Effect of combination of ezetimibe and a statin on coronary plaque regression in patients wirh acute coronary syndrome ZEUS trial (eZEtimibe Ultrasound Study)

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Abstracts

Background: Many trials have shown that statins can reduce plaque volume (PV) associated with the degree of LDL-C reduction. The goal of this study is to determine whether the combination of ezetimibe and a statin produces greater reductions in coronary plaque volume compared to statin monotherapy in patients with acute coronary syndrome (ACS).

Methods: Prospective serial intravascular ultrasound (IVUS) of non-culprit lesions of the target vessel was performed in 95 patients with ACS. Of these, 50 patients were administered combination of atorvastatin 20mg/day and ezetimibe 10mg/day. 45 subjects treated by atorvastatin 20mg/day alone were the control group. At the beginning and 24 weeks after PCI, quantitative PV was accessed by IVUS. The primary end point was the percentage change in non-culprit coronary PV.

Results: LDL-C was significantly decreased by 49.8% in the ezetimibe/atorvastatin group compared with 34.6% in the atorvastatin group. Significant regression of plaque volume was observed from baseline to follow-up in both groups. The percentage changes in PV were greater in the ezetimibe/atorvastatin group than in the atorvastatin alone group (12.5% versus 7.6%, p=0.06), but statistically not significant. In 34 diabetic patients, regression of PV was significantly greater in the ezetimibe/atorvastatin group than in the atorvastatin alone group (13.9% versus 5.1%, p=0.04) and % change of PV significantly correlated with LDL-C reduction.

Conclusions: Additional LDL-C reduction with combination therapy tended to reduce more plaque regression compared to a statin alone in patients with ACS. In diabetic patients, further reduction of LDL-C was associated with a significantly greater reduction in PV.

Introduction

A large amount of evidence was accumulated that statins can reduce major adverse cardiovascular events associated with reduce degree of LDL-C 1)-3). Intravascular ultrasound (IVUS) trials demonstrated that aggressive LDL-C lowering could reduce plaque volume (PV) and stabilize the unstable plaque 4)-7). It was also demonstrated that the magnitude of reduction in LDL-C correlated with plaque regression after statin treatment. These IVUS studies suggested that the beneficial effect of intensive lipid lowering treatment on plaque regression in patients with chronic coronary artery disease (CAD) is also found in patients with acute coronary syndrome (ACS) 8)-10). Thus, reduction in LDL-C can not only decrease cardiovascular events, but also retard PV. However, new AHA/ACC guidelines demonstrated that evidence supports high-intensity statin therapy for secondary prevention group and it does not support the use of an LDL-C target. As of yet, there are no data to show that adding non-statin drugs to high-dose statin therapy will provide incremental risk reduction benefit. The goal of this study was to determine whether combination therapy of ezetimibe and a statin was superior to a statin alone in reducing PV in patients with ACS undergoing successfully percutaneous coronary intervention (PCI).

Methods

The ZEUS (eZEtimibe Ultrasound Study) is a non-randomized, open label trial designed to assess the regression of PV resulting from the treatment with atorvastatin and ezetimibe in patients with ACS. All patients enrolled in this study received atorvastatin 20mg and ezetimibe 10mg. IVUS examination was performed at baseline and then repeated 6 months after treatment. Inclusion criteria were patients with ACS and 20 to <79 years old (at the time of giving consent) who had emergency PCI in a culprit lesion and untouched non-culprit target lesion of less 25% stenosis that could be imaged by IVUS. Exclusion criteria were failed PCI, recommended CABG, and administration of lipid-lowering drugs (statin, fibrate, probucol or analog, nicotinic acid, or other prohibited drugs) before enrollment. Patients with renal failure (Scr > 2.0 mg/dL), moderate or severe congestive heart failure, diseased bypass graft, and left main coronary artery occlusion of 50% or more were also excluded. Included patients were found to have coronary plaques (>500 μ m in thickness, or percent plaque area $\geq$

20%) in the culprit vessel at least 5 mm away from the PCI-treated lesions. First, we collected the patients from our previous IVUS study database 11). Of these patients, 45 patients with ACS and treated by atorvastatin 20 mg alone were selected according to the restricted criteria mentioned here. These patients were put into the control group. The entry criteria and protocol of the two groups were similar; the main difference was that the ZEUS trial included only patients who were treated by ezetimibe and atorvastatin. The control group enrolled atorvastatin only.

