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Rapid Effects of Simvastatin on Lipid Profile and C-Reactive Protein in Patients with Hypercholesterolemia

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Summary

Background: Rapid lowering of low-density lipoprotein (LDL) cholesterol levels as well as C-reactive protein (CRP) by administration of drugs may produce early benefit to the coronary endothelium in patients with coronary heart disease and reduce angina and coronary events after revascularization. Limited information has been available in evaluating a potentially effective first 2-week therapeutic approach for the treatment of patients with hypercholesterolemia using a statin.

Hypothesis: The study was undertaken to investigate whether a rapid LDL cholesterol and CRP reduction can be achieved by 2-week simvastatin therapy using a common lipid-lowering protocol in patients with hypercholesterolemia.

Methods: Forty-two patients were randomly assigned to 20 or 40 mg/day of simvastatin. Blood samples were drawn at Day 0 and at Day 14 for measuring lipid profile, CRP levels, and hepatic enzymes in all patients.

Results: The results showed that both doses of simvastatin (20 and 40 mg) induced significant reductions in total cholesterol (TC, 25 and 38%) and LDL cholesterol (31 and 46%) compared with baseline. However, the highest dose of simvastatin (40 mg) resulted in significantly greater reductions in TC and LDL cholesterol ($p = 0.04$, $p = 0.02$, respectively) compared with the group receiving 20 mg ($p < 0.04$, $p < 0.02$, respectively). A less significant reduction was observed in mean triglycerides (TG) level (16 and 25%) compared with TC and LDL cholesterol. There was no significant difference in mean high-density lipoprotein (HDL) cholesterol levels compared with baseline in either group. In addition, both doses of simvastatin induced significant reductions in mean CRP levels on Day 14 (22.3 and 23.1%) in a non dose-dependent manner ($p < 0.001$, respectively.

Conclusions: Our data suggest that a common daily dose of simvastatin, especially 40 mg, is an effective 2-week therapy for patients with hypercholesterolemia, and benefit to the vascular endothelium can be derived quickly by reduction of CRP levels.

Key words: simvastatin, lipid profile, C-reactive protein, hypercholesterolemia

Introduction

Reductions in low-density lipoprotein (LDL) cholesterol levels decrease coronary events in patients without previous coronary heart disease (CHD). Moreover, there is increasing evidence that CHD is a dynamic and reversible process and further episodes are preventable. Numerous trials have indicated the efficacy of statins in CHD, and aggressive lipid lowering, by either diet or combination of diet and drugs, can reduce angina and coronary events after revascularization.[1–13] When the treatment groups of both primary and secondary prevention trials are compared, the reduction in cardiovascular events is proportional to the reduction in LDL cholesterol levels.[4, 5] Therefore, rapid lowering of LDL cholesterol levels may produce early benefit to the coronary endothelium in patients with CHD, and single statin agent therapy may be useful for the management of patients in this high-risk subgroup.[6–13]

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Plasma concentration of C-reactive protein (CRP), a sensitive marker of underlying systemic inflammation, is elevated among men and women at risk for future cardiovascular events, and the addition of CRP testing to standard lipid screening seems to provide an improved method for determining vascular risk.[10–14] These data, as well as accumulating evidence that CRP may have direct inflammatory effects at the endothelial level, and that statin therapy may have important nonlipid anti-inflammatory effects are confirmed by decreasing serum inflammatory markers, such as CRP.[10, 12, 13]

However, limited information has been available in evaluating a potentially effective first 2-week therapeutic approach for the treatment of patients with hypercholesterolemia using 3-hydroxy-3methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor; this issue may be important for patients with acute coronary syndrome. The time course of changes in lipid and lipoprotein levels in the first 2 weeks of therapy with HMG-CoA reductase inhibitor in healthy subjects as well as patients,[6, 7] and the rapid reduction in CRP with an 8-week cerivastatin treatment in patients with primary hypercholesterolemia have been demonstrated recently;[11] however, limited data are available in patients with hypercholesterolemia following a 2-week statin therapy. In addition, it is uncertain whether the rapid effect of simvastatin on lipid profile as well as on CRP is generally applicable to other statin agents. The aim of this study, therefore, was to investigate whether a rapid lipid as well as CRP reduction can be achieved by 2-week simvastatin therapy using a routine lipid-lowering protocol in patients with primary hypercholesterolemia.

