SCIENTIFIC LETTER

Effects of simvastatin within two weeks on anti-inflammatory cytokine interleukin 10 in patients with unstable angina

J-J Li, Y-S Li, C-H Fang, R-T Hui, Y-J Yang, J-L Cheng, R-L Gao

Heart 2006;92:529–530. doi: 10.1136/hrt.2004.057489

Evidence has shown that the inflammatory process is involved in all stages of atherosclerosis in various clinical settings and that an imbalance between anti-inflammatory mechanisms and proinflammatory factors, in favour of the proinflammatory factors, results in rupture of atherosclerotic plaque.^{1–3} Previous data also showed that proinflammatory cytokines are important in acute coronary events and that decreased plasma concentrations of anti-inflammatory cytokine are associated with acute coronary syndromes.¹

In addition to their cholesterol lowering activity, statins have been shown to have pleiotropic effects, including anti-inflammatory effects.^{2,3} Recent studies have shown that the anti-inflammatory cytokine interleukin 10 has a protective role in both atherosclerotic formation and stability.^{4–6} However, the potential effects of statins on anti-inflammatory cytokines in patients with acute coronary disease has not been investigated. In the present study, we investigated whether a statin would affect interleukin 10 concentration within two weeks in patients with unstable angina (UA).

METHODS

Forty two patients with typical UA were enrolled and randomly assigned to either standard treatment plus 20 mg/day or 80 mg/day of simvastatin immediately after admission. The standard treatment comprised aspirin, β blocker, heparin or low molecular weight heparin, angiotensin converting enzyme inhibitors, and oral nitrates. Patients with evidence of myocardial infarction consisting of ST elevation, formation of Q waves, and increased entry concentration of troponin T or I, congestive heart failure, poorly controlled hypertension, statin treatment before hospitalisation, valvar heart disease, a history of dysphagia, swallowing and intestinal motility disorders, and untreated thyroid disease were excluded from the study.

Selective coronary angiography was performed with the standard Judkins technique. The severity of coronary stenosis was evaluated with the incremental score method as in our previous study.² Blood samples were drawn 8–12 hours after a dose of either 20 mg/day or 80 mg/day simvastatin after a 12 hour overnight fast at day 0 and day 14. Serum concentrations of total cholesterol, triglycerides, high density lipoprotein cholesterol, low density lipoprotein (LDL) cholesterol, and high sensitivity C reactive protein (CRP) were evaluated according to our previous study.³ Serum interleukin 10 concentrations were measured by enzyme linked immunosorbent assay (ELISA) (R&D Systems) as previously reported.^{4–6} The lower limit of detection was 0.5 pg/ml. No significant cross reactivity or interference was observed with recombinant human or recombinant mouse interleukin 10. The intra-assay variation between duplicates was < 10%.

Data were analysed with the use of SPSS (version 10.0; SPSS Inc, Chicago, Illinois, USA) and are presented as mean (SD). Log transformation was used for distribution dependent analyses. Differences between the two groups were analysed by *t* test or one way analysis of variance. Coefficients

of correlation (γ) were calculated by the Pearson correlation analysis (at 14 days). A probability value of $p < 0.05$ was considered significant.

RESULTS

Five patients were excluded from the study because of increased troponin T or I concentrations and coronary intervention for acute exacerbation of symptoms. Thus, data were available from 18 patients who received simvastatin 20 mg/day and from 19 patients given simvastatin 80 mg/day.

The baseline clinical characteristics age, sex, body mass index, lean body mass, systemic hypertension, diabetes mellitus, smoking, lipid profile, left ventricular function, history of coronary intervention including percutaneous transluminal coronary angioplasty or stents, severity of coronary artery stenosis, and medication did not differ between the 20 mg/day group ($n = 18$) and the 80 mg/day group ($n = 19$).

Both doses of simvastatin induced significant reductions in total cholesterol (13% and 22%) and LDL cholesterol (23% and 32%) at day 14 compared with baseline concentrations. The higher dose of simvastatin (80 mg/day) resulted in significantly greater reductions in total cholesterol and LDL cholesterol ($p < 0.01$ and $p < 0.05$, respectively) than those seen in the 20 mg/day simvastatin group. The change in mean triglyceride concentration (13% and 23%) was smaller than the reduction in total and LDL cholesterol. Mean high density lipoprotein cholesterol concentrations after simvastatin treatment did not differ significantly between the groups.

Median CRP concentrations decreased from 5.6 mg/l at baseline to 4.0 mg/l at day 14 of administration of simvastatin in the 20 mg/day treatment group and from 5.7 mg/l at baseline to 3.8 mg/l at day 14 in the 80 mg/day simvastatin treatment group (both $p < 0.01$) (table 1). Simvastatin treatment was associated with a 28% (20 mg/day group) and 33% (40 mg/day group) reduction in CRP at 14 days. The mean interleukin 10 concentration increased from 16.2 pg/ml at baseline to 22.4 pg/ml at day 14 of administration of simvastatin 20 mg/day ($p < 0.001$) and from 15.8 pg/ml at baseline to 28.5 pg/ml at day 14 in the 80 mg/day simvastatin treatment group ($p < 0.001$), indicating a significant dose dependent effect of simvastatin on interleukin 10 in this study (36% v 45%, $p < 0.05$) (table 1). In addition, a significant negative correlation between CRP and interleukin 10 was observed after treatment with simvastatin at 14 days ($\gamma = -0.334$, $p < 0.05$ in the 20 mg/day group; $\gamma = -0.463$, $p < 0.01$ in 80 m/day group).