Blood samples were obtained at baseline within 72h after PCI before administration of either a statin or ezetimibe and at 6 months follow-up. The lipid profile and other biomarkers were measured at SRL Co., Ltd., Tokyo, Japan. ACS was defined as high-risk unstable angina pectoris (UAP), non-ST elevated myocardial infarction (MI) or ST elevated MI. An increase (≥2-fold) in serum creatinine phosphokinase or troponin T positivity indicated a diagnosis of MI. High-risk UAP was defined in patients with resting or worsening chest pain that was persistent (≥20 min) along with any of the following findings: ST-segment depression of ≥0.5 mm or T-wave inversion of ≥3 mm. Diabetes patients were defined as demonstrating any one of the following: 1) Fasting plasma glucose level > 126mg/dL, 2) plasma glucose > 200mg/dL 2h after a 75g oral glucose load as in a glucose tolerance test, 3) symptoms of hyperglycemia and casual plasma glucose > 200mg/dL, and 4) glycated hemoglobin > 6.5% (NGSP (National Glycohemoglobin Standardization Program) criteria).

The study was approved by the ethical committees of each participating institutions. All patients signed informed consent before the study entry. In total, 95 patients were studied in this analysis, comprising of 45 patients enrolled in the previous trial who were treated with atorvastatin 20mg/day between November 2001 and July 2008 and 50 patients enrolled in the ZEUS trial treated with atorvastatin 20mg and ezetimibe 10mg between September 2008 and December 2009. These studies were conducted in accordance with the ‘Declaration of Helsinki’.

Intravascular Ultrasound Procedure and Examination

Image analysis was performed by two experienced readers who reached consensus for each scan at the central core-laboratory. All scans available for each subject were reviewed simultaneously but readers were blinded to any corresponding temporal or clinical information about the scans or subjects. A single lesion in a non-PCI site with a reproducible index side branch on the PCI vessel was investigated in each subject. The assessment site was selected at least 5mm to the PCI site. Details of the IVUS procedure are published elsewhere 9), 10). In summary, 40-MHz IVUS catheter (Atlantis SR

Pro2Boston Scientific, Natick, USA) was used and advanced into the target vessel after 200μg of intracoronary nitroglycerin, and a motorized pullback device withdrew the transducer at the speed of 0.5mm/s. The consoles used were ClearView or Galaxy 2 systems (Boston Scientific). The same imaging system with the same type of IVUS catheter was used for both the baseline and the follow-up examination. The target segment for analysis was identified at a non-PCI site of the culprit vessel based on some reproducible indices. Manual tracing was performed in every 0.3 mm cross-section and the software (echoPlaque2, INDEC systems Inc., Santa Clara, USA) automatically interpolated the tracings of 15 cross-sections between two manually traced images. A lesion meeting any of these criteria was not investigated: calcification, kinking, chronic complete occlusion, bypass graft site, site of coronary atherectomy before PCI, location at the left main trunk, thin small vessel (<2.0 mm), or location of distal protection device.

The primary end point was the percent change in coronary PV during the observation period. Coronary PV was calculated as the sum of the differences between the external elastic member (EEM) and lumen area across all evaluated frames. The percent change in PV was defined as the change in PV (follow-up minus baseline PV) divided by the baseline PV.

Definition of events and follow-up for major adverse events

Follow-up visits were scheduled every 2 months. Major adverse events were defined as all cause death, non-fatal ACS, target vessel revascularization, and stroke.

