Clinical Investigations

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The Effects of Statin Monotherapy and Low-Dose Statin/Ezetimibe on Lipoprotein-Associated Phospholipase A_2

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ABSTRACT

Background: Many of the pleiotropic effects of statins remain to be elucidated.

Hypothesis: Different statin regimens with similar lipid-lowering efficacy may have different effects on biomarkers of atherothrombosis including lipoprotein-associated phospholipase A_2 (Lp-PLA_2).

Methods: After a 4-week dietary lead-in, 82 hypercholesterolemic patients were randomized to 1 of 2 treatment groups: atorvastatin 20 mg or atorvastatin/ezetimibe 5 mg/5 mg. After 8 weeks of drug treatment, the groups were compared for percent change in lipid parameters, Lp-PLA_2, interleukin-6 (IL-6), monocyte chemoattractant protein-1, and fibrinogen.

Results: Low-density lipoprotein cholesterol (LDL-C) lowering was comparable between the 2 groups ($-47\% \pm 11\%$ and $-49\% \pm 7\%$ in the atorvastatin and combination groups, respectively). Although Lp-PLA_2 was reduced in both groups, the reduction was greater in the atorvastatin group (-42% and -9% [median], respectively, $P = 0.03$). Although IL-6 was decreased only in the atorvastatin group, IL-6 changes were not significantly different between the 2 groups. The changes in monocyte chemoattractant protein-1 and fibrinogen were similar in each group.

Conclusions: Atorvastatin monotherapy was stronger at reducing plasma Lp-PLA_2 than the low-dose atorvastatin/ezetimibe combination after equivalent LDL-C lowering. This result may provide evidence of potential statin effects beyond the lowering of LDL-C.

Introduction

Statins are known to reduce cardiovascular events in patients at variable risk levels.[1,2] Although the major clinical impact of statins is thought to result from a reduction in low-density lipoprotein cholesterol (LDL-C), many studies have reported pleiotropic effects, independent of LDL-C reduction. Statins are known to influence inflammatory mediators,[3,4] endothelial function,[5] angiogenesis,[6] and thrombosis.[7]

Because statins consistently reduce cholesterol levels, it is not easy to evaluate their LDL-C–independent effects on other markers. A few studies have tried to investigate pleiotropic effects of statins by comparing a higher-dose statin with a statin combined with ezetimibe, a cholesterol-absorption inhibitor, after equivalent LDL-C lowering.[8,9] However, many pleiotropic effects of statins remain to be elucidated. Our aim was therefore to compare the effects of statin monotherapy and a lower-dose statin with ezetimibe on markers of atherothrombosis. We used lipoprotein-associated phospholipase A_2 (Lp-PLA_2), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and fibrinogen as markers of atherothrombosis in our study.

Methods

Study Population

Men and women aged 20–79 years with a LDL-C >130 mg/dL and triglycerides (TG) <400 mg/dL were screened for inclusion in the study. Subjects who met the same lipid criteria after a dietary lead-in period were finally considered eligible for the study. Criteria for exclusion included familial hypercholesterolemia, pregnancy or breastfeeding, a history of acute cerebrovascular accident or myocardial infarction within 3 months of trial entry, serum creatinine >2.0 mg/dL, transaminase level >2× upper limit of normal (ULN), thyroid dysfunction, serum creatine kinase (CK) > 2.5× ULN, infection, inflammatory disease, anti-inflammatory drugs, cancer, or a history of adverse reaction to test drugs.

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A minimum of 28 patients per treatment group was planned, assuming a power of 0.80 to demonstrate inequality between the groups. A 6% ± 8% difference in Lp-PLA_2 between the 2 groups was predefined as significant. No prior study reported the effect of a statin/ezetimibe combination on Lp-PLA_2. However, it was documented that the percentage reductions of Lp-PLA_2 and C-reactive protein (CRP) with lipid lowering were similar[10] and the reduction of CRP by ezetimibe has been 6%–10%.[11] Our predefined difference in Lp-PLA_2 was based on these data. To compensate for a 20% dropout rate, at least 35 subjects were to be recruited for each group. One hundred patients were initially screened and 82 were randomized to the 2 treatment groups after the dietary lead-in period. Eighteen patients did not meet the lipid criteria for randomization.