DISCUSSION

Many investigations have suggested that administration of statins may modify CRP and other proinflammatory cytokine concentrations with a concurrent fall in cardiovascular events. The important finding of the present study is that

Table 1 Changes in median, log CRP, and interleukin 10 concentrations in patients with unstable angina after two weeks of simvastatin treatment

Time	Median hs-CRP (mg/l)		Log hs-CRP(mg/l)		Interleukin 10	
	20 mg/day	80 mg/day	20 mg/day	80 mg/day	20 mg/day	80 mg/day
Day 0	5.6	5.7	1.49 (0.43)	1.52 (0.48)	16.2 (1.2)	15.8 (1.0)
Day 14	4.0	3.8	1.21 (0.36)	1.18 (0.30)	22.4 (1.4)	28.5 (1.7)
Change	-1.6 (29%)*	-1.9 (33%)*	-0.28 (19%)*	-0.34 (23%)*	6.2 (36%)**	12.7 (45%)* †

Data are mean (SD).

*p<0.01 compared with day 0; **p<0.001 compared with day 0; †p<0.05 compared with 20 mg/day group.

hs-CRP, high sensitivity C reactive protein.

either the commonly administered or a high dose of simvastatin given at the time of admission to patients with UA not only significantly reduces LDL cholesterol and CRP concentrations within two weeks but also dramatically increases the concentration of the anti-inflammatory cytokine interleukin 10. A significant negative correlation between CRP and interleukin 10 was also observed with simvastatin treatment at 14 days ($\gamma = -0.334$, $p < 0.05$ in the 20 mg/day group; $\gamma = -0.463$, $p < 0.01$ in 80 mg/day group). This is of a great interest, especially in acute coronary syndromes, because it may balance proinflammatory and anti-inflammatory responses and signal early vascular endothelial benefit after short term simvastatin treatment.

Previous data have shown that interleukin 10 has multifaceted anti-inflammatory effects and inhibits many cellular processes that may be important in plaque progression, rupture, or thrombosis. These include inhibition of the prototypic proinflammatory transcription nuclear factor κ B, resulting in suppression of cytokine production, inhibition of matrix degrading metalloproteinase, reduction of tissue factor expression, inhibition of apoptosis of macrophages and monocytes after infection, and promotion of the phenotypic switch of lymphocytes into the T helper cell type 2 phenotype.⁴⁻⁶ Clinical studies have shown that serum interleukin 10 concentrations are significantly lower in patients with UA than in patients with stable angina, suggesting that decreased serum interleukin 10 concentrations are associated with clinical instability.^{5,6} More recent data also showed that increased serum concentrations of the anti-inflammatory cytokine interleukin 10 were associated with a significantly improved outcome of patients with acute coronary syndromes.⁴ These data further support the concept that the balance between proinflammatory and anti-inflammatory cytokines is a major determinant in the prognosis of acute coronary syndromes. Therefore, enhancing anti-inflammatory cytokine may be a promising approach for treatment of acute coronary diseases.

It has been shown that decreasing LDL cholesterol concentrations with statin in patients with coronary artery disease has been associated with a beneficial effect on the coronary endothelium by decreasing inflammatory markers, such as CRP. However, our data do not agree with the A to Z study, in which the CRP concentration in patients with acute coronary syndromes at one month of statin treatment was not

significantly decreased. Excluding patients with myonecrosis may explain this difference. Consequently, our data showed that either the common or a high dose of simvastatin given at the time of admission to patients with UA not only significantly reduced LDL cholesterol and CRP concentrations within two weeks but also dramatically increased concentrations of the anti-inflammatory cytokine interleukin 10, suggesting that statins have multiple effects on the inflammatory response, including enhancement of anti-inflammatory effects.

In this study, we did not use a placebo group as a control because of medical ethical issues. However, measuring CRP and interleukin 10 at 0 and 14 days in both dosage groups most likely biased our finding towards a null result. A second potential limitation of our study is that we did not evaluate cardiovascular events in our small sample.

Authors' affiliations

J-J Li, Y-S Li, R-T Hui, Y-J Yang, J-L Cheng, R-L Gao, Department of Cardiology, Fu Wai Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, People's Republic of China
C-H Fang, Renmin Hospital, Wuhan University School of Medicine, Wuhan, People's Republic of China

Correspondence to: Dr Jian-Jun Li, Department of Cardiology, Fu Wai Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing 100037, P R China; lijn@pku.edu.cn

Accepted 22 July 2005

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