Sample size calculation and Data Analysis

Mean % change in PV was –13.1±12.8% (SD) in the atorvastatin group in the ESTABLISH study during 6 months follow-up. In the ZEUS, LDL-C by ezetimibe in addition to atorvastatin was expected to show 15% more reduction compared to atorvastatin alone. Theoretical %change in PV was 19.7% using atorvastatin＋ezetimibe if a constant rate of % change in coronary PV of LDL-C reduction was assumed. Mean and standard deviation of the % change in coronary PV in patients receiving atorvastatin＋ezetimibe were assumed to be superior to those of atorvastatin alone. 40 patients were needed to permit us to detect a 6.6% reduction in coronary PV with a power of 0.8 and a type 1 error rate of 0.05 during the planned mean follow-up period of half year.

Statistical Analysis

We used the full analysis set (FAS) of the ZEUS for inclusion criteria. Patients were included in the FAS if they had ACS and measurable IVUS lesions both at enrollment and at follow-up. Baseline characteristics were compared for patients in both the ZEUS trial and control group. Variables of interest at baseline and 6 months in each group were compared. Continuous variables are reported as mean SD. Binary variables are reported as percentages with 95% confidence intervals. After the descriptive statistics, comparisons of continuous variables between the 2 groups were performed by the 2-sample t test or Wilcoxon rank sum test, and those between the baseline and the follow-up by 1-sample t tests or Wilcoxon sign rank test according to their distributions. Comparisons of categorical values between the 2 groups were performed by chi-square tests and Fisher exat tests. We used general liniear models to assess relationships between % change in coronary plaque volume and reduction of LDL-C level from baseline to 6 months. The level of significance is $p < 0.05$ (one-sided) for the analysis. All statistical analyses were performed by the use of the SAS system version 9.1 (SAS Institute, Cary, North Carolina).

Results

Fig. 1 shows the flow chart of patients through the present trial. Among 60 ZEUS patients, 2 withdrew consent, IVUS could not be performed in 2 patients and there was poor image quality of follow-up IVUS in 6 patients. Therefore, a total of 50 patients had evaluable IVUS images at both baseline and follow-up. Furthermore, 45 patients from the control group were selected according to the restricted current criteria mentioned in the Methods section. A total of 95 patients were evaluated with paired IVUS during 6 months.

All patients were treated by bare metal stent for culprit lesions. Baseline characteristics are summarized in Table 1. There were no significant difference between the 2 groups in age, gender, body mass index, hypertension, and type of ACS and the culprit lesion. Antiplatelet therapy including aspirin and thienopyridines was used in all patients at baseline. Furthermore, there were no differences in beta-blocker, ACEI and ARB use between the groups. Lipid profiles (Table 2) were similar at baseline except

for LDL-C/HDL-C, but differed significantly at the end of 6 months of follow-up. In the atorvastatin group, LDL-C was significantly reduced from 114.2 to 70.3 mg/dL. In the combination group, further LDL-C reduction was achieved reaching 56.8mg/dL. LDL-C at follow-up and the change in LDL-C showed significant lowering in the combination group that in the statin alone group.

IVUS results

Table 3 shows the IVUS profile at baseline and follow-up. The PV showed a significant regression compared with baseline for the combination group (-8.2 (95% CI: -5.5 to -10.9), $p < 0.0001$) and atorvastatin group (-6.2 (95% CI: -3.5 to -8.9), $p < 0.0001$). The percentage changes in PV were greater in the ezetimibe/atorvastatin group than atorvastatin alone group (12.5% versus 7.6%, $P = 0.06$), but statistically not significant. There was statistically significant correlation between % change in PV and % reduction in LDL-C ($R = 0.22$, $P = 0.03$). Intra- and interobserver variability values for measuring plaque area in our study were 0.99 and 0.98, respectively.

