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Changes of plasma inflammatory markers after withdrawal of statin therapy in patients with hyperlipidemia

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Abstract

Background: Atherosclerosis has been considered to be an inflammatory process. In addition to its lipid-lowering properties, statin has been shown to decrease the concentrations of inflammatory markers resulting in reduction of cardiovascular events. Emerging data suggest that withdrawal of statin might be associated with increased cardiac events. The mechanism for this phenomenon, however, is still unclear. We investigated whether acute termination of statin treatment could result in rebound of inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), in patients with hyperlipidemia.

Methods: Seventeen patients (11 men and 6 women, mean age 51 ± 7 years) with hyperlipidemia were given 40 mg/day of pravastatin for 6 weeks. The concentrations of plasma CRP and IL-6 were evaluated before receiving the statin therapy, immediately after 6 weeks of pravastatin therapy, and at days 1, 3 and 7 after withdrawal of pravastatin therapy. The lipid profile was also evaluated at baseline, 6 weeks of therapy, and at day 7 after terminating pravastatin.

Results: Pravastatin therapy induced significant reductions in total cholesterol (TC, 6.88 ± 0.36 vs. 5.27 ± 0.23 mmol/l, $p < 0.01$), low-density lipoprotein (LDL) cholesterol (4.28 ± 0.25 vs. 3.06 ± 0.14 mmol/l, $p < 0.01$), CRP (0.28 ± 0.16 vs. 0.20 ± 0.08 mg/l, $p < 0.01$), and IL-6 (8.4 ± 0.6 vs. 6.7 ± 0.4 pg/dl, $p < 0.01$). Although the TC and LDL-cholesterol did not change during the 7-day period after withdrawal of pravastatin therapy, the concentrations of CRP and IL-6 increased at day 3 (CRP: 0.20 ± 0.08 vs. 0.27 ± 0.12 mg/l, and IL-6: 6.7 ± 0.4 vs. 7.7 ± 0.6 pg/dl, $p < 0.05$ respectively) and at day 7 (CRP: 0.20 ± 0.08 vs. 0.30 ± 0.14 mg/l, and IL-6: 6.7 ± 0.4 vs. 8.7 ± 0.8pg/dl, $p < 0.01$ respectively) after withdrawal of pravastatin therapy. No correlation between increase of CRP as well as IL-6 and small changes of LDL-cholesterol concentrations was found after withdrawal of pravastatin therapy at day 7 ($r = -0.021$ and $r = -0.044$ respectively, $p > 0.05$ respectively).

Conclusions: 6 weeks after pravastatin therapy could significant modify the lipid profile and decrease the inflammatory markers including CRP and IL-6 in patients with hyperlididemia. Moreover, statin therapy discontinuation could induce a rebound phenomenon of inflammatory response representing an increase in some inflammatory markers, which is independent of changes of lipid parameters.

Keywords: Statin; Lipid profile; C-reactive protein; Interleukin-6; Hyperlipidemia; Coronary artery disease

1. Introduction

Hyperlipidemia is one of the major risk factors resulting in the development and progress of atherosclerosis. Clinical trial data support the efficacy of lipid-lowering agents in the primary and secondary prevention of coronary artery disease. Hydroxymethyl-glutary-CoA-reductase inhibitors (statins) offer important benefits for the large populations of individuals at high risk of coronary artery disease [1–3]. Increasing evidence suggests that reduction of cardiovascular events conferred by statins relates not only to cholesterol lowering but rather to direct effects on endothelium function

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and anti-thrombotic as well as anti-inflammatory actions [4–7].

More recently, several studies suggest that withdrawal of statin results in a rapid loss of protection for cardiovascular diseases, which were involved in increased stroke or death and nonfatal myocardial infarction or risk of other early clinical complications, fibrinolytic abnormality, platelet hyperactivity, and vascular endothelial dysfunction [9–15]. The underlying mechanisms for this phenomenon, however, are still unclear. We hypothesise that rebound of inflammatory response may play an important role for this phenomenon. The purpose of the present study, therefore, was undertaken to investigate whether acute termination of statin treatment could result in rebound of inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), in patients with hyperlipidemia.