Study Design

This was a 12-week (4-week dietary lead-in period followed by 8 weeks of drug treatment), randomized, open-label, single-center study. The study protocol was approved by the local ethical review committee, and all patients provided written informed consent. At the initial screening visit, patients were interviewed to record their medical history. They underwent a complete physical examination and a laboratory assessment. After discontinuation of any lipid-lowering agent, patients entered the 4-week dietary lead-in period. Thereafter, patients who met the lipid criteria were randomized in a 1:1 ratio into 2 treatment groups for 8 weeks: atorvastatin 20 mg (Lipitor; Pfizer, New York, NY) or atorvastatin/ezetimibe 5 mg/5 mg (Ezetrol; Merck & Co., Whitehouse Station, NJ). Other researchers examined the effects of higher-dose atorvastatin and atorvastatin/ezetimibe combination. However, we chose to use these 2 regimens, because our prior study showed that atorvastatin 20 mg and atorvastatin/ezetimibe 5 mg/5 mg reduced LDL-C appropriately down to 82–91 mg/dL in subjects with baseline LDL-C levels similar to those of the current study.[12]

Laboratory Examination

Blood samples were collected at randomization and after 8 weeks of drug treatment. Patients were instructed to fast and avoid alcohol consumption and cigarette smoking for at least 12 hours prior to sampling. Samples were analyzed within 4 hours of collection or stored at −80°C until analysis. All analyses were performed by the local laboratory, certified by the Korean Society for Laboratory Medicine. Lipid levels were measured in fasting plasma using an autoanalyzer. Biochemical tests to evaluate alanine aminotransferase (ALT), and CK levels were conducted using standard laboratory techniques. Measurement of Lp-PLA_2 mass was performed by a dual monoclonal antibody immunoassay (PLAC Test; diaDexus, Inc., South San Francisco, CA). The intra-assay and interassay variability were both <10%. Plasma levels of IL-6 and MCP-1 were measured by the quantitative enzyme-linked immunoassay technique (R&D Systems Inc., Minneapolis, MN) according to the manufacturer's instructions. The coefficients of variation for intra-assay and inter-assay precision were <7%. Fibrinogen was also measured with enzyme-linked immunosorbent assay (Innovative Research, Novi, MI) and the coefficient of variation was 4%.

Tolerability assessments were based on reported adverse reactions, physical examinations, and clinical laboratory evaluations such as liver enzyme elevation >3× ULN or CK elevation >10× ULN; and physical examinations. The causal relationship of adverse reactions to test drugs was assessed by the investigators.

Statistical Analysis

The primary endpoints were the percentage changes in levels of plasma Lp-PLA_2 mass, IL-6, MCP-1, and fibrinogen from baseline to week 8 of drug treatment. Comparison of these endpoints between the 2 groups was the focus of our study. Secondary endpoints included the percentage changes in total cholesterol (TC), TG, high-density lipoprotein cholesterol (HDL-C), and LDL-C. Efficacy analyses were conducted on the patients who completed the study. Group differences in categorical variables were assessed using the κ^2 test, and continuous variables were evaluated using the Student t test. The Mann-Whitney U test was used for parameters without normal distribution (Lp-PLA_2 and IL-6). The paired t test was used to assess the difference in parameters before and after treatment within each group. The Wilcoxon signed-rank test was used for nonparametric analysis. Differences in percentage changes of markers between the 2 groups were considered significant if the P value was <0.05 (2-sided). All data were analyzed using SPSS version 12.0 (SPSS Inc., Chicago, IL).

Results

Baseline Characteristics

Sixty of the randomized patients completed the study. Twenty-two patients were excluded from the efficacy analysis, 12 because of withdrawal of consent, 9 because of protocol violation, and 1 because of an adverse reaction (myalgia). Among 9 protocol violators, 6 did not appear on visiting dates and 3 did not take more than 85% of the medication. The clinical characteristics of the patients who completed the study are listed in Table 1. Their mean age was 61 years and 68% were female. Each group had similar clinical characteristics such as gender, medical history, and medications (Table 1). The baseline levels of lipid profile and other biomarkers were well-matched (Table 2).