The difference in LDL-C reduction and plaque change regarding diabetes

Next, we focused on the differences in plaque change regarding diabetes or not. In 34 diabetic patients, The LDL-C reduction was 33.9% in the statin alone group (18 patients) and 58.5% reduction in the combination group (16 patients). In 61 non-diabetic patients, LDL-C was decreased by 35.1% in the statin only group and 45.7% in the combination group (Fig. 2A). A more significant LDL-C reduction was achieved in the combination ezetimibe plus a statin treatment regardless of diabetes. The % change in PV in patients with or without diabetes was shown in Fig. 2B. In the non-diabetic group of patients, the % change in PV was similar between the statin alone and combination groups, approximately 9.2% and 11.9%, respectively ($P = 0.41$). In contrast, in the diabetic patients, the plaque was regressed more in the combination group than in the statin alone group (13.9% versus 5.1%, $P = 0.04$). We next examined the relationship between reduction in LDL-C and % change in PV in diabetic and non-diabetic patients. A significant correlation between LDL-C reduction and % change in PV during the 6-month follow-up was observed in diabetic patients, but not seen in non-diabetic patients (Fig. 3).

Adverse events

Atorvastatin and ezetimibe were well tolerated during the study. There was no death, myocardial infarction, and stroke in the study period. TLR was similar between atorvastatin alone and combination groups (13.3% versus 12.0%, p = 0.84).

Discussion

First, ezetimibe plus statin achieves much more reduction of LDL-C level compared to statin monotherapy. Second, early intensive lipid-lowering therapy using atorvastatin or atorvastatin＋ezetimibe in patients with ACS results in remarkable regression of coronary PV during 6-month follow-up. Third, additional LDL-C reduction with atorvastatin＋ezetimibe tended to reduce more plaque regression compared to a statin alone, but statistically not significant. However, in diabetic patients, further reduction of LDL-C using ezetimibe and a statin is associated with a significantly greater reduction in PV.

Compared with the atorvastatin alone, ezetimibe in addition to atorvastatin achieve more LDL-C reduction (a difference of −15.4 mg/dL). This difference resulted in reduced statistically % change in PV, but not statistically significantly different in the primary end point over 6 months. This result is congruous with SATURN study 12) in which rosuvastatin is not superior to atorvastatin in regard to plaque regression although the rosuvastatin group had lower levels of LDL-C than the atorvastatin group (62.6 versus 70.2 mg/dL). Our findings were also compared with the results of the ENHANCE study 13). In the ENHANCE study, a well-controlled randomized trial in another vascular bed, no statistically significant difference in the mean increase in common carotid artery intima-media thickness over 24 months was observed between a statin alone and a statin plus ezetimibe, despite a 41% versus 58% reduction in LDL-C, respectively.

Another important finding in the current study was that significant relationship between the percent change in PV and LDL-C level could be observed in the diabetic patients, and was absent in the non-diabetic patients. This finding is consistent with JAPAN-ACS, in which there was significant correlation between LDL-C and plaque regression in diabetic patients whereas no relationship was observed in non-diabetic

patients 10). In addition, Arai et al. reported that diabetic patients with LDL-C <75 had greater plaque regression compared with patients with LDL-C ≧75 from sub-analysis of JAPAN-ACS 14). One difference between JAPAN-ACS and the ZEUS is the directions for medicine; statin monotherapy was used in JAPAN-ACS which resulted in a 42% reduction in LDL in comparison with a 55% reduction when using the combination of ezetimibe with atorvastatin in the ZEUS. The ZEUS extends JAPAN-ACS to very low level of LDL-C using combination ezetimibe and atorvastatin.

