ABSTRACT

Hypercholesterolemia is a major risk factor for cardiovascular disease. Low-density lipoprotein cholesterol is an established risk factor for atherosclerotic disease, particularly coronary artery disease (CAD); therefore, management of high serum LDL-C levels is the most important goal in the treatment of dyslipidemia. Since therapy with statins alone fails to achieve the targeted LDL-C values with lesser side effects it is better to try a combination therapy having high efficacy and safety profile. This study compared the efficacy and safety of the combination of Atorvastatin 10 mg + Ezetimibe 10 mg versus Atorvastatin 10 mg alone in lowering LDL-C in newly diagnosed dyslipidemic patients. Besides, it compared the efficacy of the two drugs in lowering the TC, TG, and TC/HDL-C and LDL/HDL-C ratio. We also compared the increase in HDL-C in the two groups at the end of 12 weeks. This study was conducted on 60 hypercholesterolemic patients in SreeBalaji Medical College Hospital. The patients were randomly divided into two groups of 30 each. Group 1 was given Atorvastatin 10 mg + Ezetimibe 10 mg while Group 2 was given Atorvastatin 10 mg. The Lipid Profile, biochemical and hematological tests, clinical examination were done on Day 0, 6th week, and 12th week and these results were compared the group and
between groups from 0 to 6th week and 6th week to 12th week and 0 to 12th week. The results from our study indicated that Combination therapy with Atorvastatin 10 mg + Ezetimibe 10 mg is superior to Atorvastatin 10 mg alone in reducing LDL-C, TC, TC/HDL-C ratio and raising the HDL-C levels at the end of 12 weeks. Thus the study implies that combination therapy is superior to monotherapy in the high-risk group of dyslipidemia patients.

Keywords: Hypercholesterolemia; atorvastatin; ezetimibe; monotherapy.

1. INTRODUCTION

Dyslipidemias are disorders of lipoprotein metabolism, including overproduction of lipoprotein or their deficiency. These disorders may be manifested by elevation of the serum total cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride concentrations and, a decrease in the high-density lipoprotein (HDL) cholesterol concentration [1]. From a clinical perspective, dyslipidemia can be divided into hypercholesterolemia, hypertriglyceridemia, mixed hyperlipidemia, and disorders of HDL metabolism [2].

Primary dyslipidemia typically refers to a genetic defect in the lipid metabolism that causes abnormal lipid levels. Secondary dyslipidemia may be due to a variety of reasons; environmental factors, diseases like type 2 diabetes, hypothyroidism, obstructive jaundice etc. and medications like thiazide diuretics, progestin, anabolic steroids etc. These abnormalities in lipid metabolism give rise to a large number of disease states, and, among these, the most important is atherosclerosis, leading to various cardiovascular diseases [2].

Cardiovascular disease (CVD) related to atherosclerosis of the arterial vessel wall and thrombosis remains a leading cause of morbidity and mortality in the world 10. Hyperlipidemia is a major cause of atherosclerosis and atherosclerosis-induced conditions, such as coronary heart disease (CHD), ischemic cerebrovascular disease and peripheral vascular disease [2].

As the incidence of coronary heart disease is increased two to three folds in diabetics and hypertensive patients, the early detection and treatment of dyslipidemia with lipid-lowering agents are essential. Treatment of hypercholesterolemia with statins has reduced the relative risk of cardiovascular events in dyslipidemic patients, but most patients require treatment with multiple agents to reach the target LDL values [3].

A significant proportion of dyslipidemic patients do not meet the lipid targets recommended in current NCEP ATP-III guidelines, despite treatment with available statins. Moreover, the residual risk of major cardiovascular events remains high [4,5]. So there exists a need for more potent drugs with a lowrisk of adverse events and drug-to-drug interaction. So combination therapy with agents differing in their mechanism of action, but complement the action of the lowdose of statins may provide significant advantages over statin monotherapy [6].

Ezetimibe is a new class of hypo lipidemic drug which inhibits the intestinal absorption of cholesterol. The action of Ezetimibe 10 mg plus a 10 mg dose of a statin is equivalent to that of a statin alone at higher doses, such as 80 mg of simvastatin or 40 mg of Atorvastatin. It is used (10 mg daily) to reduce the amount of total cholesterol, LDL cholesterol and also, there are no differences in the liver or muscle-related side effects while combined with statin therapy [7,8].