Changes in Lipid Parameters and Biomarkers

The TC and LDL-C levels were significantly reduced in both groups after 8 weeks of drug treatment. The TG levels were not significantly lowered in either of the groups. High-density lipoprotein cholesterol did not change significantly in the atorvastatin group, but was elevated in the combination group ($P = 0.02$) (Table 2). The percentage change from baseline in LDL-C was comparable between the 2 groups (−47% ± 11% and −49% ± 7% in the atorvastatin and combination groups, respectively, $P = 0.40$). There were no significant differences between the groups in the percentage changes of TC and TG. The percentage elevation of HDL-C was greater, but not significantly, in the

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Table 1. Baseline Characteristics of the Patients (N = 60)

	Total (N = 60)	Atorvastatin (N = 30)	Atorvastatin/Ezetimibe (N = 30)	*P* Value
Age, y	61 ± 9	62 ± 9	60 ± 9	0.21
Female gender, n (%)	41 (68)	21 (70)	20 (67)	0.78
BMI, kg/m²	25.3 ± 3.2	25.3 ± 2.7	25.3 ± 3.8	0.93
Medical history, n (%)				
DM	6 (10)	2 (7)	4 (13)	0.39
Hypertension	31 (52)	18 (60)	13 (43)	0.20
Current smoker	2 (3)	0 (0)	2 (7)	0.21
CAD	0 (0)	0 (0)	0 (0)	—
Medications, no (%)				
β-Blockers	24 (40)	14 (47)	10 (33)	0.29
Calcium channel blockers	29 (48)	18 (60)	11 (37)	0.07
ACEI or ARB	26 (43)	16 (53)	10 (33)	0.12
Diuretics	21 (35)	9 (30)	12 (40)	0.42
Aspirin	23 (38)	13 (43)	10 (33)	0.43

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus.

combination group compared with that of the atorvastatin group (−1% ± 10% and 4% ± 11%, respectively, $P = 0.08$; Table 2 and Figure).

Both groups had reduced levels of Lp-PLA$_2$. Interleukin-6 was reduced in the atorvastatin group, whereas it was not significantly lowered in the combination group. Neither group saw a significant change in MCP-1 (Table 2). The percentage reduction in Lp-PLA$_2$ was significantly greater (−42% and −9% [median] in the atorvastatin and the combination groups, respectively, $P = 0.03$), whereas the change in IL-6 was not significantly different between the 2 groups. The percentage change of MCP-1 was similar between the 2 groups. Fibrinogen levels were not significantly changed in either group, and the percentage change in fibrinogen did not differ between the groups (Table 2 and Figure).

Tolerability

Both regimens were well tolerated. Although 1 patient in the atorvastatin group discontinued the study because of an adverse reaction (myalgia), there were no instances of elevation of ALT >3× ULN or CK >10× ULN. The level of ALT slightly increased in the combination group but did not change in the atorvastatin group. Neither group showed a significant change in CK levels.

Discussion

In this study, we found that atorvastatin monotherapy had different effects on the levels of several biomarkers compared with a low-dose atorvastatin/ezetimibe combination. The major findings were: (1) Lp-PLA$_2$ was reduced in both groups, and the percentage change was significantly greater in the atorvastatin group; (2) the IL-6 level was reduced only in the atorvastatin group, but its change was not statistically different from that of the combination group; (3) LDL-C lowering was comparable in the 2 treatments; and (4) HDL-C was elevated only in the combination group, but the percentage change was not different between the 2 groups.

