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Effect of Ezetimibe/Simvastatin and Atorvastatin with Conventional Dose on Achieving Target Low Density Lipoprotein Cholesterol Goal

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Abstract : Although recent lipid-lowering agents were effective in reducing low-density lipoprotein (LDL) cholesterol level, many patients treated with lipid-lowering therapy did not achieve target LDL cholesterol level, especially in very high risk hypercholesterolemic patients. The aim of this study is to evaluate the efficacy of ezetimibe/simvastatin and atorvastatin with conventional dose on reducing lipid levels and achieving target LDL cholesterol level in very high risk hypercholesterolemic patients. A total of 79 patients in very high risk hypercholesterolemia were enrolled in the study. Patients are randomly grouped in 2: Group 1, ezetimibe/simvastatin 10/20 mg/day and Group 2, atorvastatin 10 mg/day. Target level of LDL cholesterol was defined less than <70 mg/dl at follow-up. The follow-up plasma lipid data were obtained after 8 weeks of treatment. Baseline plasma lipid data were similar between the two groups. Achieving target LDL cholesterol level was observed in 64% of the Group 1 and 40% of Group 2 at 8-week follow-up ($p<0.05$). Compared with Group 2, Group 1 showed a significantly reduction in LDL cholesterol and non-high density lipoprotein cholesterol and a trend toward to a greater reduction in total cholesterol and apolipoprotein A-1. In patients with very high risk hypercholesterolemia, ezetimibe/simvastatin 10/20 mg was superior to atorvastatin 10 mg/day in attainment of target LDL- cholesterol goal and in efficacy with other lipoprotein parameters.

Key Words : atorvastatin, ezetimibe, lipoprotein, simvastatin

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Introduction

Current lipid management guidelines have reported the association of major coronary heart disease(CHD) events with cholesterol profile as indicated by meta-analysis of several randomized clinical trials based on a composite of major CHD events, including CHD death, non-fatal myocardial infarction, or myocardial revascularization procedures [1]. The National Cholesterol Education Program(NCEP) Adult Treatment Panel (ATP) III recently recommended a lower and more aggressive low-density lipoprotein (LDL)-cholesterol target of less than 70mg/dL as a therapeutic option for very high risk hypercholesterolemia. The effect of lowering plasma LDL-cholesterol levels to achieve reductions in coronary vascular disease(CVD) events has been well demonstrated in patients with established CHD-very high risk very high risk hypercholesterolemic patients [2]. Thus, more effective lipid-lowering therapies are needed to reach the established LDL-cholesterol level, especially since the achievement of target LDL-cholesterol in patients at very high risk of coronary heart disease presents a challenge, particularly in achieving the optimal LDL-cholesterol level of less than 70 mg/dL in the population of patients with high baseline LDL-cholesterol level.

Plasma cholesterol derives primarily from 2 sources, endogenous synthesis and intestinal absorption. The major effect of statin is to reduce LDL-cholesterol by inhibiting cholesterol synthesis. Treatment with several 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors has shown to significantly reduce the risk of coronary artery disease(CAD) events [3]. Statins are also known to affect other lipid variables associated with CAD risk, such as high-density lipoprotein(HDL) cholesterol and triglyceride(TG), which are dependent upon different classes of statins and the patient phenotypes[4,5].

Ezetimibe, new class of medication, is a cholesterol absorption inhibitor that blocks the intestinal absorption of biliary and dietary cholesterol without affecting the uptake of TG or fat-solutable vitamins[6]. The co-administration of ezetimibe with statins resulted in significant incremental reductions in LDL-cholesterol[7]. Specifically, ezetimibe in combination with simvastatin has shown the effectiveness in reducing LDL- cholesterol levels through its dual inhibition of cholesterol absorption and biosynthesis[8]. Most of ezetimbe/simvastatin(EZE/SIMVA) and atorvastatin prescribed by the usual recommended starting dosage(EZE/SIMVA, 10/20 mg/d, and atorvastatin, 10 or 20 mg/d). Therefore, the purpose of this study was to compare the proportion of high risk hypercholesterolemic patients achieving target LDL-cholesterol level on the usual recommended starting dose of EZE/SIMVA versus atorvastatin.