With this background information and the availability of newer combination drugs with more potency, fewer drug interactions and many added advantages considering the longevity of treatment required for dyslipidemia, the present study was planned to evaluate and compare the efficacy and safety of Atorvastatin 10 mg versus Atorvastatin 10 mg plus Ezetimibe 10 mg combination therapy in newly diagnosed dyslipidemic patients.

2. MATERIALS AND METHODS

The prospective, comparator-controlled, randomized, open, parallel group and 2- arm study. Hypercholesterolemic patients attending outpatient Department of Endocrinology of Sree Balaji Medical College and Hospital, Chromepet, Chennai.

The total sample size consisted of 60 patients. The total duration of the study was 12 weeks.

Study group 1: Tablet Atorvastatin10 mg+Ezetimibe10 mg once daily.
Study group 2: Tablet Atorvastatin 10 mg once daily.

The screening procedure consisted of a detailed medical and drug history, thorough clinical examination followed by laboratory investigations – which included fasting lipid profile, the liver function tests and Fasting blood sugar. Total 150 patients were screened, among them 60 participants were selected for the study. All the patients were made to undergo baseline investigations before enrollment. Patients were explained the detailed study pattern, possible risks and benefits of study drugs, following which, informed written consent was obtained from all patients in their own language before enrolling them into the trial. Case record forms were prepared for each of the patients and kept with the investigator.

2.1 Randomization

The study subjects were randomly assigned using simple block randomization method to either of the two groups Group 1 and Group 2, each group consisting of 30 patients.

2.2 Group Allocation

Group 1 – Patients in this group treated with a combination of Tab Atorvastatin with Ezetimibe.

Group 2 – Patients in this group treated with Tab. Atorvastatin once daily

Dosage regimen - Study Group 1 Tab. Atorvastatin 10 mg + Ezetimibe 10 mg once daily for 12 weeks.

Study Group 2 Tab. Atorvastatin 10 mg once daily for 12 weeks.

Patients were advised to take one tablet daily after dinner with half a glass of water. At the first visit, tablets were given for 6 weeks according to the above dosage regimen. Drug compliance was assessed and the appropriate amount of tablets was given for the next visits at 6th week and 12th week. The physical, general, and systemic examinations were repeated at 6th week and 12th weeks. The lipid profile, the liver function tests and blood sugar analysis were repeated at the 6th and 12th week. Adverse events were enquired and monitored during all the visits. The administration of the drug was continued after the duration of the study in accordance to the physician’s discretion.

Blood sugar levels were monitored and maintained under normal levels by treating the patient with oral hypoglycemic agents as advised by the endocrinologist. Standard therapies for underlying disease as received by the patients before enrolment were allowed to continue without any changes.

Blood samples were collected with the patient fasting for at least 12 h. Biochemical and hematological measurements were done at the central laboratory of SreeBalaji medical college. This was measured by an automated enzymatic method. Blood samples were collected once before randomization, the 6th week, 12th week. The following investigations were done during the study period:

- Lipid Profile: LDL-C, HDL-C, Total Cholesterol, Triglycerides, Total Cholesterol/HDL-C ratio, LDL-C / HDL-C ratio.
- Fasting blood sugar level.
- Serum ALT and Serum AST

All patients are questioned about adverse events at each follow up visit. Safety assessment included biochemical blood tests; physical, general and systemic examination was done.

2.3 Statistical Analysis

The study subjects of Atorvastatin 10mg - Ezetimibe 10 mg were taken as Group 1 and the Atorvastatin 10 mg was treated as Group 2. The two groups were matched in respect of their age, sex and baseline lipid profiles such as Total Cholesterol, LDL and HDL, Triglycerides, TC/HDL and LDL / HDL ratio. In the above matching the measurable variables were analyzed by independent students' \( t \) test and the categorical variables matching were done by Chi-square (\( \chi^2 \)) test. The improvement or efficacy of the drug within the group i.e. base through 12th week was analyzed by Students paired \( t \) test. The efficacy of the drug between groups (base to 12th week) was analyzed by independent students \( t \) test. The above statistical procedures were performed with available appropriate standard statistical packages. The \( P \) – values less than 0.05 (\( P<0.05 \)) were treated as statistically significant in two-tailed test.

