ORIGINAL REPORT

Short-Term Therapy with High Dose Atorvastatin in Patients with Coronary Artery Disease Can Reduce Inflammatory Process

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Abstract- Coronary heart disease is the leading cause of death and disability in adults. The association between acute coronary syndrom (ACS) and elevated serum high sensitivity c-reactive protein (hsCRP) suggests that chronic inflammation of the coronary arterial wall may play an important role. A number of drugs used in the treatment of cardiovascular disease reduce serum CRP. It* is therefore possible that reduced inflammation contributes to the beneficial effects of these medications. This was a double blind randomized clinical trial on 52 patients were admitted because of ACS at the Mazandaran Heart Center, Iran in 2007. The patients were divided to three randomized groups which received 20, 40, 80* mg Atorvastatin daily for 6 months. At the time of study enrollment and 1, 3 and 6 months after initiation hsCRP were measured. 1 and 3 month after 20mg atorvastatin therapy the median serum concentration of hsCRP did not decrease significantly, but at the end of 6th month it was* significant difference. At 40mg dosage from 3th month to 6th month versus 1st month to 3th month it was significant decrease, at the end of 1th month and 3rd month it was not significant. At 80mg dose at the end of 1th month it was not significant but at the* end of 3th month and end of 6th month it was significant. Intensive lipid-lowering therapy with high-dose atorvastatin therapy relative to moderate lipid-lowering therapy with low-dose atorvastatin reduces hsCRP better. We found that treatment with greater dose of atorvastatin might decrease greater in plasma level of hsCRP.

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Key words: Hydroxymethylglutaryl-CoA reductase inhibitors; C-reactive protein; coronary disease

Introduction

Coronary heart disease is the leading cause of death and disability in adults in the United States, accounting for about one-third of all deaths in subjects over age 35. Mortality from coronary heart disease (CHD) is expected to increase in developing countries, from an estimated 9 million in 1990 to a projected 19 million by 2020 (1). Established cardiovascular risk factors include older age, smoking, diabetes (which is considered a coronary equivalent), dyslipidemia, and hypertension. Multivariable risk models have been created, such as the Framingham risk score and the SCORE project in Europe, that permit estimation of cardiovascular risk in individual patients. Even borderline values for some of these risk factors (e.g., prehypertension, impaired fasting glucose without overt diabetes, and LDL-cholesterol 100 to 159 mg/dL [2.6 to 4.1 mmol/L]) have predictive value (2). The primary pathophysiologic event in an acute coronary syndrome (ACS) is thought to be plaque rupture followed by thrombus formation. Acute coronary syndromes appear to be caused by rupture of an unstable coronary plaque that appears as a single lesion on angiography. However, there is increasing evidence that systemic effects, such as inflammation, are more widespread within the coronary circulation and lead to instability of multiple plaques (2).The sequence of events leading to plaque rupture and the factors that predispose to these events are incompletely understood. The association between ACS and elevated serum concentrations of acute phase reactants, such as CRP (3), suggests that chronic inflammation of the coronary arterial wall may play an important role (4). When considered alone or in combination with traditional risk factors, elevated serum or plasma CRP has been associated with a higher risk of future cardiovascular events (5). Experimental and clinical evidence accumulated since 1990 have established inflammatory

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processes as important contributors to atherogenesis, as well as to the vulnerability of an atherosclerotic lesion to rupture or erosion (6, 7). Based upon this evidence, protein markers of inflammation have been studied as noninvasive indicators of underlying atherosclerosis in apparently healthy individuals and of the risk of recurrent events in patients with established atherosclerotic vascular disease. The most extensively studied biomarker of inflammation in cardiovascular diseases is C-reactive protein (CRP), for which standardized high-sensitivity assays (hs-CRP) are widely available (8). HS-CRP is an acute phase protein that is produced predominantly by hepatocytes under the influence of cytokines such as interleukin (IL)-6 and tumor necrosis factor-alpha (9). In patients with established cardiovascular disease, the predictive value of hsCRP for disease severity and prognosis has been studied in a wide variety of settings. In addition to the association with cardiovascular outcomes, serum CRP may predict coronary disease progression (7). Despite a lack of specificity for the cause of inflammation, data from more than 30 epidemiologic studies have shown a significant association between elevated serum or plasma concentrations of hsCRP and the prevalence of underlying atherosclerosis, the risk of recurrent cardiovascular events among patients with established disease, and the incidence of first cardiovascular events among individuals at risk for atherosclerosis (10). A number of drugs used in the treatment of cardiovascular disease and certain dietary modifications reduce serum hsCRP. It is therefore possible that reduced inflammation contributes to the beneficial effects of these medications (9). Multiple statins significantly decrease serum hsCRP in patients with hyperlipidemia; this decrease appears to be independent of reductions in LDL-cholesterol (LDL-C) (8). The effect of statins on hsCRP may be mediated in part by reduced monocyte expression of IL-6 and tumor necrosis factor-alpha or by direct suppression of hsCRP gene transcription (10). The observations that statins therapy reduces serum hsCRP and that serum hsCRP is correlated with cardiovascular risk raises the possibility that the risk reduction with statin therapy may be attributed, at least in part, to antiinflammatory effects. Atorvastatin is an antilipemic agent, which is HMG-CoA Reductase Inhibitor. Its initial dose is 10-20 mg once daily range to 80 mg once daily (11). The available generics products in IRAN are 20 mg, 40 mg, 80 mg. Atorvastatin is used to treatment of dyslipidemias, to reduce elevations in total cholesterol, LDL-C, apolipoprotein B, and triglycerides in patients with elevations of one or more components, and/or to increase HDL-C (9) Atorvastatin is the most powerful drug for lowering LDL-C and are the most effective lipid lowering drugs when used for primary and secondary prevention of cardiovascular disease (8). Therefore we want to compare effectiveness of various doses of Atorvastatin in lowering hsCRP in coronary heart disease.

