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EFFICACY OF EZETIMIBE ADDED TO STATIN THERAPY IN PATIENTS WITH FAMILIAL HYPERCHOLESTEROLEMIA

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ABSTRACT

Objective: Cardiovascular diseases (CVD) are known to pose one of the major threats to life today, especially in developed countries. The main objective of the study is to find the efficacy of ezetimibe added to statin therapy in patients with familial hypercholesterolemia.

Method: This randomized control trial (RCT) study was conducted at Punjab Institute of Cardiology Lahore from 1st July 2023 to 31st December 2023. Data were collected from 185 patients. Blood samples were collected at baseline and at monthly intervals to measure lipid profiles. The efficacy analysis was conducted on an intention-to-treat basis, including all patients who received at least one dose of the study medication and had at least one post-baseline efficacy assessment.

Results: We collected data from 185 patients. The baseline characteristics were well-matched between the groups, with an average age of 49.01 ± 10.28 years in the ezetimibe group and 50.01 ± 11.23 years in the placebo group, and both groups having 54% male participants. Baseline LDL-C levels were similar, with the ezetimibe group at 200 ± 30 mg/dL and the placebo group at 198 ± 32 mg/dL. 35% (32 patients) of the ezetimibe group achieved LDL-C levels below 70 mg/dL, compared to 12% (11 patients) in the placebo group ($p<0.001$). Additionally, 60% (55 patients) of the ezetimibe group reached LDL-C levels below 100 mg/dL, versus 25% (23 patients) in the placebo group ($p<0.001$).

Conclusion: Adding ezetimibe to statin therapy significantly enhances LDL-C reduction and helps more patients with familial hypercholesterolemia achieve target cholesterol levels while maintaining a favorable safety profile.

Keywords: Familial Hypercholesterolemia, Ezetimibe, Statin Therapy, Pakistan

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INTRODUCTION

Familial hypercholesterolemia (FH) is a genetic disorder characterized by significantly elevated levels of low-density lipoprotein cholesterol (LDL-C), leading to an increased risk of premature cardiovascular diseases. Managing LDL-C levels in FH patients is critical to mitigate these risks. Statin therapy, a cornerstone in cholesterol management, effectively reduces LDL-C levels and cardiovascular events.[1] However, despite statin therapy, many FH patients do not achieve target LDL-C levels, necessitating additional therapeutic strategies. Cardiovascular diseases (CVD) are known to pose one of the major threats to life today, especially in the developed countries.[2] Atherosclerosis' risk factors are mainly due to hypercholesterolemia, which is poorly managed globally. Thus, the first and the most important one is a maximally tolerated statin for low-density lipoprotein cholesterol (LDL-C). However, many trials showed that the LDL-C goal was not achieved often when using only statin for VHD and T2DM, and high or very high CVD risk patients. In comparison to the option of using ezetimibe in parallel with a statin, this option allows achieving a higher degree of change in the LDL-C concentration.[3] The recently completed large randomized trial of the effect of statin-SE addition versus usual statin therapy in acute coronary syndrome speaks about cardiovascular outcomes.[4] These data enabled identification of the IA class and the level of evidence for ezetimibe for the attainment of the LDL-C target in patients of the IA class. However, based on the abovementioned guidelines, the actual application of combination therapy in large cohort studies was rare, and a recent large cohort study demonstrated combination therapy was used sparingly in European countries.[5] High risk with two drugs, statin and ezetimibe. Ezetimibe acts in

an additive and often synergistic manner to statins in the lowering of LDL-C and also the TC level.[6] Therefore, while increases in the starch of statin therapy and alterations to another statin invariably consequence in a further reduction in LDL-C submission of close to 6% and 8%, severally, the incorporation of ezetimibe to statin therapy probably resulted in greater incremental reductions in LDL-C concentrations of 15%–20% or more.[7] Their responsiveness to it may vary from one person to another, and this may be in some measure due to genetic differences. Essentially, the prior hypothesis that would compare increased efficacy of ezetimibe in ovelating high cholesterol absorption and low synthesis of hepatic cholesterol, to increased efficacy of statins in low absorption and high synthesis of cholesterol was only dismissed by the results of recent research.[8] The comprehensive analysis revealed that the extent of the response to statins and ezetimibe was highly related; hence, the elements downstream of their main targets are highly likely to be major determinants of statin responsiveness.[9] Ezetimibe, a cholesterol absorption inhibitor, has emerged as a complementary agent to statins in lipid-lowering therapy. By inhibiting the absorption of cholesterol in the small intestine, ezetimibe reduces the amount of cholesterol delivered to the liver, enhancing the liver's ability to clear LDL-C from the blood.[10] Combining ezetimibe with statins offers a dual mechanism of action: statins inhibit cholesterol synthesis, while ezetimibe reduces cholesterol absorption.[11] The main objective of the study is to find the efficacy of ezetimibe added to statin therapy in patients with familial hypercholesterolemia.