Materials and Methods

Study Population

This is a randomized, open-label, parallel-group study with acute coronary syndrome (ACS) patients or CHD patients, who were identified based on major risk factors, such as

diabetes, peripheral artery disease, and cerebrovascular accidents according to NCEP ATP III guidelines. The study was conducted from June 2006 to March 2007. Patients were randomly assigned to EZE/SIMVA 10/20 mg/d or atorvastatin 10 mg/d. Inclusion criteria of patients over 18 years with hypercholesterolemia and a history of acute coronary syndrome or chronic CHD with major risk factors were eligible for randomization if the mean of their LDL-cholesterol was < 250 mg/dL and TG concentration of < 350 mg/dL, LDL cholesterol was calculated by the Friedewald formula [9].

Exclusion criteria included a history of statin-induced myopathy or serious hypersensitivity reaction to statins and/or ezetimibe; patients considered unstable after a myocardial infarction, unstable angina, myocardial revascularization, coronary artery bypass graft, transient ischemic attack, or stroke; history of malignancy; current active liver disease (alanine aminotransferase [ALT] or serum glutamic pyruvic transaminase > 2 times the upper normal limit) or severe hepatic impairments; unexplained serum creatine kinase (CK) ≥ 1 times the upper normal limit; women who were pregnant or breast-feeding, or of childbearing potential, but not using contraception. Subjects taking hormone replacement therapy or oral contraceptives initiated or changed with 3 months before enrollment in the dietary lead-in were also excluded.

End points

The primary end point was the percentage of patients achieving the NCEP ATP III LDL cholesterol goal (<70 mg/dL) after 8 weeks of treatment. Secondary end points included the percentage change of lipid profile, such as TC, TG, HDL-cholesterol, LDL-cholesterol, non HDL-cholesterol, apolipoprotein B/apolipoprotein A-1 ratio. Baseline lipid parameters were obtained at one week before and on the randomization day prior to active therapy. All lipid measurements were made after a fast of at least 12 hours safety and tolerability assessment was made by monitoring clinical adverse events(CAE) and laboratory adverse events(LAE).

Statistical analyses

With the aim of detecting a statistically significant difference between EZE/SIMVA and atorvastatin, treatment and baseline LDL- cholesterol were used to compare by chi-square and independent t-test. Patients achieving target goals and percent change from baseline in lipid and lipoprotein levels were compared between both groups using analysis of variance, with separate model fitted for each lipid parameter. P value less than 0.05 was specified for statistical significance.

Results

Baseline Clinical Characteristics

Total of 79 patients with ACS who underwent percutaneous coronary intervention were randomized and followed up: 39 patients in EZE/SIMVA 10/20 10/20 mg/day and 40 patients in atorvastatin 10

mg/day. All randomized patients were monitored for 8 weeks of treatment period. Both groups had similar baseline characteristics in demographic and clinical variables. However, EZE/SIMVA group comprised of more complex CAD than atorvastatin group. Percentage of patients with single vessel disease was 41% and multiple vessel disease was 59% in EZE/SIMVA group. Percentage of patients with single vessel disease was 77.5% and multiple vessel was 22.5% in atorvastatin group (p<0.001, Table 1). Patients in both groups have successfully completed the treatment period with high compliance in medications per pill count.

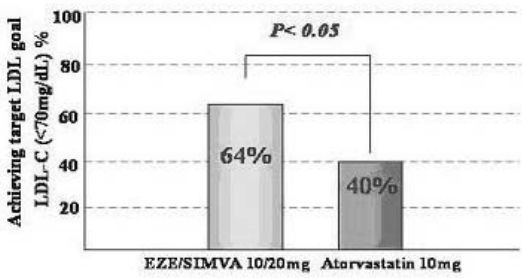

Fig. 1. Achieving LDL Goal (<70 mg/dL) Target goal attainment of LDL-cholesterol was significantly higher in EZE/SIMVA group compared to atorvastatin group at 8 weeks follow up (64% versus 40%, p<0.05)

Efficacy

The incidence of achieving target LDL-cholesterol level was much higher in the EZE/SIMVA 10/20 mg/day group than atorvastatin 10 mg/day group after 8 weeks of active treatment (64% versus 40%, p <0.05; Fig. 1). At 8 weeks later, change of LDL-cholesterol level was 57.9 ± 45.2 mg/dL in EZE/SIMVA group and 39.2 ± 35.0 mg/dL in atorvastatin group (p <0.05). However, there was no statistical significance in percentage change from baseline (38.7% decreased in EZE/SIMVA group and 29.4% in atorvastatin group). Nevertheless EZE/SIMVA group had favorable trend toward reduction of LDL-cholesterol percent change. In other lipid parameters, the change of non-HDL level was 61.1 ± 48.7 mg/dL in EZE/SIMVA and 42.3 (33.9 mg/dL in atorvastatin group (p <0.05). And percent variation of lipid parameters was 35.2% in EZE/SIMVA group and 26.8% in atorvastatin group. However, there was no statistical significance in both groups for non-HDL. EZE/SIMVA group showed a favorable trend toward reduction of non-HDL percent change. The change of HDL- cholesterol level increased 4.2 (9.9 mg/dL in EZE/SIMVA group, 3.4 (15.0 mg/dl in atorvastatin group and percent change was 9.8% and 8.5%, respectively (Fig. 2).

