ORIGINAL RESEARCH

Effect of simvastatin on plasma interleukin-6 in patients with unstable angina

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Abstract

Purpose: The primary aim of the study was to investigate the effect of simvastatin on plasma interleukin-6 (IL-6) in patients with unstable angina pectoris (UAP).

Methods: Eighty-six patients with UAP were randomized into simvastatin (40 mg/d for 4 weeks) and the placebo group. Plasma IL-6 was measured by ELISA.

Results: There was a reduction in the plasma total cholesterol and LDL in the simvastatin group ($P < 0.01$). The simvastatin group also had better angina control than the placebo group (post-treatment angina score, 0.72 ± 0.59 vs 1.07 ± 0.76 , $P < 0.05$). Following treatment, the average left ventricular ejection fraction in the simvastatin group was higher than in the placebo group (0.54 ± 0.06 vs 0.51 ± 0.05 , $P < 0.05$), whereas the plasma BNP levels were lower (16.8 ± 6.6 vs 26.4 ± 1.4 , $P < 0.01$). Before treatment, there was no difference in the plasma levels of IL-6 between the simvastatin and the placebo groups ($P > 0.05$). Following treatment, the IL-6 levels in the simvastatin group were lower than in the placebo group (0.7 ± 0.4 vs 1.2 ± 0.4 pg/ml, $P < 0.05$).

Conclusions: Short-term treatment with simvastatin reduces plasma IL-6. The anti-inflammatory effect of simvastatin may contribute to its beneficial effects on the ventricular function and angina control.

Hyperlipidemia is a major risk factor for coronary heart disease.¹ Inflammation also plays a critical role in the pathogenesis of atherogenesis.² C-reactive protein, the prototypic marker of inflammation, is related to future cardiovascular events by promoting atherothrombosis.^{2,3} Monocytes are pivotal cells in all stages of atherogenesis and secrete proinflammatory cytokines such as interleukin (IL)-1 β , IL-6, and tumor necrosis factor, which in turn promote CRP synthesis.⁴

Treatment with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) clearly results in reduced cardiovascular-related mortality and morbidity.^{5,6} The reduction in cardiovascular events observed with statins appears to be the result of their beneficial effects on lipids and other pleiotropic antiinflammatory effects.⁷ Statin-induced reductions of serum interleukin levels, CRP and matrix metalloproteinase activity have been described previously.⁸⁻¹⁴ However, there is a paucity of data in patients with unstable angina. In this study, we investigated the pleiotropic effects of simvastatin on serum levels of IL-6 in patients with unstable angina.

Patients and Methods

This study was approved by the institution review board of Liaocheng People's Hospital. Written informed consent was obtained from all participants. Between March 2004 and July 2006, 86 patients with newly diagnosed unstable angina were approached and agreed to participate in this study. There were 57 men and 29 women, with an average age of 58.2 ± 9.1 years (range 39-76 yr).

The inclusion criteria were age >18 yr, ischemic symptoms < 72 h, absence of cardiogenic shock, and not previously treated with a statin. Patients with severe renal dysfunction, primary cardiomyopathy or chronic obstructive pulmonary disease, or taking anti-inflammatory drugs other than aspirin were excluded from this study.

Unstable angina was defined by typical ischemic symptoms and ECG changes such as ST depression of at least 0.5 mm, or T-wave inversion of at least 3 mm in three or more ECG leads. Patients with elevated cardiac markers (CK-MB or troponin I) were excluded from this study.

The severity of unstable angina was rated by a 4-point scale: 3: severe chest pain at least once daily in the past 3 days; 2: moderate chest pain one or more times in the past 3 days; 1: mild chest pain one or more times in the past three days; and 0: no chest pain in the past 3 days.

Drug administration

After admission, patients were randomized to receive either placebo or simvastatin (40 mg/d) groups. The placebo or statin was administered daily for a period of 4 weeks. All other pharmacological treatments were in accordance with standard clinical protocols. Patients and the investigators who performed data collection and analysis were not aware of a patient's grouping.

Assessment of the left ventricular function

After admission, full physical examination was performed and blood biochemistry was assessed. Two-dimensional and colour Doppler echocardiography (Acuson Sequoia 512, transducer frequency 2.5-3.5 MHz) was performed by two experienced cardiologists to assess the left ventricular function.

