The Effects of Statin and Niacin on Plaque Stability, Plaque Regression, Inflammation and Oxidative Stress in Patients With Mild to Moderate Coronary Artery Stenosis

Kyounghoon Lee, MD, Tae Hoon Ahn, MD, Woong Chol Kang, MD, Seung Hwan Han, MD, In Suck Choi, MD, and Eak Kyun Shin, MD
Department of Cardiology, Gil Hospital, Gachon University of Medicine and Science, Incheon, Korea

ABSTRACT

Background and Objectives: The aim of this study was to compare the effects of a combination of niacin and simvastatin to simvastatin alone, on plaque regression and inflammatory markers. Subjects and Methods: The study had a prospective, randomized design. Subjects were patients with intermediate coronary artery stenosis. A total of 28 patients received a combination of niacin 1,000 mg plus simvastatin 40 mg (N+S group, n=14); the other group received simvastatin 40 mg alone (S group, n=14). All patients had a baseline and a 9-month follow-up coronary angiogram and an intravascular ultrasound procedure. Parameters such as normalized total atheroma volume (nTAV) and percent atheroma volume (PAV) were analyzed before and after treatment as were inflammatory markers such as high sensitivity C-reactive protein (hs-CRP), Matrix metalloproteinase-9 (MMP-9) and soluble CD40 ligand (sCD40L). Results: There was no difference in baseline characteristics between the two groups. The nTAV and PAV in the N+S group before and after treatment were not different than those in the S group. But the degree of changes (delta) in nTAV in the N+S group was greater than that in the S group (-21.6±10.68 vs. 5.25±42.19, respectively, p=0.024). Also, the change in PAV in the NS group was higher than that in the S group (-1.2±2.5 vs. -0.6±5, respectively, p=0.047). Changes in hs-CRP, MMP-9, and sCD40L in the NS group were significantly greater than those of the S group (-0.71±1.25, 73.5±64.9, -1,970±1,925 vs. -0.32±0.96, 62.5±30.6, -1,673±2,628, respectively). Conclusion: The combination of niacin plus simvastatin decreases coronary plaque volume and attenuates the inflammatory response in patients with intermediate coronary artery stenosis. (Korean Circ J 2011;41:641-648)

KEY WORDS: Niacin; HMG-CoA reductase; Coronary stenosis; Inflammation; Intravascular ultrasonography.

Introduction

A family of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors known as statins reduce blood levels of low density lipoprotein-cholesterol (LDL-C) and form the cornerstone of treatment of hyperlipidemia to reduce cardiovascular morbidity and mortality.1-4 Low serum concentrations of high density lipoprotein-cholesterol (HDL-C) are one of the major risk factors for adverse events related to coronary atherosclerosis5 and are highly prevalent among patients with acute coronary syndrome.6 A previous study showed that each 1 mg/dL increase in HDL-C is associated with a 2% to 4% reduction in coronary heart disease (CHD) outcomes.6 According to the National Cholesterol Education Program, low levels of HDL-C (<40 mg/dL) have been identified as a coronary risk factor within the guidelines for treatment of hyperlipidemia.7 Niacin at pharmacologic doses reduces total cholesterol, triglycerides (TGs), very-low-density lipoprotein (VLDL), LDL-C, and lipoprotein(a) [Lp(a)], and increases HDL-C levels.8,9 Of available lipid-regulating agents used to increase HDL levels, Niacin is the most potent. Several studies demonstrate that treatment with niacin, alone or in combination with other...
lipid-lowering agents, significantly reduces total mortality and coronary events, and retards the progression and induces regression of coronary atherosclerosis.²⁶ The HDL Atherosclerosis Treatment Study (HATS) demonstrated that the combined use of niacin and simvastatin dramatically improved angiographic end points and led to a significant reduction in clinical cardiovascular events (>80% decrease) and significant coronary stenosis regression compared with placebo.²⁶ The recent ARBITER 2 and 3 trials showed that extended-release niacin significantly increases HDL-C and induces regression of atherosclerosis measured by carotid intima-media thickness (CIMT) when added to statin therapy.¹¹¹² But, there is little data that the combined effects of extended-release niacin and statin are synergistic in inducing regression of atherosclerosis measured by intravascular ultrasound (IVUS). Accordingly, the purpose of the present trial was to identify any synergy between niacin and simvastatin compared with simvastatin alone on plaque regression (measured by serial IVUS) and on inflammatory markers.

