Archive of SID

Double Blind Randomized Clinical Trial of Ezetimibe versus Atorvastatin in Patients with Primary Hypercholesterolemia

M. Momtahen MD, F. Farsad PharmD, M. Abbas MD, S. Momtahen MD and A.S. Kazzazi MD

Abstract

Objective- This randomized, double blind trial was designed to compare the efficacy and safety of ezetimibe, a new cholesterol-lowering agent with atorvastatin (Lipitor), a potent cholesterol-inhibitor derivative.

Method- Between September 2004 and March 2005, a total of 120 hyperlipidemic patients, aged 28-80 years, were randomized to receive ezetimibe 10 mg or atorvastatin 10 mg orally daily for 8 weeks after a 4-week washout phase and diet on NCEP step II. Mean changes of serum lipoproteins after 4 and 8 weeks of drug therapy were measured and compared in both groups of patients.

Results- Ezetimibe reduced LDLc and total cholesterol by a mean of 27% and 16% compared with 32% and 24% for atorvastatin, respectively. The difference was not statistically significant.

Conclusion- Ezetimibe and atorvastatin both reduced LDLc and TC with no statistically significant difference ***(Iranian Heart Journal 2007; 8 (1): 33-37)***.

Key words: ezetimibe ■ atorvastatin■ hypercholesterolemia

Reduction of low-density lipoprotein cholesterol (LDLc) has been well-established as a primary strategy for lowering the risk of coronary heart disease.[1] Primary and secondary prevention trials involving 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) therapy consistently have demonstrated that reducing levels of (LDLc) leads to a reduction in cardiovascular morbidity and mortality.[2]

Because of these beneficial effects, statins have become the preferred agents for the treatment of hypercholesterolemia.[3] However, despite the effectiveness of statins in lowering LDLc, morbidity and mortality, only less than 40% of patients achieve their target LDLc goals. This percentage is even lower (18%) with highest-risk patients with established coronary heart diseases.[4]

The largest degree of LDLc reduction is attained with the starting dosage of a statin, and every subsequent doubling of the dose leads to only an additional 6% decrease in LDLc from the original baseline level.[5] Furthermore, side effects of many lipid-lowering agents increase with higher doses or with various combination regimens. [6]

Due to these limitations of the available lipid-lowering therapies, new agents with mechanisms complementary to statins and good side-effect profiles would help more patients to reach their LDLc goal.

The selective cholesterol absorption inhibitors are a novel class of agents that possess these characteristics. Ezetimibe, the first agent of the class to be approved by the Food and Drug Administration for treatment in the

Received Aug. 28, 2005; Accepted for publication Aug. 22, 2006.
From the Department of Cardiology, Shaheed Rajaie Cardiovascular Medical Center, Iran University of Medical Sciences, Tehran, Iran.
Corresponding author: M. Momtahen, MD, Associate Professor in Cardiology, Shaheed Rajaie Cardiovascular Medical Center, Mellat Park, Vali- Asr Ave., Tehran, Iran. E-mail: Mohmoudm@rhc.ac.ir

www.SID.ir

Archive of SID

United States, has demonstrated a favorable adverse-event profile while reducing LDL when given as monotherapy or in combination therapy.
This study compares the efficacy and safety of a new selective cholesterol absorption inhibitor, i.e. ezetimibe 10 mg/day, to atorvastatin 10 mg/day in 120 patients with primary hypercholesterolemia.

Methods

Design: This double blind, randomized clinical trial consisted of two phases: a 4-week initial screening / drug- washout phase and an 8- week double- blind treatment phase. Patients of either sex younger than 80 years of age were enrolled between September 2004 and March 2005 with a diagnosis of primary hypercholesterolemia (calculated LDLc more than 130 mg/dl in patients without coronary artery disease risk factors or LDLc more than 100 mg/dl in patients with coronary artery disease or diabetes) after adequate lipid-lowering drug washout.
Key exclusion criteria included pregnancy or lactation; age more than 80 years old; uncontrolled cardiac arrhythmia; myocardial infarction; disorders of the hematological, digestive or central nervous system, which would limit evaluation or participation; uncontrolled diabetes mellitus; and uncontrolled endocrine or metabolic diseases known to influence serum lipids or lipoproteins, hepatic disease, coagulopathy.
Cardiovascular drugs were allowed during the study.

Study drugs: The patients were randomly assigned to treatment with either ezetimibe 10 mg or atorvastatin 10 mg in a 1:1 ratio according to a computerized randomization schedule. A single tablet was administered orally once daily in the morning for 8 weeks, without reference to meals.

Measurement of lipids: The primary efficacy variable was the percent change from baseline to end point (week 8) in the plasma concentration of direct LDLc. Secondary variables included change and percent changes from baseline in total cholesterol, triglycerides, HDLc and (CRP) C-reactive protein at end point (week 8). After baseline measurements and randomized treatment assignment, samples for lipid measurements were collected at weeks 4 and 8.