To assess the left ventricular function further, plasma BNP was measured at baseline and at the end of the 4-week therapy. We recently reported the methodology of BNP measurements, using Triage[®] BNP Test kit (Biosite, San Diego CA).¹⁵ The device was run daily to confirm laser stability, alignment, and calibration. The inter- and intra-assay variability was 5.5% and 4.5%, respectively. The measurable range of the test is from 5 to 1300 pg/ml.

Measurement of IL-6

Venous blood was obtained at baseline and at the end of the study for measurement of the lipid profile, and for isolation of monocytes for cytokines. All tests were conducted by the standard laboratory techniques in the central biochemistry laboratory of Liaocheng People's Hospital.

ELISA was used to measure the plasma levels of IL-6. The reagents and testing kits for the measurement of IL-6 were purchased from Hongyuan-Yishi Biotech Co. (Dongwu City, China).

Statistical analysis

Data are presented as means $\pm$ SD. Differences in numerical data such as age, lipid profiles, and IL-6 between groups were analyzed by a student *t* test. Categorical data were analyzed with a Chi-square test. $P < 0.05$ was considered to be statistically significant. All data analysis was performed with a SPSS Statistical Package (SPSS 11.0).

Results

General findings

As shown in Table 1, there were no differences in age, sex, baseline blood pressure, heart rate, or other cardiovascular risk factors between the simvastatin and the placebo groups ($P>0.05$). The use of medications for angina during the study was also similar between the two groups ($P>0.05$). None of the patients received emergency percutaneous coronary intervention (PCI) or coronary bypass surgery at the beginning of the study. One patient in the placebo group received PCI during the course of therapy due to worsening angina. There was no myocardial infarction or death at the end of the trial.

In the simvastatin group, a 50-100% elevation of serum ALT and AST from the baseline value was found in 3 patients. The dosage of simvastatin was halved and the AST and ALT returned to the baseline levels two weeks after the dosage reduction. Five patients in the simvastatin group experienced mild indigestion which did not require cessation of simvastatin. There was no abnormal hepatic function or indigestion in the placebo group.

TABLE 1. Baseline characteristics and pharmacological management of the patients.

	Simvastatin (n=43)	Placebo (n=43)	P
Age	58.1±10.9	59.1±9.8	NS
Sex(male)	27(62.8%)	30(69.8%)	NS
SBP(mmHg)	132.2±18.7	128.1±16.8	NS
DBP(mmHg)	72.9±12.7	74.6±11.7	NS
HR(bpm)	75±11	78±13	NS
Diabetes	12(27.9%)	10(23.3%)	NS
Hypertension	21(48.8%)	18(41.9%)	NS
Aspirin	34(79.0%)	31(72.0%)	NS
Clopidogrel	12(27.9%)	14(32.6%)	NS
Nitrates	40(93.0%)	38(88.4%)	NS
Beta-blockers	36(83.7%)	37(86.0%)	NS
ACEI	28(65.1%)	31(72.1%)	NS
Heparin	36(83.7%)	38(88.4%)	NS

ACEI: angiotensin-converting enzyme inhibitor; SBP and DBP: systolic and diastolic blood pressure.

Angina control and changes in blood lipid levels

At the end of the 4 week trial, there was improvement in the angina score in both groups (Table 2). However, the average angina score in the simvastatin group was lower than in the placebo group following treatment ($P<0.05$).

Total blood cholesterol, low-density (LDL) and high-density lipoprotein (HDL) in the placebo group remained unchanged following the study ($P>0.05$, Table 2). However, the total cholesterol and LDL were reduced ($P<0.01$), and HDL level was elevated ($P<0.05$) in the simvastatin group.

Effect on the left ventricular function and BNP (Table 2)

At the end of the treatment, no patient experienced clinical symptoms of heart failure. There was a modest increase in the left ventricular ejection fraction in both groups ($P<0.05$). The average left ventricular ejection fraction in the simvastatin group was higher than in the placebo group ($P<0.05$). There was a reduction in the plasma BNP in both groups ($P<0.05$). The post-treatment BNP in the simvastatin group was lower than in the placebo group ($P<0.05$).