3. RESULTS AND DISCUSSION

3.1 Matching of the two groups

The two groups were matched in respect of their age and lipid profile before undergoing the respective treatment.
The age and lipid profiles of the two groups were matched in the above Table 1.

The number of males and females of the two groups were matched in the above Table 2.

The improvements of the drug from baseline to 12 weeks were compared between the groups to identify the superiority of the drug in the improvement of the lipid profile.

In the Table 3, the improvements of TC between the two groups were compared. The reduction of 86.6±18.8 mg/dl TC by drug Atorvastatin 10 mg-Ezetimibe 10 mg (group-1) was significantly greater than the reduction of 59.6±14.0 mg/dl TC by drug Atorvastatin 10 mg (group-2). The reduction is statistically very highly significant (P<0.001).

The above improvements (reductions) were statistically very highly significant (P<0.001).

In the Table 4, the improvements of LDL between the two groups were compared. The reduction of 83.4±19.5 mg/dl LDL by drug Atorvastatin 10 mg -Ezetimibe 10 mg (group-1) was significantly greater than the reduction of 56.6±11.8 mg/dl LDL by drug Atorvastatin 10 mg (group-2). The reduction is statistically very highly significant (P<0.001).

In the Table 5, the improvements of HDL between the two groups were compared. The increase of 6.4±2.4 mg/dl HDL by drug Atorvastatin 10mg + Ezetimibe 10 mg (group-1) was significantly greater than the increase of 4.1±1.6 mg/dl HDL by drug Atorvastatin 10 mg (group-2). The increase was statistically significant (P<0.001).

Table 1. Matching of the two groups according to their age and baseline Lipid profile

| Variable   | Group1. (Atv+Ezt) n= 30 | Group 2. (Atv) n=30 |
|------------|-------------------------|---------------------|
| Age(years) | 53.1 ± 6.3              | 53.9 ± 7.0          |
| TC         | 246.6 ± 19.3            | 238.0 ± 11.8        |
| LDL        | 171.3 ± 19.1            | 162.9 ± 13.4        |
| HDL        | 42.7 ± 4.8              | 42.6 ± 4.4          |
| TG         | 157.3 ± 19.6            | 157.0 ± 12.8        |
| TC/HDL     | 5.67 ± 0.7              | 5.6 ± 0.6           |
| LDL/HDL    | 4.0 ± 0.7               | 3.8 ± 0.7           |

Table 2. Matching of the two groups according to their sex

| Sex        | Group-1 (Atv+Ezt) | Group-2 (Atv) | Total |
|------------|-------------------|---------------|-------|
|            | No    | %   | No   | %   | No   | %   |
| Male       | 15    | 50.0| 17   | 56.7| 32   | 53.3|
| Female     | 15    | 50.0| 13   | 43.3| 28   | 46.7|
| Total      | 30    | 100.0| 30   | 100.0| 60   | 100.0|

Table 3. Comparison of TC reduction between the groups 1 and 2 from base to 12th week

| Period | Group-1 (Atv+Ezt) | Group-2 (Atv) | Difference b/w means | Significance |
|--------|-------------------|---------------|----------------------|-------------|
| B to 12th W | 86.6 ± 18.8 | 59.6 ± 14.0 | 27.0 | P<0.001 |

Table 4. Comparison of LDL reduction between the groups 1 and 2 from base to 12th week

| Period | Group-1 (Atv+Ezt) | Group-2 (Atv) | Difference b/w means | Significance |
|--------|-------------------|---------------|----------------------|-------------|
| B to 12th W | 83.4 ± 19.5 | 56.6 ± 11.8 | 26.8 | P<0.001 |
In the Table 6, the improvements of TG between the two groups were compared. The reduction of 47.6±19.1 mg/dl TG by drug Atorvastatin 10mg - Ezetimibe 10 mg (group-1) was not significantly greater than the reduction of 41.7±9.4 mg/dl TG by drug Atorvastatin 10 mg (group-2). The reduction was not statistically significant (P>0.05).

In the Table 7, the improvements of TC/ HDL ratio between the two groups were compared. The reduction of 2.5±0.4 TC/ HDL ratio by drug Atorvastatin 10 mg - Ezetimibe 10 mg (group-1) was significantly greater than the reduction of 1.9±0.4 TC/ HDL ratio by drug Atorvastatin 10 mg (group-2). The reduction was statistically very highly significant (P<0.001).