It is interesting to find that plaque response to LDL-C lowering when adding ezetimibe to a statin in patients with diabetes differs from that in non-diabetic patients. This finding was keeping up with clinical outcome studies in which absolute risk reductions in those with CAD plus diabetes are twice as great as in those with CAD without diabetes when reducing LDL cholesterol from 70 to 40 mg/dL 15). Thus, patients with CAD with diabetes would be expected to more reduction in the absolute risk for events when treated from a LDL cholesterol level of less than 70 mg/dL. In fact, the rationale for the current National Cholesterol Education Program is to recommend achieving LDL cholesterol levels < 70 mg/dL as an optional goal for patients with diabetes with established CAD. Otherwise, in non-diabetic patients, achieving apparently low LDL-C beyond a certain point by intensive lipid lowering therapy may not necessarily improve status of atherosclerosis.

The exact mechanism of LDL-C-dependent plaque regression in diabetic patients remains uncertain. In general, the presence of diabetes was associated with a greater atherosclerotic burden and a more necrotic and lipid core and calcium content 16), 17). Experimental data suggest that high glucose potentiates foam cell generation by enhancing macrophage entry into vascular wall and inhibiting cholesterol efflux 18). Retention of Apo B-lipoproteins, cholesterol and other toxic lipids, and foam cells within the arterial wall was emigrated to out of the arterial wall 19). As a result, lipid and necrotic core and other components of the plaque were removed. In fact, lipid lowering therapy reduced the lipid core through decreasing the number of macrophages and proteolytic activity and increasing collagen content of established atheroma in rabbits 20). The IVUS study also demonstrated that statin treatment reduced PV due to absorption of the lipid core 21). It can be assumed that some of these mechanisms are dependent of LDL-C level. These putative pathways provide a biological rationale for our clinical observation of response of plaque change to LDL-C diabetes patients.

Clinical implications

A lot of studies have supported the theory that ‘the lower, the better’ with regard to

LDL-C 1)-3). To achieve aggressive reduction in LDL-C, lipid lowering therapy with a statin alone is limited; maximum doses of statin in clinical practice achieved 70 mg/dL of LDL-C level in Japan. The combination of a statin and ezetimibe in order to achieve intensive lipid-lowering can therefore be an attractive therapy considering the beneficial effects on plaque regression in diabetic patients with ACS. Furthermore, it is important to establish that plaque response to LDL-C when adding ezetimibe to a statin in patients with diabetes differs from that in non-diabetic patients. Recently FDA's Drug safety Communication announced that high-dose statins may raise the risk of diabetes, while, aggressive reduction of the LDL-C levels might induce a greater degree of plaque regression in diabetes patients. To achieve very low LDL-C level safely, the combination of statin plus ezetimibe would be essential.

Study limitations

The present study has several limitations although the present IVUS analysis of patients with ACS was pre-specified in the ZEUS protocol. First, a 3-year time lag exists between the ZEUS and control patients that are being compared. Comprehensive medical therapy has improved with time. Despite the use of same protocol and same analysis of plaque volume, it is difficult to fully adjust for the differences between the ZEUS patients and control group and to exclude unknown selection bias. However, these limitations in the current study were minimized by carrying out strict entry criteria. A substantial number of patients were excluded from the IVUS analysis due to suboptimal image quality and severe calcification precluding accurate plaque size assessment and were also excluded from our accumulated IVUS database due to strict entry criteria. These strict criteria were likely to have influenced both groups equally, however, and were therefore unlikely to have changed the results.

There is another criticism in which evaluation of a single plaque of the culprit vessel may not represent pan-coronary characteristics. Otherwise, ACS may represent the pan-coronary process of vulnerable plaque, suggesting that a single plaque can reflect general feature of whole coronary artery. Furthermore, it is impossible to perform IVUS to all coronary arteries for ethical reason because of emergency cases in this current trial. In this analysis, we set up the primary end point as a plaque change. The clinical implications of a drug benefit derived from IVUS remain uncertain. However, we

already reported that plaque regression was correlated with the risk of clinical events.