**Subjects and Methods**

**Study population**

This study was a pilot, prospective, randomized and open-label study. It focused on coronary plaque regression in angina patients who had mild to moderate degree of coronary stenosis and who received niacin 1,000 mg plus simvastatin 40 mg or simvastatin 40 mg alone. The hypothesis of this study was that the combination of niacin and simvastatin would cause more regression of plaque than simvastatin alone, where plaque was measured by serial IVUS. The primary end point was the change in total and percent atheroma volume (TAV and PAV). Secondary end points were changes in high sensitivity C-reactive protein (hs-CRP), matrix metalloproteinase-9 (MMP-9) and soluble CD40 ligand (sCD40L). Patients were randomized to take either niacin 1,000 mg plus simvastatin 40 mg or simvastatin 40 mg alone. The study medication was taken at night, and it was recommended that it be taken with the subjects’ usual daily dose of anti-anginal medication. All patients taking other medications such as fish-oil more than 200 mg/day, antacid, anti-coagulant, immune depressant, corticosteroid, erythromycin, clarithromycin, systemic itraconazole and ketoconazole were strongly encouraged to discontinue their use of these supplements during the study to avoid possible interference with the response to niacin. The authors decided the dose of niacin based on a recent study and the dose of statin based on highest tolerable dose to Koreans.

**Methods**

**Study process**

After informed consent was obtained, subjects were randomized (allocation concealed) in a 1 : 1 fashion to receive either niacin 1,000 mg plus simvastatin 40 mg or simvastatin 40 mg alone. Randomization was done with a computer-generated sequence of random numbers. Study medication was initiated at a daily dose of 500 mg for 30 days, which was then increased to 1,000 mg for the duration of the 9-month study period. The study medication was taken at night, and it was recommended that it be taken with the subjects’ usual daily dose of anti-anginal medication. All patients taking other medications such as fish-oil more than 200 mg/day, antacid, anti-coagulant, immune depressant, corticosteroid, erythromycin, clarithromycin, systemic itraconazole and ketoconazole were strongly encouraged to discontinue their use of these supplements during the study to avoid possible interference with the response to niacin. The authors decided the dose of niacin based on a recent study and the dose of statin based on highest tolerable dose to Koreans.

**Laboratory analysis**

For all patients, serum samples were collected before coronary angiography for measuring lipid profiles, hs-CRP, blood urea nitrogen (BUN), creatinine, AST and ALT. Serum levels of total cholesterol, LDL-C, HDL-C and TG were measured by standard enzymatic methods. hs-CRP was analyzed using commercial kits containing a nephrometry system. MMP-9 and sCD40L were analyzed using commercially available ELISA kits. Serum levels of total cholesterol, LDL-C, HDL-C, TGs, hs-CRP, BUN, creatinine, AST and ALT were measured at baseline and at 9-month follow-up.
Intravascular ultrasound imaging and analysis

Intravascular ultrasound imaging and analysis was done at baseline and at the 9-month follow-up. IVUS examinations were done after intracoronary administration of 200 μg nitroglycerin using a commercially available IVUS system (Boston Scientific Corporation/SCI Med, Minneapolis, MN, USA). The IVUS catheter was advanced distal to the target lesion, and imaging was done retrograde to the aorto-ostial junction at an automatic pullback speed of 0.5 mm/s. The same anatomic image slices were analyzed at baseline and at follow-up. By using axial landmarks (i.e., side branches, calcifications or unusual plaque shapes) and the known pullback speed, identical cross-sectional image slices on serial studies could be identified for making comparisons. We measured IVUS images that were precisely spaced 1 mm apart. The leading edges of the external elastic membrane (EEM) and lumen were traced manually in accordance with the guidelines for IVUS of the American College of Cardiology Clinical Expert Consensus Document on Standards for the Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies. The total atheroma volume (TAV) was calculated by summation of the atheroma areas from each measured image: TAV=Σ (the EEM area-the lumen area). The PAV was determined using the formula: PAV= 100×{Σ (the EEM area-the lumen area)/Σ (EEM areas)}.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) for Windows, version 12.0 (Chicago, IL, USA) was used for all analyses. Continuous variables are presented as mean values±standard deviations (SDs); they were compared using paired or unpaired Student’s t-tests or the nonparametric Wilcoxon test if the normality assumption was violated. Discrete variables are presented as percentages and relative frequencies. A repeated measured analysis of variance (ANOVA) test was used for comparing continuous variables before and after treatment. Linear regression analysis was used to evaluate associations between continuous variables. A p<0.05 was considered statistically significant.