Safety and Tolerability

Both treatments were well tolerated, and the overall frequency and type of adverse events were similar between treatment groups. Total adverse events were experienced by 15.4% and 12.5% of patients receiving in EZE/simvastatin group and atrovastatin, but there were no statistically significant differences. CAEs' were related with gastrointestinal trouble, hepatitis, rash or allergy, and LAE occurred in 1 patient (2.6%) in EZE/SIMVA group. No patients had a creatine kinase elevation 10 or more times the upper limit of normal (ULN), with or without muscle symptoms (Table 2).

Table 1. Baseline characteristics of studied patients from two groups

	Group 1 (N=39)	Group 2 (N=39)	*P*-value
Age	64.1 ± 0.9	60.7 ± 10.8	0.149
Male	27 (69.1%)	30 (75%)	0.425
Hypertension	22 (56.4%)	24 (60%)	0.821
Diabetes	11 (28.2%)	8 (20%)	0.439
Smoking	14 (35.9%)	18 (45%)	0.494
Hypercholesterolemia	3 (7.7%)	8 (20%)	0.193
Ejection Fraction, %	54.2 ± 11.8	54.2 ± 9.9	0.985
Disease			< 0.001
Single- vessel disease	41%	77.5%	
Multi- vessel disease	59%	22.5%	
Coronary Disease			0.190
Stable Angina	31.9%	22.5%	
Acute coronary syndrome	64.1%	77.5%	
Cholesterol level, mg/dL			
Total cholesterol	197.7 ± 43.7	191.2 ± 34.2	0.466
HDL-cholesterol	45.2 ± 8.9	43.9 ± 11.2	0.552
Non HDL-cholesterol	152.4 ± 43.5	147.3 ± 34.9	0.566
LDL-cholesterol	122.6 ± 39.8	117.8 ± 27.7	0.511
Triglyceride	125.9 ± 59.1	127.2 ± 39.8	0.284
Apo-A cholesterol	120.5 ± 20.6	128.6 ± 25.9	0.132
Apo-B cholesterol	80.4 ± 18.8	85.9 ± 17.9	0.185
Apo B/A ratio	0.6 ± 0.2	0.7 ± 0.2	0.903

Apo: Apo-lipoprotein, HDL: high density lipoprotein, LDL: Low density lipoprotein
Group 1: ezetimibe/simvasttin 10/20 mg/day; Group 2: atorvastatin 10 mg/day

Discussion

Our study demonstrated that EZE/SIMVA 10/20 mg was more effective than atorvastatin 10 mg in reducing LDL-cholesterol in very high risk patients. NCEP ATP III has recommended an optimal LDL-cholesterol target of less than 70 mg/dL for very high risk patients with CVD [9]. Heart Protection Study, including 5963 patients with

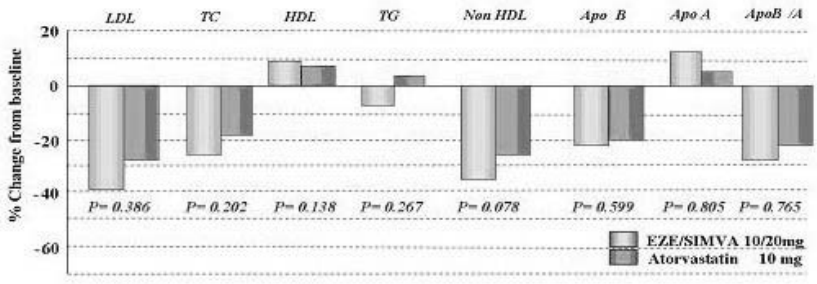

Fig. 2. Percent change form baseline in Lipid profile Compare with atorvastatin group, EZE/SIMVA 10/20 group had trend toward reduction in LDL-cholesterol, TC, TG, non HDL-cholesterol and apo B/A-1 ratio and increase in HDL-cholesterol and Apo A.