In the Table 8, the improvements of LDL/HDL ratio between the two groups were compared. The reduction of 2.2±0.6 LDL/HDL ratio by drug Atorvastatin 10 mg - Ezetimibe 10 mg (group-1) was significantly greater than the reduction of 1.6±0.6 LDL/HDL ratio by drug Atorvastatin 10 mg (group-2). The reduction was statistically very highly significant (P<0.001).

The mean percentages of reduction between the two groups in TC and LDL were statistically very highly significant (p<0.001). The increase of mean percentage of HDL between the two groups was statistically very highly significant (p<0.001). But the mean percentage of reduction of TG is not statistically significant (P>0.05).

### Table 5. Comparison of HDL increase between the groups 1 and 2 from base to 12th week

| Period      | Group-1 (Atv+Ezt) | Group-2 (Atv) | Difference b/w means | Significance |
|-------------|-------------------|---------------|----------------------|--------------|
| B to 12th W | 6.4 ± 2.4         | 4.1 ± 1.6     | 2.3                  | P<0.001      |

### Table 6. Comparison of TG reduction between the groups 1 and 2 from base to 12th week

| Period      | Group-1 (Atv+Ezt) | Group-2 (Atv) | Difference b/w means | Significance |
|-------------|-------------------|---------------|----------------------|--------------|
| B to 12th W | 47.6 ± 19.1       | 41.7 ± 9.4    | 5.9                  | P=0.132      |

### Table 7. Comparison of TC/ HDL reduction between the groups 1 and 2 from base line to 12th week

| Period      | Group-1 (Atv+Ezt) | Group-2 (Atv) | Difference b/w means | Significance |
|-------------|-------------------|---------------|----------------------|--------------|
| B to 12th W | 2.5 ± 0.4         | 1.9 ± 0.4     | 0.6                  | P<0.001      |

### Table 8. Comparison of LDL/HDL ratio reduction between the groups 1 and 2 from base to 12th week

| Period      | Group-1 (Atv+Ezt) | Group-2 (Atv) | Difference b/w means | Significance |
|-------------|-------------------|---------------|----------------------|--------------|
| B to 12th W | 2.2 ± 0.6         | 1.6 ± 0.6     | 0.6                  | P<0.001      |

### Table 9. Comparison of percentages of improvements between groups

| Variable | Group1 (Atv+Ezt) | Group 2 (Atv) | Difference | Significance |
|----------|------------------|---------------|------------|--------------|
| TC       | 32.1 ±7.0        | 22.1 ± 4.3    | 10.0       | P<0.001      |
| LDL      | 48.2 ± 7.6       | 34.6 ± 5.7    | 13.6       | P<0.001      |
| HDL      | 14.9 ± 6.5       | 9.7 ± 4.1     | 5.2        | P<0.001      |
| TG       | 29.7 ± 10.4      | 26.5 ± 5.6    | 3.2        | P=0.146      |
In population studies, the serum total cholesterol is a good surrogate for LDL-cholesterol levels. The Framingham Heart Study [9], the Multiple Risk Factor Intervention Trial (MRFIT) [9], and the Lipid Research Clinics (LRC) [10] trial found a direct relationship between levels of LDL cholesterol (or total cholesterol) and the rate of new-onset CHD in men and women who were initially free of CHD.

3.2 Effect on LDL-C

Low-density lipoprotein cholesterol (LDL-C) remains the primary target of lipid-lowering therapy. Achieving LDL-C goals as outlined by the National Cholesterol Education Program Adult Treatment Panel III can be difficult with statins alone; therefore, adjunctive therapy is often indicated to reduce cardiovascular risk.

In this study comparing the effect of Atorvastatin in combination with Ezetimibe and Atorvastatin monotherapy, there is a mean percentage reduction of 48.2% and 34.6% respectively in LDL cholesterol levels after 12 weeks of treatment. The mean percentage reductions in both the groups are statistically significant. In a double-blinded study with 628 patients with the same combination of drugs and monotherapy of statins the LDL-C levels wereevauated after 12 weeks of treatment. Coadministration of Ezetimibe provided a significant additional 12% reduction in LDL-C [11].

