beyond LDL-C reduction.[11-15] Many pleiotropic effects of statin are demonstrated by different studies.[12,13,16] Although statins have proven efficacy, some of the patients needs higher dose of statin or combination of statin with other lipid lowering agent. Ezetimibe can be added to ongoing statin therapy in order to reduce the dose of statins in patients who can't tolerate higher dose of statin.[17]

CONCLUSION

The results of this study demonstrate that Atorvastatin plus Ezetimibe combination therapy results in a greater percentage reduction in LDL-C, T. Cholesterol and triglycerides when compared with Atorvastatin monotherapy. Significantly more no. of patients receiving combination therapy attained the LDL-C target levels (≤100mg/dl or ≤70mg/dl) or 30% reduction in LDL-C levels as stipulated by NCEP ATP III guidelines. Combination was well tolerated, with an overall safety profile similar to that of Atorvastatin alone.

Therefore, we conclude that addition of Ezetimibe to Atorvastatin offers a very effective and well tolerated option for patients with CHD and hypertension having LDL-C levels of >100mg/dl.

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