Subjects

The protocol of the study was approved by the Ethics Review Board of Renmin Hospital, Wuhan University School of Medicine, and all patients provided informed consent. Forty-two patients with mixed hypercholesterolemia were enrolled. All subjects agreed to follow an American Heart Association Step I diet (≤ 30% of total calories from fat, < 10% of calories saturated fatty acids, < 300 mg cholesterol per day) during and for 4 weeks before the study, eating at least two meals per day. Eligible patients included men and women at least 18 years of age, with moderate hypercholesterolemia defined as LDL ≥ 160 mg/dl and triglyceride (TG) ≤ 300 mg/dl, who were not receiving lipid-lowering medication. Patients were randomly assigned to a simvastatin dose of either 20 mg/day (n = 21, 14 men, 7 women, mean age 47 ± 2 years) or 40 mg/day (n = 21, 15 men, 6 women, mean age 50 ± 3 years). All subjects had normal hepatic and renal function. Patients with evidence of myocardial infarction, valvular heart disease, congestive heart failure, a history of dysphagia, swallowing or intestinal motility disorders, untreated thyroid disease, poorly controlled hypertension (systolic blood pressure > 160 mmHg or diastolic blood pressure > 105 mmHg), were excluded from the study. Patients taking drugs that could affect lipid metabolism, such as steroids, thiazide diuretics, or beta blockers, were required to be on stable doses for 2 weeks before screening. In addition, all patients were instructed to maintain their normal lifestyles to avoid any factors that might affect CRP changes during the 2 weeks of treatment.

Methods

Lipid and Hepatic Enzyme Measurement

Blood samples for measurement of lipid were drawn 8–12 h following a dose of either 20 or 40 mg/day of simvastatin after a 12-h overnight fast at Day 0 and at Day 14. Serum levels of TC and TG were measured using enzymatic methods measured by an AE 1000 analyzer (Olympus Optical CO., Ltd, Tokyo, Japan). The HDL cholesterol levels were determined by an anionic detergent method (Sigma Biochemical, Poole, U.K.), and LDL cholesterol concentration was computed using the Friedewald formula as previously reported.[14] During the same time, we measured serum hepatic enzymes including glutamic pyruvic transaminase (GPT), glutamic oxaloacetic transaminase (GOT), and total lactic dehydrogenase (LDH) in all patients in both treatment groups on Day 0 and Day 14 (Biochemical analyzer, CL 1000, Olympus Optical Co., Ltd, Tokyo).

C-Reactive Protein Determination

EDTA-anticoagulated peripheral blood samples were taken after a 12-h overnight fast on Day 0 and Day 14, and plasma was obtained after a centrifugation of 3,000 rpm at 4˚C for 15 min. The CRP levels were determined using immunoturbidometry (Beckmann Assay 360, Bera, Calif., USA). Antiserum antibody and standard agents were supplied by the Beckmann company as previously reported.[14] The median normal value for CRP is 0.08 mg/dl, with 90% of normal values < 0.03 mg/dl. The interassay coefficients of variation were 4.4 and 4.8%, respectively, and intra-assay coefficients of variation were 3.5 and 5.1%, respectively.

Statistical Analysis

The results are expressed as mean ± standard deviation. The baseline and post-treatment lipid components were averaged for each dosage study group and means were compared using a paired *t*-test to calculate the significance of changes in lipid parameters caused by simvastatin therapy. The difference between the two groups was analyzed by paired 2-tailed *t*-test. Because the distribution of CRP is skewed rightward, median concentrations were computed at baseline and at study completion, and the significance of any difference in distributions was assessed by the Wilcoxon rank-sum test. We also computed the absolute and percent change in CRP observed over time for each study subject. A *t*-test was used to evaluate the significance of any difference in mean CRP changes over time, both overall and within each dose stratum. A p value of < 0.05 was considered statistically significant.