Results

Baseline characteristics

There was a total of 28 subjects. Mean age was 60.8±8.0 years in the simvastatin group and 58.1±7.0 years in the niacin/simvastatin group. Seven patients (50%) in the simvastatin group and 7 patients (50%) in the niacin/simvastatin group were males. No patients dropped out because of side effects to niacin or simvastatin. There was no difference in risk factors such as diabetes mellitus, hypertension, smoking and clinical diagnosis between the two groups. Ejection fraction on echocardiograms and results from coronary angiograms were not different between the two groups (Table 1). Laboratory findings between the two groups were not different (Table 2).

Comparison of coronary angiograms and intravascular ultrasound findings between the two groups

A paired t-test showed no difference in the coronary angiogram or in the IVUS before and after treatment (Table 3). Repeated measured ANOVA adjusted by the initial measurement and changes showed a statistically significant difference. The

| Table 1. Baseline characteristics of study patients |
|---------------------------------|-----------------|-----------------|---|
| Age (years) | Statin group (n=14) | Niacin/Statin group (n=14) | p |
| Height (cm) | 60.8±8.0 | 58.1±7.0 | 0.359 |
| Weight (kg) | 63.5±8.5 | 63.5±10.6 | 0.983 |
| Male (%) | 7 (50.0) | 7 (50.0) | 1.000 |
| Dx. | | | |
| SA (%) | 7 (50.0) | 5 (35.7) | 0.689 |
| UA (%) | 6 (42.9) | 7 (50.0) | |
| AMI (%) | 1 (7.1) | 2 (14.3) | |
| Risk | | | |
| CVA (%) | 0 (0) | 1 (7.1) | 0.144 |
| MI (%) | 0 (0) | 0 (0) | |
| DM (%) | 8 (57.1) | 5 (35.7) | 0.256 |
| Hypertension (%) | 4 (28.6) | 5 (35.7) | 0.686 |
| Smoke (current) (%) | 3 (21.4) | 5 (35.7) | 0.403 |
| Procedures | | | |
| Previous PCI | 3 (21.4) | 1 (7.1) | 0.280 |
| Target vessel (%) (LAD/LCX/RCA/LM) | 66.7/11.1/22.2/0 | 85.7/14.3/0/0 | 0.283 |

Dx.: Diagnosis, SA: stable angina, UA: unstable angina, AMI: acute myocardial infarction, CVA: cerebrovascular accident, MI: myocardial infarction, DM: diabetes mellitus, PCI: percutaneous coronary intervention, LAD: left anterior descending artery, LCX: left circumflex artery, RCA: right coronary artery, LM: left main
Table 2. Laboratory characteristics of study patients

|                        | Statin group (n=14) | Niacin/Statin group (n=14) | p   |
|------------------------|---------------------|----------------------------|-----|
| SBP (mm Hg)            | 118.6±14.9          | 120.9±16.0                 | 0.691|
| DBP (mm Hg)            | 72.0±8.9            | 72.3±11.7                  | 0.943|
| HR (per minute)        | 69.4±11.6           | 71.7±9.4                   | 0.572|
| LVEF (%)               | 65.5±7.9            | 59.7±8.7                   | 0.094|
| Total cholesterol (mg/dL) | 204.6±36.3      | 190.9±5.3                  | 0.275|
| TG (mg/dL)             | 147.9±83.4          | 171.9±137.6                | 0.582|
| HDL-C (mg/dL)          | 48.6±10.0           | 49.0±5.3                   | 0.907|
| LDL-C (mg/dL)          | 127.1±23.5          | 116.0±33.5                 | 0.320|
| WBC (/mm$^3$)          | 6953.6±1541.7       | 7620.0±1792.2              | 0.301|
| Fasting glucose (mg/dL)| 119.2±66.3          | 111.9±28.1                 | 0.709|
| Insulin (mg/dL)        | 22.6±51.1           | 12.4±10.6                  | 0.471|
| hsCRP (mg/dL)          | 0.66±1.29           | 0.85±1.19                  | 0.702|
| Fibrinogen (pg/dL)     | 427.1±168.0         | 458.3±104.1                | 0.560|
| MMP-9 (ng/mL)          | 10.0±9.8            | 11.2±6.2                   | 0.715|
| sCD40L (ng/L)          | 2634.0±1594.8       | 2803.6±2033.5              | 0.815|

SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, TG: triglyceride, HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, WBC: white blood cell, hs-CRP: high-sensitivity C-reactive protein, MMP-9: matrix metalloproteinase-9, sCD40L: soluble CD40 ligand