Assessment of diet: During the screening and or drug-washout phase, the patients received dietary counseling, and all prior lipid-altering drugs were discontinued except for beta adrenoceptor antagonists. All the patients were instructed to follow a low fat, low-cholesterol diet (NCEP Step II) to be started during this period and maintained throughout the 8-week study.

Safety and tolerability: Safety was evaluated through the investigators' observation reports of the patients and results of specific tests and measurements. At each visit, the investigator recorded adverse events reported by the patients since the last visit.
Other measures of safety included the results of laboratory tests (blood chemistry, hematology), physical examinations and electrocardiograms.

Statistical analysis: The total target sample size was 120 patients: 60 patients treated with ezetimibe 10 mg/day and 60 patients treated with atorvastatin 10 mg/day. The primary efficacy analysis included all the patients who received randomized treatment assignment and had at least one post-baseline lipid determination.
Comparisons between the treatment groups were made using the analysis of variance model; significance was defined as $P<0.05$. Statistical analysis was conducted using SPSS software.

www.SID.ir

Archive of SID

Results

The mean baseline plasma concentration of LDLc was approximately 160 mg/dl for the patients in the ezetimibe group and 156 mg/dl for those in the atorvastatin group.

In general, the 2 treatment groups were comparable in terms of gender, weight, age, diet, race, physical activity and smoking history (Table I).

Changes in lipid parameters: ezetimibe 10 mg resulted in a mean percent reduction in the plasma concentration of LDLc of approximately (27%), compared with (32.64%) for atorvastatin (non-significant, Fig. 1).

The effect of ezetimibe on LDLc was generally consistent among the subgroups analyzed, regardless of risk factor status, race, gender, age and baseline lipid profile. Among the other parameters, the reduction in mean total cholesterol was 16.18% in the ezetimibe group versus (24.52%) in the atorvastatin group (statistically non-significant).

The reduction in triglycerides and CRP was better achieved in the atorvastatin group. The HDLc level revealed non-significant changes in both groups (Table II). No adverse side effect was recorded in both treatment groups.

Table I. Baseline demographic characteristics for all randomized patients.

Characteristic	Ezetimibe 10 mg N=60	Atorvastatin 10 mg N=60
Age (yrs)	58.57(37-80)	58.7(28-79)
Women/ Men	36/24	32/28
CAD	96%	90%
Diabetes	28%	31%
Hypertension	51%	33%

Table II. Baseline mean values and mean percentage changes in plasma concentrations of various lipid- related variables and CRP from baseline to end point.

Variable	Ezetimibe (n=60)		Atorvastatin		P value
	Baseline	% change	Baseline	% change	
LDLc (mg/dl)	160	-27.1	151	-32.64	9.46
Total -chol (mg/dl)	251	-16.18	245	-24.15	0.07
Triglycerides (mg/dl)	180	-5.64	194	-16.96	0.33
HDLc (mg/dl)	55	+1.74	55	-6	0.06
CRP (mg/lit)	1	-59.22	1	-71	0.86

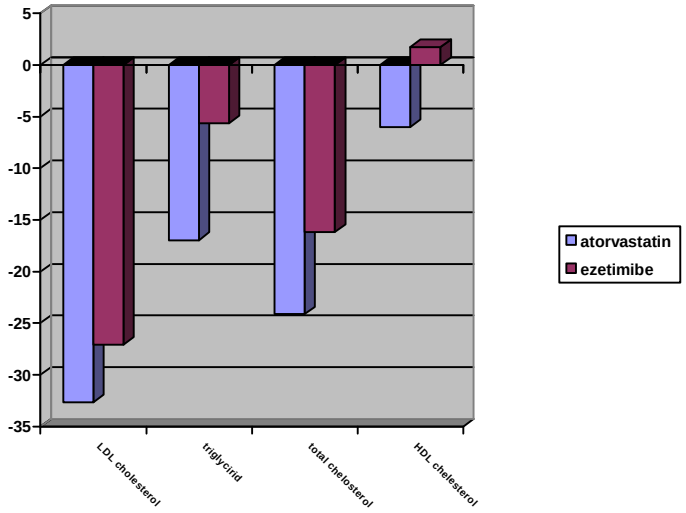

Fig. 1. Mean percent changes in plasma concentrations of LDLc, triglycerides, HDLc and total cholesterol from baseline to end point for all randomized patients; no significant difference was detected between ezetimibe and atorvastatin.