TABLE I Baseline characteristics of patients with hypercholesterolemia (mean ± standard deviation)

Variable	20 mg/day group (n = 21)	40 mg/day group (n = 21)
Age (years)	47 ± 2	50 ± 3
Men/women	14/7	15/6
Body mass index (kg/m^2)	22 ± 2.0	20 ± 1.8
Systemic hypertension (%)	10 (48)	9 (43)
Diabetes mellitus (%)	4 (19)	3 (14)
Smoking use (%)	3 (14)	3 (14)
History of coronary intervention [a] (%)	5 (24)	4 (19)
Medications		
Nitrates (%)	16 (76)	14 (67)
Beta blocker (%)	3 (14)	5 (24)
Calcium blocker (%)	14 (67)	13 (62)
Diuretics (%)	6 (29)	4 (19)

[a] History of coronary intervention indicates percutaneous transluminal angiography and/or stents.

Results

Rapid Changes in Lipid Parameters

Baseline characteristics of patients receiving 20 and 40 mg/day of simvastatin therapy are shown in Table I. There were no significant differences in baseline characteristics between the 20 mg/day group (n = 21) and the 40 mg/day group (n = 21) of simvastatin therapy regarding age, gender, body mass index, hypertension, diabetes, smoking use, and history of coronary intervention including percutaneous transluminal coronary angioplasty and/or stents, and medications.

As shown in Table II, both doses of simvastatin (20 and 40 mg) induced significant reductions in TC (25 and 38%), and LDL cholesterol (31 and 46%) compared with baseline. However, the higher dose of simvastatin (40 mg) resulted in significantly greater reductions in TC and LDL cholesterol ($p = 0.04$, $p = 0.02$, respectively) compared with simvastatin 20 mg. Compared with reduction of TC and LDL cholesterol, a less significant change (16 and 25%) was observed in mean TG level. There was no significant difference in mean HDL cholesterol level from baseline to Day 14 after simvastatin therapy in either group.

Rapid Reduction in Plasma C-Reactive Protein Levels

As shown in Table III, median CRP levels deceased from 0.13 mg/ml at baseline to 0.11 mg/ml after a 2-week 20 mg/day simvastatin treatment, while these levels decreased from 0.14 mg/ml at baseline to 0.11 mg/ml after a 2-week 40 mg/day simvastatin treatment. These 15.4 and 21.5% reduction in median levels were attributed to simvastatin therapy. Moreover, mean levels of CRP decreased from 0.36 to 0.28 mg/dl (an average reduction of 22.3%) after 2-week 20 mg/day simvastatin treatment, and from 0.39 to 0.30 mg/dl (23.1%) in the 40 mg/day treatment group. Overall, simvastatin resulted in a 15.8% reduction in median CRP levels and a 22.4% reduction in mean CRP levels. However, no clear dose-dependent effect of simvastatin on CRP was observed in this study.

No Adverse Effects on Hepatic Enzyme Levels

We also measured serum hepatic enzymes including GPT, GOT, and total LDH in all patients from each treatment group on Day 0 and Day 14. There was no significant difference between the two groups in any of the examined hepatic enzymes

TABLE II Changes in mean lipid profile levels (mg/ml) after 2-week simvastatin therapy (mean ± standard deviation)

	TC		HDL-C		LDL-C		TG	
Time	20 mg	40 mg	20 mg	40 mg	20 mg	40 mg	20 mg	40 mg
Day 0	260 ± 14.5	264 ± 14.0	41 ± 3.0	42 ± 3.1	165 ± 10.1	163 ± 10.8	142 ± 9.4	147 ± 9.8
Day 14	208 ± 9.4	192 ± 8.9	41 ± 3.0	44 ± 3.2	126 ± 8.3	112 ± 5.5	122 ± 6.5	118 ± 5.8
% Change								
Day 14 (%)	2 25	2 38 [a]	0	+5	2 31	2 46 [b]	2 16	2 25

[a] $p < 0.04$ compared with 20 mg/day group.

[b] $p < 0.02$ compared with 20 mg/day group.

Abbreviations: TC = total cholesterol, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TG = triglycerides.