Addition of ezetimibe to statins produced greater reduction in CRP than statin monotherapy.[13] However, it has not been clearly defined whether the effects on inflammation of a higher-dose statin differ from those of a lower-dose statin/ezetimibe.[14] Piorkowski et al tested the platelet inhibition and anti-inflammatory effects of 2 regimens similar to those in the current study. They showed that a high-dose statin is superior in reducing levels of platelet reactivity as well as a plasma chemokine (regulated on activation normally T-cell expressed and secreted [RANTES]).[8] Recently, Liu et al reported greater effects of higher-dose statins on Rho kinase activity and endothelial function, a known pleiotropic effect of statins independent of lipid reduction.[9]

Our study is the first to compare the effects of a higher-dose statin and a lower-dose statin/ezetimibe combination on plasma Lp-PLA$_2$. Schaefer et al evaluated the effects of several statins on Lp-PLA$_2$ and demonstrated that only atorvastatin results in significant reduction.[10] Ky et al also tested several statin regimens and reported that only pravastatin leads to a significant reduction of Lp-PLA$_2$.[15] In contrast, Saougos et al reported that ezetimibe monotherapy also reduces the activity and the mass of the enzyme, although the degree of reduction is modest.[4] An important finding of our study is that Lp-PLA$_2$ was decreased by both atorvastatin 20 mg ($P < 0.001$) and atorvastatin/ezetimibe 5 mg/5 mg ($P = 0.02$), and that

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Table 2. Changes in Laboratory Parameters After Drug Treatment (N = 60)

Parameter		Atorvastatin (N = 30)	Atorvastatin/ Ezetimibe (N = 30)	*P* Value[a]
TC, mg/dL	Before	239 ± 16	43 ± 27	0.49
	After	158 ± 30	158 ± 3	0.99
	P value[b]	<0.001	<0.001	
TG, mg/dL	Before	128 ± 38	134 ± 52	0.63
	After	116 ± 51	117 ± 42	0.90
	P value[b]	0.20	0.12	
HDL-C, mg/dL	Before	50.5 ± 8.8	49.7 ± 7.8	0.71
	After	49.7 ± 7.8	53.6 ± 12.0	0.14
	P value[b]	0.46	0.02	
LDL-C, mg/dL	Before	164 ± 12	163 ± 23	0.94
	After	87 ± 23	82 ± 14	0.38
	P value[b]	<0.001	<0.001	
Lp-PLA_2, ng/mL[c]	Before	338 (101, 798)	265 (97, 1012)	0.13
	After	226 (31, 451)	250 (93, 553)	0.79
	P value[b]	<0.001	0.02	
IL-6, pg/mL[c]	Before	1.40 (0.43, 5.38)	1.14 (0.43, 4.36)	0.15
	After	1.26 (0.42, 2.24)	1.04 (0.41, 4.03)	0.64
	P value[b]	0.047	0.98	
MCP-1, pg/mL	Before	214 ± 66	227 ± 101	0.58
	After	235 ± 72	271 ± 126	0.17
	P value[b]	0.33	0.14	
Fibrinogen, mg/dL	Before	183 ± 31	193 ± 28	0.21
	After	175 ± 27	180 ± 16	0.32
	P value[b]	0.24	0.10	

Abbreviations: HDL-C, high-density lipoprotein cholesterol, IL-6: interleukin-6; LDL-C, low-density lipoprotein cholesterol; Lp-PLA_2, lipoprotein associated phospholipase A_2; MCP-1, monocyte chemoattractant protein-1; TC, total cholesterol; TG, triglycerides.
[a]Comparison between groups.
[b]Comparison in a group before and after treatment.
[c]Numbers presented as medians and ranges.