Low-density lipoprotein cholesterol (LDL-C) remains the primary target of lipid-lowering therapy. Achieving LDL-C goals as outlined by the National Cholesterol Education Program Adult Treatment Panel III can be difficult with statins alone; therefore, adjunctive therapy is often indicated to reduce cardiovascular risk.

3.3 Effect on Total Cholesterol

In this study comparing the effect of Atorvastatin in combination with Ezetimibe and Atorvastatin monotherapy, there is a mean percentage reduction of 32.1 and 22.1 respectively in total cholesterol levels after 12 weeks of treatment. Wolffenbuttel et al in his study with 78 patients taking 5 mg Atorvastatin alone were evaluated for the reduction in the levels of total and LDL cholesterol at 4th week of treatment, the study found a reduction in the levels of total and LDL cholesterol by 21 and 27% respectively [12]. In a meta-analysis study with 26 trials involving

![Comparison of percentages of improvements between groups](image-url)
38,817 participants, for the effect of Atorvastatin on cholesterol profile, the study concluded that there is a dose dependant reduction in the levels of LDL cholesterol and total cholesterol after 3 to 12 weeks of treatment [13].

Ezetimibe decreases the intestinal absorption of cholesterol and hence reducing the levels of total cholesterol and LDL. Sudhop in his study evaluated the effect of Ezetimibe (10 mg/d) on cholesterol absorption and synthesis, sterol excretion, and plasma concentrations of cholesterol and no cholesterol sterols in 18 patients. After a 2 week period it was found that there was 54% reduction in cholesterol absorption which was highly significant compared to the placebo group in the randomized double blind, placebo-controlled, crossover study [14].

3.4 Effect on HDL Cholesterol

There was a statistically significant increase in HDL-C level in the present study in both the treatment group. An increase of 14.9% in baseline HDL-C level was seen in a group of patients taking Atorvastatin along with Ezetimibe at the end of the study. In the Atorvastatin monotherapy group an increase of 9.7% in baseline HDL-C level at the end of study. The difference between both the groups was 5.2% which showed that combination therapy is more effective in increasing HDL-C levels than Atorvastatin monotherapy. In a double-blind, placebo-controlled study with 769 patients of hypercholesterolemia treated with a combination of Ezetimibe with statin and statin monotherapy showed only a 1% increase in HDL cholesterol as compared to our study showing about 5.2% which was statistically significant. Ballantyne et al in his study with 628 patients reported a significant increase of 3% in HDL-C when Atorvastatin was administered with Ezetimibe [15].

3.5 Effect on Triglycerides, TC/ HDL, LDL/HDL

There are varying reports on the role of Ezetimibe in the reduction of Triglycerides. Samaha et al in their study with 84 patients taking Ezetimibe 10mg reported no significant reduction in levels of triglycerides after 12 weeks of therapy [16]. In our study also there is no significant reduction in the levels of triglyceride on the 12th week in between the groups. In another study with 827 patients, there was a decline in triglyceride levels after Ezetimibe combination therapy but there was no statistical significance [17-20].

The TC/HDL-C ratio was also decreased significantly in the present study in both the groups. TC/HDL-C ratio in combination therapy group was a mean reduction of 3.5 as compared to 2.9 reductions in patients taking Atorvastatin monotherapy from the baseline. TC/HDL-C ratio at the end of the study was showed to be statistically significant. Similarly, there was a significant reduction in LDL/HDL-C levels after 12 weeks of treatment in both the groups with combination therapy group showing a statistically significant mean reduction of 2.2 as compared to Atorvastatin monotherapy 1.6.

4. CONCLUSION

Atorvastatin 10mg in combination with Ezetimibe 10mg is more effective in the reduction of Total Cholesterol, LDL Cholesterol, and TC/HDL-C and LDL/HDL-C levels and increases HDL-C levels as compared to Atorvastatin 10mg monotherapy after 12 weeks of treatment. Atorvastatin with Ezetimibe showed efficient activity in the study.

CONSENT AND ETHICAL APPROVAL

This study was conducted in compliance with the protocol, after getting approval from the Institutional Ethics Committee (IEC), and according to informed consent regulations and the ICH/GCP Guidelines. Informed written consent was obtained from all patients in their own language before enrolling them into the trial.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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