Table 2. Number of Patients with Adverse events

	EZE/SIMVA 10/20 mg	Atrovastatin 10 mg
Rhadomyolysis	0 (0.0%)	0 (0.0%)
Acute hepatic disease	1 (2.6%)	0 (0.0%)
Myositis	0 (0.0%)	0 (0.0%)
Gastrointestinal trouble	5 (12.8%)	5 (12.5%)
Total	6 (15.4%)	5 (12.5%)

*All p values are not significant ($p > 0.05$)

diabetes, had shown that large percent of LDL-cholesterol reduction was associated with significant reduction of major coronary events [10]. In Heart Protection Study, intensive treatment of patients with 40mg of simvastatin resulted in reductions in major CHD events regardless of baseline LDL-cholesterol levels. Other studies with atorvastatin treatment have also demonstrated that intensive lipid lowering therapy (LDL-cholesterol < 100 mg/dL) was associated with favorable clinical outcomes in high risk patients [11,12]. Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial has shown that intensive statin therapy was significant in reducing clinical end points of death, myocardial infarction, or rehospitalization for recurrent ACS [13].

In general, standard dose of EZE/SIMVA and atorvastatin was 10/20mg and 10mg, respectively. Goldberg et al[14] have demonstrated the LDL-cholesterol goal attainment (<70 mg/dL) of EZE/SIMVA 10/20 mg and atorvastatin 10mg in diabetic patients. In this study, EZE/SIMVA 10/20 mg was superior to atorvastatin 10mg in attainment of LDL-cholesterol level less than 70 mg/dL. Similar to Goldberg et al study, our data also indicated that attainment of LDL-cholesterol level of less than 70 mg/dL in very high risk patients was achieved more with EZE/SIMVA group than with atorvastatin group (64% versus 40%, p =0.043 respectively). In addition to reducing LDL-cholesterol, improving other variables of the lipid profile may be beneficial in reducing risks in patients with CHD [15]. In this study, compared with atorvastatin alone, EZE/SIMVA group significantly decreased non HDL-cholesterol and other lipid components, such as TC and

apolipoprotein A-1.

The safety and tolerability of both drugs are consistent with previous studies [14,16-18]. In Vytorin versus Atrovastatin in Patients with Type 2 Diabetes Mellitus and Hypercholesterolemia (VYTAL study), incidences of CAE, including serious drug-related and pre-specified gastrointestinal-, gallbladder-, and hepatitis-related allergic reactions or rash events, and LAE including repeated elevation of hepatic transaminases or creatine kinase levels, were similar [14]. There was no difference between coadministration of EZE/SIMVA and atorvastatin monotherapy with regard to incidence of adverse clinical or laboratory events in our study.

This study demonstrated that coadministration of EZE/SIMVA 10/20 mg was superior to atorvastatin 10 mg in attainment of target LDL-cholesterol goal and in efficacy with other lipoprotein parameters. However, this study has several limitations. First of all, small number of patients was represented. Second, the study duration of follow up was relatively short. Relatively short term follow allowed only two lipid profile assessments. Third, we did not evaluate clinical outcomes of both groups. Finally, the dose comparison between atorvastatin 10 mg and EZE/SIMVA 10/20 mg was not comparable. However, atorvastatin 10 mg is the approved starting conventional dose in Korea, due to differences in life style pattern, such as low fat and fish-rich diet and lower mean body mass index, compared with western patients. Because low dose atorvastatin and EZE/SIMVA have different potency and mechanism, compare with high dose atorvastatin and EZE/SIMVA study would be helpful to evaluate effectiveness in lipid profile in high risk patients in Korean patients.

Summary

Recent lipid-lowering agents were effective in reducing LDL cholesterol level, However, many patients treated with lipid-lowering therapy may not achieve target LDL-cholesterol level, even in high risk patients. The aim of this study is to evaluate the efficacy of ezetimbe/simvastatin and atorvastatin with usual dose on reducing lipid level and achieving target LDL-cholesterol level in high risk patients.

Total of 79 consecutive patients with ACS who underwent percutaneous coronary intervention were enrolled. All patients were randomly assigned to EZE/SIMVA with 10/20 mg/d or atorvastatin with 10 mg/d. Patients with achieving target LDL-cholesterol level were observed in 64% of the EZE/SIMVA group and 40% of atorvastatin group at 8-weeks follow-up ($p < 0.05$). Compared with atorvastatin group, the EZE/SIMVA group showed a significantly reduction in LDL-cholesterol, non HDL-cholesterol and a trend toward to a greater reduction in total cholesterol, Apo A-1.

The dual cholesterol-lowering mechanism of EZE/SIMVA provides an effective and well-tolerated option as first-line lipid-modifying therapy for patients with very high risk patients.

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