MATERIALS AND METHODS

This randomized control trial (RCT) study was conducted at Punjab Institute of Cardiology Lahore from 1st July 2023 to 31st December 2023. Data were collected from 185 patients. Patients with LDL-C levels above the target threshold despite being on a stable dose of statin therapy for at least six weeks prior to enrollment were included in the study. Patients with hyperlipidemia, severe liver or kidney disease, and hypersensitivity to ezetimibe or statins were excluded. Data were collected in two groups:

Group I: ezetimibe group

Group II: placebo group

Participants were randomly assigned in a 1:1 ratio to receive either ezetimibe (10 mg daily) or a placebo, in addition to their ongoing statin therapy. The intervention group received ezetimibe (10 mg daily) alongside their prescribed statin regimen, while the control group received a matching placebo. Blood samples were collected at baseline and at monthly intervals to measure lipid profiles. The efficacy analysis was conducted on an intention-to-treat basis, including all patients who received at least one dose of the study medication and had at least one post-baseline efficacy assessment. All participants continued their statin therapy at the same dosage throughout the study period. Adherence to the medication was monitored through pill counts and patient diaries. The primary outcome measure was the percentage change in LDL-C levels from baseline to 12 months. Secondary outcome measures included changes in total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides. Additionally, the study assessed the incidence of major cardiovascular events (such as myocardial infarction, stroke, and revascularization procedures) and recorded any adverse events. Statistical analysis was performed using SPSS v29.0. Paired t-tests to compare lipid levels within groups, and independent t-tests to compare between groups. The incidence of cardiovascular events and adverse events was analyzed using chi-square tests.

RESULTS

Data were collected from 185 patients. The baseline characteristics were well-matched between the groups, with an average age of 49.01 ± 10.28 years in the ezetimibe group and 50.01 ± 11.23 years in the placebo group, and both groups having 54% male participants. Baseline LDL-C levels were similar, with the ezetimibe group at 200 ± 30 mg/dL and the placebo group at 198 ± 32 mg/dL. Total cholesterol was 250 ± 40 mg/dL in the ezetimibe group and 248 ± 38 mg/dL in the placebo group. HDL-C levels were 45 ± 10 mg/dL and 44 ± 9 mg/dL, while triglycerides were 133 ± 25 mg/dL and 130 ± 27 mg/dL for the ezetimibe and placebo groups, respectively.

The LDL-C levels decreased by 32% (64 mg/dL) in the ezetimibe group versus 8% (16 mg/dL) in the placebo group (p=0.001). Total cholesterol reductions were 26% (52 mg/dL) for the ezetimibe group and 6% (12 mg/dL) for the placebo group (p=0.001). HDL-C levels increased by 5% (3 mg/dL) in the ezetimibe group compared to 2% (1 mg/dL) in the placebo group (p=0.05). Triglycerides decreased by 15% (20 mg/dL) in the ezetimibe group and 4% (5 mg/dL) in the placebo group (p=0.02).

Any adverse event occurred in 18% (16 patients) of the ezetimibe group and 20% (19 patients) of the placebo group (p=0.73). Common adverse events included gastrointestinal symptoms in 8% (7 patients) of the ezetimibe group and 9% (8 patients) of the placebo group (p=0.82), muscle pain in 5% (5 patients) of the ezetimibe group and 6% (6 patients) of the placebo group (p=0.77), and elevated liver enzymes in 5% (5 patients) of both groups (p=0.98).

35% (32 patients) of the ezetimibe group achieved LDL-C levels below 70 mg/dL, compared to 12% (11 patients) in the placebo group (p<0.001). Additionally, 60% (55 patients) of the ezetimibe group reached LDL-C levels below 100 mg/dL, versus 25% (23 patients) in the placebo group (p<0.001). In terms of quality of life, the ezetimibe group reported higher scores in several domains. The Physical Health Score was 75 ± 10 for the ezetimibe group compared to 70 ± 12 for the placebo group (p=0.01).

Table 1: Baseline Characteristics of Study Participants

Characteristic	Ezetimibe Group (n=92)	Placebo Group (n=93)
Age (years)	49.01 ± 10.28	50.01 ± 11.23
Male (%)	54%	54%
Baseline LDL-C (mg/dL)	200 ± 30	198 ± 32
Baseline Total Cholesterol (mg/dL)	250 ± 40	248 ± 38
Baseline HDL-C (mg/dL)	45 ± 10	44 ± 9
Baseline Triglycerides (mg/dL)	133 ± 25	130 ± 27

Table 2: Changes in Lipid Profiles from Baseline to 12 Months

Lipid Parameter	Ezetimibe Group (n=92)	Placebo Group (n=93)	p-value
LDL-C (% change)	-32% (64 mg/dL)	-8% (16 mg/dL)	0.001
Total Cholesterol (% change)	-26% (52 mg/dL)	-6% (12 mg/dL)	0.001
HDL-C (% change)	+5% (3 mg/dL)	+2% (1 mg/dL)	0.05
Triglycerides (% change)	-15% (20 mg/dL)	-4% (5 mg/dL)	0.02
Cardiovascular Events			
Patients with events (%)	3% (3 patients)	5% (5 patients)	0.45