2. Subjects

The protocol of the study were approved by the Ethics Review Board of Fu Wai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, and all the patients provided informed consent. Seventeen patients (11 men and 6 women, mean age 51±7 years) with mixed hyperlipidemia were enrolled in this study. 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) for 4 weeks before the study, and during the study, while eating at least two meals per day. Eligible patients including men and women at least 18 years old with moderate hypercholesterolemia defined as LDL ≥160 mg/dl and triglyceride (TG) ≤300 mg/dl who were not on lipid-lowering medication. Patients were given a statin therapy using pravastatin at a dose of 40 mg per day for 6 weeks. 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 as well as intestinal motility disorders, untreated thyroid disease, poorly controlled hypertension (systolic blood pressure >160 mm Hg or diastolic blood pressure >105 mm Hg), were excluded from the study. Patients taking drugs that could affect lipid metabolism, such as steroids, thiazid diuretics, or β-blockers, were required to have stable doses for 2 weeks before screening. Medications for other disease were maintained and not changed during pravastatin therapy.

3. Methods

3.1. Lipid measurement

Blood samples for measurement of lipid were drawn 8–12 h following a dose of 40 mg/day pravastatin after 12-h overnight fast at baseline (day 0), and immediately after 6 weeks of therapy, and at day 7 after withdrawal of pravastatin therapy. Serum concentrations of total cholesterol (TC) and triglycerides (TG) were measured using oxidase method (CHOD-PAP) and glycerol-phosphate oxidase method (GPO-PAP) measured by an Olympus AE 1000 analyzer as we previously reported [3]. High-density lipoprotein (HDL) cholesterol concentrations were determined by an anionic detergent method (Sigma Biochemical, Poole, UK), LDL cholesterol concentration was computed using the Friedewald formula as we previously reported [3].

3.2. CRP and IL-6 determination

EDTA-anticoagulated peripheral blood sample were taken after a 12-h overnight fast at baseline (day 0), and immediately after 6 weeks of the therapy, and at days 1, 3, 7 after withdrawal of pravastatin therapy. The plasma was obtained after a centrifugation of 3000 rpm at 4 °C for 15 min. The concentrations of high-sensitivity CRP were determined using immunoturbidometry (Beckmann Assay 360) as we previously reported [3]. The median normal value for CRP is 0.8 mg/l, with 90% of normal values <0.3 mg/l, with a lower detection limit of 0.2 mg/l. The inter-assay coefficients of variation were 4.4% and 4.8%, respectively, and intra-assay CVs were 3.5% and 5.1%, respectively. IL-6 was measured with a commercial assay kit (Quantikine human IL-6, R&D System). IL-6 measurements were performed from plasma in duplicate, and both intra- and inter-assay CVs were <10%. The range of values detected by the assay for IL-6 was 3 to 5000 pg/ml.

3.3. Statistical analysis

The results are expressed as mean±S.D. unless otherwise indicated. The baseline and post-treatment lipid component were averaged for study group and means compared using a paired t or one-way ANOVA test to calculate the significance of changes in lipid parameters caused by pravastatin therapy. Because the distribution of CRP is skewed rightward, log transformation was made at baseline and at study completion, and the significance of any difference in distributions was assessed by the Wilcoxon rank-sum test as our previously reported [3]. Coefficients of correlation (γ) were calculated by the Pearson coefficient analysis. A $p<0.05$ was considered significant.

4. Results

All patients strictly follow the therapy protocol throughout the study. No changes of body mass index (BMI) were observed following the pravastatin therapy (23±3 kg/m^2 at baseline (day 0) vs. 22±3 kg/m^2 at the end of study (after 6 weeks), $p>0.05$) in the present study.