Table 3. Angiogram and IVUS before and after treatment

|                        | Statin group (n=14) | Niacin/Statin group (n=14) | p   |
|------------------------|---------------------|-----------------------------|-----|
| Proximal RD (mm$^2$)   | 3.09±0.42           | 2.93±0.52                   | 0.534|
| Post                   | 3.07±0.39           | 3.09±0.55                   | 0.943|
| MLD (mm)               | 2.11±0.49           | 1.74±0.31                   | 0.100|
| Pre                    | 2.13±0.44           | 2.03±0.32                   | 0.620|
| Distal RD (mm)         | 2.73±0.46           | 2.66±0.36                   | 0.753|
| Post                   | 2.68±0.59           | 2.75±0.25                   | 0.771|
| Lesion length (mm)     | 17.1±6.3            | 23.3±12.3                   | 0.251|
| Pre                    | 17.9±6.2            | 23.3±12.2                   | 0.204|
| Lumen CSA (mm$^3$)     | 6.31±2.11           | 5.92±0.82                   | 0.647|
| Pre                    | 6.57±1.55           | 5.54±0.95                   | 0.146|
| EEM CSA (mm$^3$)       | 11.49±3.35          | 12.01±1.71                  | 0.710|
| Pre                    | 11.70±2.08          | 10.98±1.33                  | 0.439|
| Atheroma CSA (mm$^3$)  | 5.17±1.93           | 6.11±2.03                   | 0.360|
| Pre                    | 5.22±1.38           | 5.45±1.92                   | 0.784|
| nTAV                   | 170.6±63.6          | 175.9±66.9                  | 0.364|
| Post                   | 175.9±46.9          | 179.7±63.8                  | 0.891|
| % AV                   | 45.4±9.6            | 49.8±10.7                   | 0.407|
| Pre                    | 44.3±9.9            | 48.6±12.4                   | 0.451|

RD: reference diameter, MLD: minimal luminal diameter, CSA: cross-sectional area, EEM: external elastic membrane, nTAV: normalized total atheroma volume, AV: atheroma volume

Comparison of biomarkers of inflammation and oxidative stress between the two groups

After 9 months, hsCRP decreased in the simvastatin group, from 0.661±1.298 mg/dL to 0.341±0.573 mg/dL and decreased in the niacin/simvastatin group from 0.894±1.233 mg/dL to 0.186±0.351 mg/dL (p=0.001) (Fig. 4) (Table 4). After 9 months, MMP-9 increased in the simvastatin group from 48.6±12.4 to 54.5±19.2 mg/dL (p=0.001) (Table 4).

Fig. 1. Flow diagram of the study.
10.2±9.8 to 72.5±33.9 and increased in the niacin/simvas-
tatin group from 11.2±6.2 to 84.7±63.3 (p=0.017) (Fig. 5) (Ta-
ble 4). After 9 months, sCD40L decreased in the simvastatin
group from 2,634±1,594 to 961±1,529 and decreased in the
niacin/simvastatin group from 2,803±2,033 to 836±1,034
(p<0.001) (Fig. 6) (Table 4).

**Discussion**

The present study demonstrates that lipid lowering therapy
with niacin plus simvastatin induces significant plaque re-
gression and stabilization in angina patients who had a mild
to moderate degree of coronary stenosis. The main focus of the
present study was to show that the combination of niacin plus
simvastatin showed a greater decrease in the TAV and the
PAV measured by IVUS, a greater decrease in inflammatory
response measured by biomarkers, and a greater decrease in
platelet activation as measured by sCD40L (Fig. 7).