TABLE III Changes of median and mean C-reactive protein (CRP) levels after 2-week simvastatin therapy (mean ± standard deviation)

	Median CRP (mg/dl)		Mean CRP (mg/dl)	
Time	20 mg	40 mg	20 mg	40 mg
Day 0	0.13	0.14	0.36 ± 0.10	0.39 ± 0.13
Day 14	0.11 [a]	0.11 [a]	0.28 ± 0.08 [b]	0.30 ± 0.10 [b]
Change (%)	0.02 (15.4)	0.03 (21.5)	0.08 (22.3)	0.09 (23.1)

[a] $p < 0.01$ compared with Day 0.
[b] $p < 0.001$ compared with Day 0.

following simvastatin therapy over time compared with baseline data (data not shown).

Discussion

The evaluation for the changes in lipid and lipoprotein levels within the first 2 weeks of statin therapy is relatively limited. In this randomized intervention study performed in patients with mixed hypercholesterolemia, we observed highly significant reductions in TC and LDL cholesterol associated with both low-dose (20 mg/day) and high-dose (40 mg/day) simvastatin given over a 2-week period. We also found significant plasma CRP reduction in the first 2 weeks of simvastatin treatment in patients with hypercholesterolemia. This is of importance, especially in acute coronary syndromes, because it may signal early onset of vascular endothelial benefit after short-term simvastatin therapy.

It has been demonstrated that patients with CHD and abnormalities of serum lipid level often have endothelial vasodilator dysfunction, which may contribute to ischemic cardiac events.[15–17] The LDL cholesterol reduction by statin appears to be a sufficient explanation for the benefits seen in those studies. In vitro studies have shown that LDL cholesterol and, in particular, its oxidized derivative are injurious to the endothelium. Furthermore, decreasing LDL cholesterol levels with statin in patients with coronary disease has been associated with a beneficial effect on coronary endothelium by decreasing inflammatory markers such as CRP.[8]

Elevated plasma CRP concentration has been shown to be a marker for vascular inflammation and identifies persons at increased risk of future cardiovascular events.[14] In the Cholesterol and Recurrent Events (CARE) study, CRP reduction with pravastatin therapy was associated with significant reductions in coronary events.[15] Participants with a > 50 mg/dl reduction in LDL cholesterol had the largest reduction in CRP level. Although time course of this relation and benefit have not been fully elucidated, perhaps both rapid reduction and degree of LDL cholesterol lowering resulted in early reduction of coronary vascular inflammation. In the present study, we found significant plasma CRP reduction in the first 2-week course of simvastatin therapy in patients with hypercholesterolemia. The median CRP levels deceased from 0.13 mg/ml at baseline to 0.11 mg/ml after a 2-week 20 mg/day simvastatin treatment, and from 0.14 mg/ml at baseline to 0.11 mg/ml after a 2-week 40 mg/day simvastatin treatment. Obviously, these 15.4 and 21.5% reductions in median levels were attributed to simvastatin therapy. Moreover, mean levels of CRP decreased from 0.36 to 0.28 mg/dl (an average reduction of 22.3%) after 2-week 20 mg/day simvastatin treatment, and from 0.39 to 0.30 mg/dl (23.1%) in the 40 mg/day treatment group. Overall, simvastatin resulted in a 15.8% reduction in median CRP levels and a 22.4% reduction in mean CRP levels. Taken together, the rapid onset and degree of LDL cholesterol and CRP lowering produced by simvastatin intervention suggest that the benefit to the vascular endothelium might occur quickly in patients with CHD, which is a critical issue for this high-risk subgroup.

Study Limitations

This study had several limitations. The study was not designed to measure the changes of endothelial function following 2-week simvastatin treatment. In addition, the fact that cardiovascular events were not evaluated in our small group study is a potential limitation. Moreover, we did not use a placebo group as control because of issues of medical ethics; this may also be a limitation.

Conclusion

Our study demonstrated that either 20 or 40 mg/day of simvastatin could be efficient in decreasing TC, LDL cholesterol, and TG in a dose- and time-dependent manner following two 2-week courses of therapy, but neither dose effected changes in HDL cholesterol in patients with mixed hypercholesterolemia. A significant plasma CRP reduction was also found in the first 2 weeks of simvastatin treatment in our patients. These data suggest that a common daily dose of simvastatin, especially 40 mg, is an effective 2-week therapy for patients with mixed hypercholesterolemia, and that benefit to the vascular endothelium can be derived quickly by a reduction in plasma CRP levels.

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