Compared with statin doses used in Western countries, lower doses of statins (atorvastatin 20mg) have been shown to have a similar effect on Japanese patients as high dose statins have on Western patients (atorvastatin 20mg) 22). Thus, what may be considered to be a relatively intensive dose in ACS patients in Japan. Therefore, direct comparisons between doses used in ACS patients in Western and Japanese studies may not be possible.

The net efficacy of a statin and ezetimibe in plaque change was not proved conclusively because there was no prospective randomized study and no direct comparison of PV between 2 groups. To validate this hypothesis and our findings, especially in diabetic patients, we need and try the prospective, large-scale, randomized trials as next step.

Conclusions

Early intensive lipid-lowering therapy using, atorvastatin or atorvastatin and ezetimibe in patients after ACS results in remarkable regression of coronary PV. Additional LDL-C reduction (less than 70 mg/dL) with ezetimibe and a statin provides no further plaque regression. However, in diabetic patients, further reduction of LDL-C with ezetimibe and a statin was associated with a significantly greater reduction in PV.

Conflict of interest

Dr Daida has received lecture fees from MSD K.K., AstraZeneca K.K., Kowa Pharmaceutical Company LTD., Sanofi-Aventis K.K., GlaxoSmithKline K.K., Shionogi & Co., Ltd., Daiichi-Sankyo Company, Limited, Takeda Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corp., Pfizer Co., Ltd., Bristol-Myers Squibb Company, Nippon Boehringer Ingelheim Co., Ltd., Astellas Pharma Inc., Novartis Pharma K.K., MSD K.K., Otsuka Pharmaceutical Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Teijin Limited, Morinaga Milk Industry Co., Ltd., Dr Miyauchi has received lecture fees

from MSD K.K., Pfizer Co., Ltd., and Astellas Pharma Inc.

Acknowledgement

We greatly acknowledge the contributions made by Ms. Maiko Hirano for IVUS core laboratory managements and IVUS planimetry and Ms. Yumi Nozawa and Ms. Tomoko Sakurada for data managements.

Figure Legends

Figure 1
Flow of patients through the study.

Figure 2
Percent change in LDL-C (A) and in plaque volume (B) according to treatment without and with diabetic patients. (A) % change in LDL-C during 6-month follow-up period according to atorvastatin 20mg/day or combination ezetimibe 10mg/day plus atorvastatin 20mg/day. LDL-C was lower in combination than that in statin alone. Values are mean ± SE. (B) % change in plaque volume during 6-month follow-up period according to atorvastatin 20mg/day or combination ezetimibe 10mg/day plus atorvastatin 20mg/day. In diabetic patient, the percent change in PV at the 6-month follow up was significantly lower in combination group compared with statin alone. Otherwise, in non-diabetic patients, no differences was seen in PV reduction between 2 groups. Values are mean ± SE.

Figure 3
Relationship between % reduction in LDL-C and % change in plaque volume in non-diabetic patients (A) and diabetic patients (B). (A) No relationship between % reduction of LDL-C and % change in plaque volume with statin or statin＋ezetimibe treatment were observed in non-diabetic patients. (B) There were significant correlations between % reduction of LDL-C and % change in plaque volume (PV) in non-diabetic patients with statin or statin＋ezetimibe treatment.

Table legends

Table 1 Baseline characteristics.
STEMI, ST-elevation myocardial infarction; NSTEMI, non ST-elevation myocardial infarction; UAP, unstable angina pectoris; RCA, right coronary artery; LAD, left anterior descending; LCX, left circumflex branch; ARB, angiotensin receptor blocker; ACE, angiotensin-converting enzyme; CCB, calcium channel blocker; PPAR, peroxisome proliferator-activated receptor.

Table 2 Laboratory results.
Values are mg/dL unless otherwise indicated. Continuous variables were represented by mean±SD. The last column indicates the comparison of percent change in variables between atorvastatin and atorvastatin＋ezetimibe group.
LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; BNP, brain natriuretic peptide.

Table 3 Volume parameters from IVUS results.

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