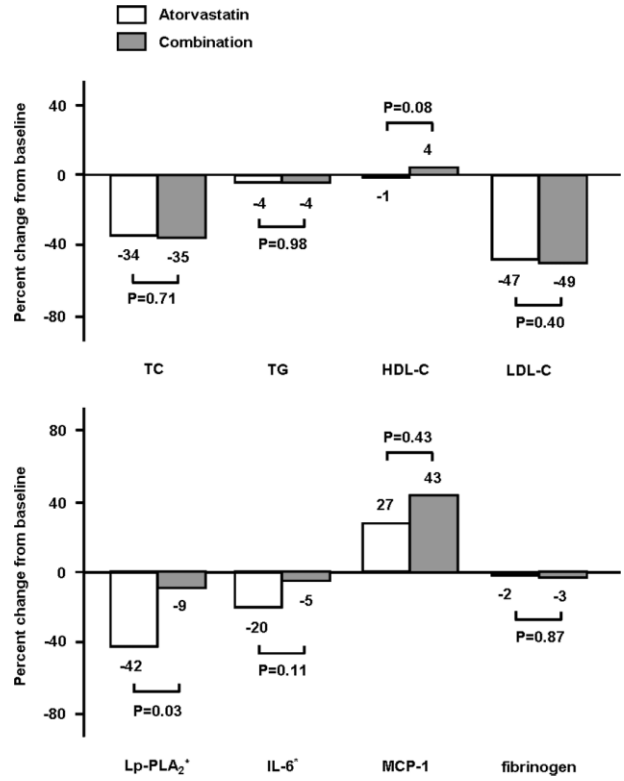

Figure 1. Bar graph showing the effect of atorvastatin vs atorvastatin/ezetimibe on plasma levels of TC, TG, HDL-C, LDL-C (upper panel), Lp-PLA_2, IL-6, MCP-1, and fibrinogen (lower panel). Abbreviations: HDL-C, high-density lipoprotein cholesterol; IL-6, interleukin-6; Lp-PLA_2, lipoprotein-associated phospholipase A_2; LDL-C, low-density lipoprotein cholesterol; MCP-1, monocyte chemoattractant protein-1; TC, total cholesterol; TG, triglycerides. Note: *indicates median.

the percentage change was significantly greater in the atorvastatin group ($P = 0.03$). The changes in Lp-PLA_2 in our study were significantly correlated with changes in LDL-C ($P = 0.04$). However, the difference in Lp-PLA_2 change between the 2 groups persists after adjusting changes in LDL-C levels. Our results provide further evidence for additional effects of a higher-dose statin beyond lowering of LDL-C. The baseline Lp-PLA_2 level was higher, though it was not statistically significant, in the atorvastatin group. Greater reduction in this parameter was correlated with its higher baseline level ($P = 0.02$). However, in our analysis, differential effects of the 2 regimens on Lp-PLA_2 were maintained after controlling of its baseline level ($P = 0.03$).

In our study, IL-6 was reduced only in the higher-dose atorvastatin group. Although the difference between the 2 groups was not statistically significant ($P = 0.11$), it could have been clearer with a larger sample size. Monocyte chemoattractant protein-1 recruits monocytes to vessel walls and is important for the pathogenesis of atherosclerosis. Its prognostic value for vascular disease has recently been reported.[16] Here we found that neither regimen had significant effects on plasma MCP-1 levels. The effects of statins on MCP-1 levels currently remain unclear. In a study by Hanefeld et al, a 12-week treatment with simvastatin was not shown to reduce MCP-1 levels,[17] whereas the same agent was shown to significantly decrease MCP-1 levels in another study.[18] In our study, the reduction of fibrinogen levels by the 2 regimens was similar, although the reduction was statistically significant only in the combination group. We are aware of only a few studies that examined the effect of ezetimibe on fibrinogen levels. Pitsavos et al found no difference in fibrinogen when ezetimibe is coadministered

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with a statin, despite observing a greater reduction of LDL-C.[19]

One of the results of our study is a significant elevation of HDL-C in the lower-dose statin/ezetimibe combination group, whereas HDL-C was not changed in the higher-dose statin group. This is in agreement with a prior report[20] that showed an inverse relationship between HDL-C elevation and atorvastatin dose.

We note that our study has several limitations. First, although possible mechanisms explaining our results were discussed, the underlying mechanism of the findings cannot be completely understood by the present data. However, the elucidation of the exact mechanism is beyond the purpose of our study. Second, because the evaluation of overall clinical impact of a statin regimen by our biomarkers can be incomplete, our results should be interpreted with caution. Third, the total number of study subjects was not sufficiently large, and some variables might not have obtained statistical significance. However, our study was performed with a protocol with reasonably calculated sample size, and it could have minimized this limitation. Finally, a high dropout rate and the open-label study design can be pointed out as weaknesses of the current study.

Conclusion

Atorvastatin monotherapy was more effective in reducing plasma Lp-PLA_2 than a lower-dose atorvastatin/ezetimibe combination after comparable LDL-C reduction. The 2 statin regimens had similar effects on other markers of atherothrombosis. Although the clinical implication of our findings remains to be elucidated, they indicate evidence of potential statin effects beyond the lowering of LDL-C.

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