Effect on plasma IL-6

Table 3 shows the values of IL-6 before and after the treatment. At baseline, the average IL-6 was similar between the simvastatin and the placebo group ($P>0.05$). After 2 weeks of treatment, IL-6 in the simvastatin group was lower than in the placebo group ($P<0.05$).

Discussion

The main findings of this study are: 1) Simvastatin therapy in this group of UAP patients was associated with reduction in plasma total cholesterol and LDL, and better angina control; 2) Simvastatin therapy was also associated with an improvement in left ventricu-

TABLE 2. Effect on lipids and the left ventricular function.

	Simvastatin (n=43)	Placebo (n=43)
Total cholesterol(mmol/L)		
Before	5.86±0.85	5.72±0.82
After	4.52±0.17**#	5.70±0.79
LDL(mmol/L)		
Before	3.57±0.63	3.62±0.70
After	2.36±0.44**#	3.55±0.73
HDL(mmol/L)		
Before	1.06±0.27	1.02±0.26
After	1.19±0.40*#	1.05±0.28
Angina scores		
Before	2.31±0.71	2.25±0.64
After	0.72±0.59**#	1.07±0.76*
LVEF		
Before	0.48±0.05	0.47±0.06
After	0.54±0.06*#	0.51±0.05*
BNP (pg/ml)		
Before	40.32±3.45	39.55±3.22
After	16.78±6.55**#	26.44±1.35*

*Comparison before and after treatment, $P<0.05$; **Comparison before and after treatment $P<0.01$; # Comparison between simvastatin and placebo group after treatment, $P<0.05$.

LVEF: left ventricular ejection fraction; BNP: B-type natriuretic peptide.

lar ejection fraction and a reduction in the plasma BNP levels; 3) Plasma IL-6 levels in the simvastatin treatment group were lower than in the placebo group.

Previous studies have shown that statin treatment results in reduced serum cholesterol levels, inhibits inflammatory processes and stabilizes atheromatous plaques.^{16,17} Our study also shows that statin treatment for 4 weeks is associated with lower serum levels of total cholesterol, LDL, and IL-6. Accompanying these biochemical changes, there was improved angina control and left ventricular ejection fraction. Although previous studies have shown that simvastatin reduces expression of IL-6 in patients with hypercholesterolemia,^{10, 11} there is little information on the inhibitory effect of simvastatin on IL-6 in patients with UAP. Our study has demonstrated that 4-week therapy with

TABLE 3. Measurements of plasma interleukin-6 (IL-6, pg/ml).

	Simvastatin (n=43)	Placebo (n=43)
Before	1.4±2.1	1.5±2.3
After	0.7±0.4*#	1.2±0.4#

*Comparison before and after treatment, $P<0.05$; # Comparison between simvastatin and placebo group after treatment, $P<0.05$.

a moderate dose of simvastatin was associated with a reduction in plasma IL-6.

The mechanisms by which simvastatin reduced IL-6, as observed in the present study, are unclear. Monocytes are known to secrete proinflammatory cytokines such as IL-6. Also, monocytes are crucial with respect to the adipose tissue contribution to inflammation.⁴ About 30% of plasma IL-6 derives from adipose tissue.¹⁸ *In vitro* and *in vivo* studies on human monocytes have demonstrated that statins decrease the release of IL-6 from the monocytes IL-6.^{4,10} Whether inhibition of monocyte function and direct actions on adipose tissues were the main reasons of IL-6 reduction in our patients require further investigation. Along with the reduction in plasma IL-6, there was also a reduction in plasma BNP, which is a sensible biomarker for left ventricular dysfunction.^{15,19} We could not find any published evidence that simvastatin, or the resultant reduction in IL-6, would have a direct impact on the plasma levels of BNP. Therefore, the changes in BNP may be due to the improvement in the left ventricular function. One of the potential limitations of the present study was that, due to ethical considerations, the course of simvastatin therapy (4 weeks) was kept relatively short. A longer course of therapy may be required in order to demonstrate the impact of IL-2 reduction on the major cardiac events in the patients with unstable angina.

In conclusion, in patients with unstable angina, simvastatin therapy was associated with reduction in plasma IL-6. The reduction was associated with better angina control and improvement in left ventricular function. These results provide further evidence to support the use of statins in all patients with unstable angina.

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