Currently, the treatment of lipid abnormalities involves the
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primary use of statins to reduce serum levels of LDL-C. Multiple studies have shown that statins lower the mortality and morbidity of patients with coronary artery disease and other atherosclerotic vascular diseases.\textsuperscript{1-4} Statins effectively inhibit mevalonate synthesis and lower LDL-C levels. Beyond lowering the blood lipoprotein level, statins have favorable effects on vascular inflammation,\textsuperscript{14} endothelial function,\textsuperscript{15} and plaque regression.\textsuperscript{16-18} Despite substantial reductions in cardiovascular morbidity and mortality that have been achieved with statins, the protection afforded by these drugs is incomplete. Thus, combination therapies directed at increasing HDL-C are an attractive but unproven approach. This study was the first demonstration of an incremental, independent effect of combination therapy with statin and niacin compared with statin monotherapy to retard the progression of atherosclerosis as measured by IVUS in Korean patients.
Niacin has been in clinical use for 4 decades and is the most effective treatment currently available to increase low levels of HDL-C. The current understanding of its place in an era of potent therapies directed at LDL-C was limited by a lack of studies assessing its incremental effect on atherosclerosis and coronary outcomes. The most recent demonstration of this was the HATS.10 This placebo-controlled study of combined low-dose simvastatin (10 to 20 mg/d) and high dose niacin (2 to 4 mg/d) showed the ability of combination therapy to largely stabilize coronary atherosclerosis with an associated substantial 13% absolute risk reduction (up to 90% relative risk reduction) for cardiovascular outcomes. The absence of a statin monotherapy control group and the use of relatively high doses of niacin, however, limit the capacity to extrapolate the data to a stepwise additive approach to combination therapy in clinical practice that might typically use lower doses of niacin. The data from ARBITER 2 extended our understanding of the potential benefit of combination therapy with statin and niacin in patients with known CHD and moderately low levels of HDL-C beyond previous studies that included niacin as a component of combination therapy.20 ARBITER 2 showed a significant progression of carotid intima media thickness (CIMT) in the placebo (statin monotherapy) group, despite a mean LDL-C of 100 mg/dL, a result that was consistent with previous placebo-controlled studies of statin monotherapy and atherosclerosis progression.11,12,20 Such progression of atherosclerosis in the setting of a statin administered long term differed from the observed initial results of statin administration, likely due to the influence of other lipids (e.g., low HDL-C) and non-lipid risk factors.

Recent data showed that enhanced sCD40L is associated with platelet activation in the setting of hypercholesterolemia, related to an increase in sCD40L to the prothrombotic state previously described in hypercholesterolemia, and provided in vivo evidence that statins might significantly reduce sCD40L and the CD40L-associated prothrombotic state.21 The present study shows that combination therapy of niacin plus simvastatin decreases sCD40L and supports the inhibition of plaque progression.

There is evidence that CRP has proinflammatory and proatherogenic effects via modulation of endothelial, inflammatory and smooth muscle cells of the arterial wall. The proinflammatory, proatherogenic effects of CRP that have been documented in endothelial cells include: 1) decreased nitric oxide and prostacyclin production, and 2) increased production of endothelin-1, cell adhesion molecules, monocyte chemoattractant protein-1, IL-8, and plasminogen activator inhibitor-1.22,23 The present study shows that combination therapy of niacin plus simvastatin decreases hsCRP and explains the inhibition of atherosclerosis progression.

In soft, lipid-rich plaques, especially ones obtained from patients who died of acute coronary syndrome, inflammatory cells including activated macrophages and mast cells accumulate in high concentration. There is an increased rate of formation of MMP enzymes in the ruptured atherosclerotic plaque. Active rupture of the vulnerable plaque by these proteinases is one of the triggers causing subsequent thrombus formation and acute coronary syndrome. This is clinically significant because, serial changes in peripheral blood levels of MMP-2 and MMP-9 were observed in patients with acute coronary syndrome, which implicates a role for these enzymes in the molecular mechanism of plaque destabilization in acute coronary syndrome. Macrophages and smooth muscle cells of human atherosclerotic plaques have been shown to synthesize MMP-3 and MMP-9.24 MMP-9 might directly affect thrombus maturation and dissolution. MMP-9 was able to inhibit platelet aggregation in response to thrombin or collagen25 and can degrade fibrin.26 Furthermore, thrombus formation can induce MMP-9 release from surrounding cells,27 and MMP-9 knockout mice have an increased propensity to hemorrhage.28 Therefore, MMP-9 can reduce thrombus size, and its increased expression may promote smooth muscle cell-directed healing after atherosclerotic plaque rupture, resulting in retardation of plaque expansion and increased stability of the newly forming cap. Another study showed that MMP-9-dependent processes are activated that initiate a healing response that is involved in the recruitment of smooth muscle cells and in the elaboration of matrix when an acute plaque rupture takes place. Hence, after an acute coronary event, increases in the plasma MMP-9 concentration might be the consequence of a healing response rather than of the initial plaque rupture.29 The present study showed that combination therapy of niacin plus simvastatin increases MMP-9 and explains the plaque stabilization as do the other biomarkers.

The present study has two limitations. First, the study size was relatively small. Second, there was selection bias due to patients being enrolled in a single center. In spite of the limitations, the present study shows two important differences. First, this is the first study, to our knowledge, to show a combined effect of statin and niacin using IVUS parameters in Koreans. Second, the present study shows the additive effect of niacin to high dose statin therapy.

In conclusion, the combination of niacin plus simvastatin reduces TAV and PAV measured by IVUS, reduces inflammatory responses measured by biomarkers and decreases platelet activation measured by sCD40L.

Acknowledgments

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