Patients and Methods

This was a double blind randomized clinical trial. The study population was drawn from 52 patients were admitted because of ACS at the Mazandaran Heart Center in 2007.All patients had previously undergone coronary angiography and were confirmed to have athermanous lesions. Patients who had unstable angina, who was sensitive to statins, who had hepatobiliari disease, who had Cr>2, or who had LAD involvement were excluded. The patients were divided to three randomized groups which received 20, 40, 80 mg Atorvastatin daily for 6 months. At the time of study enrollment and 1, 3and 6 months after initiation patients were visited and samples of venous blood were collected for high-sensitive C-reactive protein (hsCRP). The SPSS statistical Package version 13.0 was employed for analysis of all data. A value of $p<0.05$ was considered statistically significant. Comparison of treatment effects were performed using t-test. Lab test and drug was free for patients. Furthermore, this research had been approved in research committee of Mazandaran University of Medical Science and had no ethical problem.

Results

52 patients were divides randomly to 3 groups with 20,40,80 mg statin.40 patients remain till end of research.12 patients were Singe Vessel Disease, 6 patients were Two Vessels Disease, 21 patients were Three Vessels Disease ,3 patients were multi Vessels Disease. In Framingham scoring 3 patients were low risk (7.5%),16 patients were moderate risk(4.5%),21 patients were high risk (52.5%).9 patients received 20 mg atorvastatin (22.5%),18 patients received 40 mg (60%),13 patients received 80 mg (32.5%).

1 month after 20 mg atorvastatin therapy the median serum concentration of hsCRP did not decrease significantly (P=0.169).from 3th month to 6th month there was no significant different too (P=0.594), but at the end of 6th month it was significant difference (P=0.001).

Table 1. Reduction of hsCRP after 6 month in different dose of atorvastatin

Atorvastatin Dosage	20 mg	40 mg	80 mg
Reduction of hsCRP	20%	30%	40%

Table 2. P-Value of hsCRP reduction after treatment

Atorvastatin Dosage	20 mg	40 mg	80 mg
After 1month	0.169	0.579	0.279
After 3month	0.594	0.415	0.036
After 6month	0.001	0.013	0.002

Decrease of hsCRP was 20% and it became 80% initial measurement.(Table-1)At 40 mg dosage from 3th month to 6th month (P=0.013) versus 1th month to 3th month (P=0.688) it was significant decrease , at the end of 1th month (P=0.579) and 3th month (P=0.415) it was not significant (Table-2). Decrease of hsCRP was 30% and it became 70% initial measurement. At 80 mg dose at the end of 1th month it was not significant (P=0.2791) but at the end of 3th month (P=0.036) and end of 6th month (P=0.002) it was significant. Decrease of hsCRP was 40% and it became 60% initial measurement.

Discussion

Among our patients there was 7.5% low risk, 45% moderate risk, 52.5% high risk. LDL and hs-CRP are risk factors for vascular events and can be modified by Statin (10). Studies suggest that serum proinflammatory cytokines play an important role in the pathophysiology of the acute coronary syndromes. The reduction of these factors by atorvastatin administration may provide a new insight into the effects of statins on unstable coronary artery disease (11).

In our study Atorvastatin reduced plasma level of hsCRP in most patients but the reduction did not reach statistical significant in all patients and all dosages.

In 10,001 patients with stable coronary artery disease (CAD) enrolled in the Treating to New Targets (TNT) trial, 80 mg/d of atorvastatin (high-dose regimen) reduced the composite primary end point of death from CAD, nonfatal myocardial infarction, resuscitation from cardiac arrest, or stroke by 22% relative to 10 mg/d (low-dose regimen) (10).

A recent study suggest that intensive statin therapy according to the Adult Treatment Panel III guidelines improves arterial elasticity in CAD patients selected for medical treatment. The beneficial vascular effect of atorvastatin on arterial elasticity was independent of lipid parameters (10) and recent evidence suggests that higher doses of statins could improve clinical outcomes compared to conventional doses (8); previous studies in patients with acute and chronic CHD have evaluated the benefit of lipid-lowering therapy on outcomes (11).

We tested the hypothesis that atorvastatin 80 mg/day would have beneficial effects on hsCRP and therefore cardiovascular events. Changes in level of hsCRP, in patients treated with atorvastatin were positively correlated with dosage of atorvastatin, that is, the reduction in hsCRP produced by high dose atorvastatin was greater and it was earlier.

Reduction of hsCRP at dose 20 mg was at the end of 3rd month of therapy and at the dose of 40 mg was after 3rd month but it was not statistically significant, at the dose of 80 mg it was from first month of therapy and it was statistically significant. Thus different dose of atorvastatin had different results in reducing hsCRP and such reduction was more manifest and earlier at 80 mg.

Previous animal and human studies reported detrimental influences of serum level of hsCRP on cardiovascular complications and mortality and morbidity (7). When considered alone or in combination with traditional risk factors, elevated serum or plasma CRP has been associated with a higher risk of future cardiovascular events (5).

The present study indicate that treatment with high dose of atorvastatin may decrease greater in plasma level of hsCRP ,so it can control cardiovascular events in our patients and have better outcomes in future. In summary, we found that high-dose atorvastatin therapy reduced hsCRP relative to low-dose therapy to an extent more sufficient to prevent cardiovascular disease.

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