Discussion

Ezetimibe is a new cholesterol absorption inhibitor that potently inhibits dietary and biliary cholesterol absorption at the brush border of the intestine without affecting the absorption of triglycerides or fat-soluble vitamins.

www.SID.ir

Archive of SID

Ezetimibe is rapidly absorbed, extensively conjugated to glucuronide in the intestine and excreted primarily in the stool. This agent circulates enterohepatically repeatedly, delivering the agent back to the intestine and reducing systemic exposure.[7,9] These properties and its 24- hour half-life allow for once-daily dosing at any time.[10]

No clinically important gender or food effects, CYP 3A4 drug interactions or known drug- drug interactions have been identified.[8,11]

In this randomized, double blind trial, ezetimibe 10 mg taken orally once daily in the morning for 8 weeks by patients with mild to moderate primary hypercholesterolemia was shown to be an effective LDL-lowering agent and comparable with atorvastatin 10 mg once daily.

Ezetimibe caused a mean percent decrease from baseline to end point in LDLc of about 27%, which is comparable to atorvastatin at 32%. The LDLc reduction was apparent at 4 weeks, which was maintained to end point. This result is better than those from previous trials of ezetimibe study group[6] and also better than the result of a companion study.[12]

In this trial, the mean percentage increase in HDLc was 1.74% with ezetimibe versus a decrease of about 6% with atorvastatin (statistically non-significant).

The mean plasma concentration of triglycerides decreased significantly from baseline to end point with atorvastatin but not with ezetimibe. Therefore, ezetimibe is not as effective as atorvastatin in triglyceride-lowering treatment.

This result was different from other ezetimibe study results, in which ezetimibe significantly reduced the triglycerides level relative to placebo.[6] The reason for this difference may be due to the presence of the high percentage of coronary artery disease patients in our study, all of whom received beta-blockers. Nevertheless, this result was not unexpected because anti-hypercholesterolemic agents that act by interfering with enterohepatic recycling of bile acids have been associated with increases in triglyceride concentration.[10,11]

CRP reduction with ezetimibe 10 mg once daily was not statistically significant. This result was not unexpected, because no study has proved an anti-inflammatory effect for ezetimibe. Adverse events were not reported in our study.

Conclusion

This study showed that ezetimibe decreased LDLc and TC in comparison to atorvastatin with no statistically significant difference.

References

1. Summary of the second report of the National Cholesterol Education Program (NCEP) expert panel on detection evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II). JAMA 1993; 269: 3015-3023.

2. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. JAMA 1999, 282: 2340-6.

3. 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.

4. Pearson TA, Laurora L, Chu H, Kafonek S. The lipid treatment assessment project (L-TAP): a multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. Arch Intern Med 2000; 160: 459-67.

5. Knopp RH. Drug treatment of lipid disorders. N Engl J Med 1999; 341: 498-511.

6. Dujovne CA, Ettinger MP, McNeer JF, Lipka LJ, LeBeaut AP, Suresh R, Yang B, Veltri EP. Efficacy and safety of a potent new seiective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. Ezetimibe study group. Am J Cardiol 2002, 90: 1092-1097.

www.SID.ir

Archive of SID

7. VanHeek M, Farley C, Compton DS, Hoos L, Davis H. The potent cholesterol absorption inhibitor, ezetimibe is glucuronidated in the intestine, localizes to the intestine and circulates enterohepatically (abstr). Atherosclerosis 2000; 151-155.

8. Zhu Y, Statkevich P, Kosoglou T, Maxwell SE, Calzetta A, Cayen PJ, Batra V. The effect of gender on the pharmacokinetics of SCH 58235, a cholesterol absorption inhibitor (abstr). AAPS Pharmaceutical Science 1999 AAPS Annual Meeting Supplement; 1999: 1: s-24.

9. VanHeek M, Farley C, Comptom DS, Hoosl, Alton KB, sybertz EJ, Davis HRJr. Comparison of the activity and disposition of the novel cholesterol absorption inhibitor, SCH58235, and its glucuronide SCH60663. Br J Pharmacol 2000: 129: 1748-54.

10. Bays HE, Moore PB, Drehobl MA, Rosenblatt S, Toth PD, Dujovne CA, Knopp RH, Lipka LJ, LeBeaut AP, Yang B, Mellars LE, Cuffie-Jackson C, Veltri EP: Ezetimibe Study Group. Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: pooled analysis of two phase II studies. Clin Ther 2001; 23: 1209- 1230.

11. Zhu Y, Statkevich P, Kosoglou T, Zambas D, Patrick J, Cayen MN, Batra V. Effect of ezetimibe (SCH 58235) on the activity of drug metabolizing enzymes in vivo (abstr). Clin Pharmacol Ther 2000; 67: 152.

12. Knopp RH, Gitter H, T, Lipka LJ, LeBeaut AP, Suresh R, Veltri EP, for the Ezetimibe Study Group. Ezetimibe reduces low density lipoprotein cholesterol: results of a phase III randomized, double-blind, placebo-controlled trial (abstr). Atherosclerosis 2001; 2 (suppl): 38.

www.SID.ir