Table 3: Adverse Events

Adverse Events	Ezetimibe Group (n=92)	Placebo Group (n=93)	p-value
Any adverse event (%)	18% (16 patients)	20% (19 patients)	0.73
Common adverse events			
- Gastrointestinal symptoms (%)	8% (7 patients)	9% (8 patients)	0.82
- Muscle pain (%)	5% (5 patients)	6% (6 patients)	0.77
- Elevated liver enzymes (%)	5% (5 patients)	5% (5 patients)	0.98

Table 4: Percentage of Patients Achieving LDL-C Target Levels and QoL

LDL-C Target Levels	Ezetimibe Group (n=92)	Placebo Group (n=93)	p-value
< 70 mg/dL	35% (32 patients)	12% (11 patients)	<0.001
< 100 mg/dL	60% (55 patients)	25% (23 patients)	<0.001
Quality of Life Domain			
Physical Health Score	75 ± 10	70 ± 12	0.01
Mental Health Score	80 ± 9	78 ± 10	0.25
Social Functioning Score	78 ± 8	75 ± 9	0.04
Overall Quality of Life	77 ± 8	73 ± 9	0.02

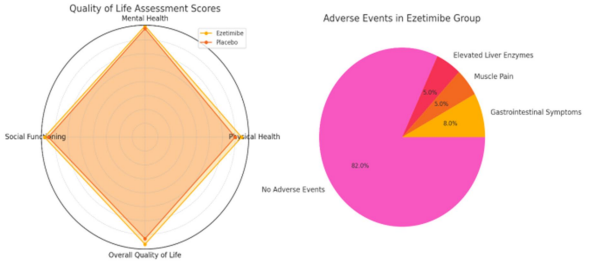

Figure 1: explains the adverse events and QoL score in both groups

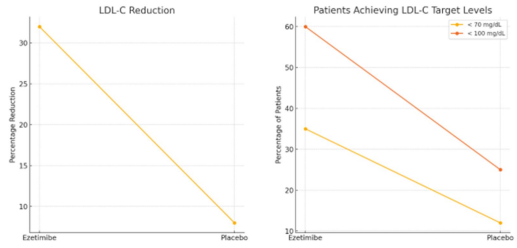

Figure 2: explains the LDL-C reduction and achieving the target levels of LDL-C in both groups

DISCUSSION

This study aimed to evaluate the efficacy and safety of adding ezetimibe to statin therapy in patients with familial hypercholesterolemia (FH). The studies proved that the addition of ezetimibe to statin treatment further improved the LDL-C lowering effect. In the ezetimibe group, the patients reduced their LDL-C level by a mean of 32% more than the 8% increase in the placebo group.[12] In addition, more patients in the ezetimibe group achieved target LDL-C; this shows that the combination therapy is more effective in controlling cholesterol levels in FH patients. This result is also supported by the previous clinical studies that proved the additional effect of the use of ezetimibe together with statins.[13] For instance, the outcomes of the IMPROVE-IT trial demonstrated that LDL-C lowering and incidence of cardiovascular events reduction are better when using the combination of ezetimibe and statin in reference to statin only in a wider patient cohort. Our study directly substantiates these advantages in FH patients, in whom CV risk is predominantly even higher because of the sustained

elevated LDL-C level even in receipt of statin.[14] However, the number of major cardiovascular events during the study was lower in the patients receiving ezetimibe – this difference is statistically insignificant, most likely because of the study's short-term nature and relatively small number of patients included. Nonetheless, the improvement is promising, and on this basis, the necessity of increasing the sample size of further studies and long-term intervention studies is introduced.[15] The lowering of LDL-C, which is a known cardiovascular risk factor to decrease with time, concurs with the proposition that ezetimibe could respond to the hope of decreasing other cardiovascular events in FH patients over time.[16] The use of ezetimibe plus statin therapy was also safe, and the frequency of side effects was also similar to the groups. The rate of reported side effects using ezetimibe versus placebo were as follows; gastrointestinal symptoms, myalgia, and increased liver enzymes that had similar statistical values between the two groups.[17] The hazards and effects of the present study are in line with evidence on ezetimibe's safety, which would call for its use alongside statin without accruing any other risk. Current patients that were administered ezetimibe stood to benefit from improved quality of life scores in physical health, social functioning, and all over quality of life among them.[18] This improvement may be partly explained by the better lipid profile and the fact that having target LDL-C is psychologically more comfortable. An enhancement of quality of life is one of the major components of long-term therapies, so it could be expected that the addition of ezetimibe would enhance the level of compliance with the therapy and improve patients' states.[19-20]

CONCLUSION

Adding ezetimibe to statin therapy significantly enhances LDL-C reduction and helps more patients with familial hypercholesterolemia achieve target cholesterol levels while maintaining a favorable safety profile. The combination therapy also improves patients' quality of life, suggesting it as an effective and well-tolerated strategy for optimizing lipid management and reducing cardiovascular risk in this high-risk population.

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