EARLY AND LATE EFFECT OF HIGH DOSE ATORVASTATIN AND LOW DOSE ATORVASTATIN ON SERUM C - REACTIVE PROTEIN REDUCTION IN NON ST ELEVATION MYOCARDIAL INFARCTION

Masoumeh Sadeghi[(1)], Narges Sadat Razavi[(2)], Nizal Sarrafzadegan[(3)], Mahzad Saeedifar[(4)], MohammadTalaee[(5)]

Abstract

INTRODUCTION: Inflammation is now recognized to play an important role at all stages of the atherogenic process that are precursors of myocardial infarction (MI). hs-CRP is one of this markers of inflammation and Statins have both lipid lowering and anti inflammatory effects and it is proposed that aggressive statins treatment can cause lower serum CRP levels. In this study, we compared intensive and moderate atorvastatin treatment effects on mean serum CRP reduction.

METHODS: This study is a double-blind clinical trial**.** Some patients who were up 21 years old and recently suffered non-ST elevation MI during 24 hours and went to the emergency department of Feiz hospital and/or Chamran hospital and were confined to bed in the CCU were entered in study. A total number of 50 patients were divided to two groups of equal number: A-25 patients under treatment with 80 mg Atorvastatin B-25 patients under treatment with 20 mg Atorvastatin. The examinations hs-CRP and lipid profile were done at admission to CCU, discharge from hospital and two months after treatments and results compared in two groups.

RESULTS: It was specified that in group treated with 80 mg atorvastatin 12 patients (48%) were males and 9 patients (52%) were females and mean age was 60.1 ± 13.4 years. In group treated with 20mg atorvastatin, 16 patients (64%) were males and 9 patients (36%) were males and mean age was 59.6 ± 11.2 years. In group treated with 80mg atorvastatin mean CRP at CCU admission (baseline), discharge and two months latter was 7 ± 5.5, 5.3 ± 4.1 and 2.3 ± 4.3 respectively and in group treated with 20mg atorvastatin was 7.1 ± 8.3, 5.7 ± 7.4 and 3.5 ± 5.1 respectively. Mean serum LDL (Low density lipoprotein) in patients before and after treatment in group treated with 80 mg atorvastatin was 134.2 ± 33.2 and 117.5 ± 31.9 and in group treated with 20 mg atorvastatin was 141.07 ± 33.4 and 126.4 ± 32.5. Mean serum CRP decreased in both groups after treatment but mean CRP decreased to lower levels in patients treated with 80mg atorvastatin either at discharge from hospital ($P = 0.32$) or two months after treatment($P = 0.02$) compared patients treated with 20mg atorvastatin and this difference between two groups was more significant two months after treatment than at discharge. Also serum LDL was decrease in both groups after treatment but no significant difference was detected ($P = 0.77$). With Pearson correlation there was correlation between the percent reductions in LDL cholesterol and in CRP levels only for the total patients ($P < 0.001$), not for the high dose atorvastatin group alone or the low dose atorvastatin group alone ($P > 0.05$).

CONCLUSION: high dose statins cause lower serum CRP levels and their effect on lowering CRP is separated from their lipid lowering effects and is due to their anti inflammatory effects.

Keywords: atorvastatin, CRP, MI, st elevation MI

***ARYA Atherosclerosis Journal* 2008, 4(1): 6-12**

Date of submission: 23 Sep 2007, ***Date of acceptance:*** 30 Jan 2008

1) Associate Professor of Cardiology, Isfahan Cardiovascular Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: sadeghimasoumeh@gmail.com
2) Resident of cardiology, Isfahan University of Medical Sciences, Isfahan, Iran.
3) Professor of Cardiology, Isfahan Cardiovascular Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.
4) Isfahan University of Medical Sciences, Isfahan, Iran.
5) Researcher Methodology and statistic consultant, Isfahan Cardiovascular Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.

Corresponding author: *Masoumeh Sadeghi*

Introduction

Coronary heart disease (CHD), including acute myocardial infarction (MI), angina pectoris, and other ischemic and atherosclerotic heart disease, affects an estimated 13.2 million persons, or 6.9% of the U.S. population. MI is the most common form of CHD with a prevalence of 7.2 million persons.[1]

The association between raised plasma cholesterol and cardiovascular risk is well established, with consistent evidence associating LDL-cholesterol reduction with a reduction in primary and secondary cardiovascular events. It is believed that intensive lipid lowering may improve clinical outcomes further by acting to stabilize plaque and preventing plaque progression, ultimately reducing plaque vulnerability.[2]

Inflammation is now also recognized to play an important role at all stages of the atherogenic process, from the development of fatty streaks in the arterial intimae to formation of complex atherosclerotic lesions and to the rupture of unstable plaques.[3] Different markers of inflammation are measurable in the blood and have been analyzed retrospectively in several major clinical trials in attempts to further refine risk factors for CHD events and to define independent predictive risk beyond lipid risk factors.[4] one of this inflammatory markers is high sensitivity C-reactive protein (hs-CRP).

Markers of inflammation such as hs-CRP have been shown to add further prognostic information about patients at risk of cardiovascular disease who may benefit from statin therapy .Statin therapy is thought to mediate cardio protective effects that influence endothelial function, inflammatory responses, plaque stability and thrombus formation, processes involved in atherosclerosis.[5]

In this study, we compared mean serum hs-CRP level changes in patients with non st elevation MI receiving high dose and low dose atorvastatin at admission, discharge from hospital and two months after treatment and also with other studies.

Materials and Methods

Study design and sampling

This clinical trial was presented by double-blind (statistical analyzer and a person who randomizes without having information about the sort of tablet). There are two groups in the study: A-Some patients under treatment with 80 mg Atorvastatin B-some patients under treatment with 20 mg Atorvastatin.

Some patients who have necessary conditions for entering to the study are investigated with the convenience method of sampling and are placed at upper two groups. According to influences due to disordering elements such as diabetes, sex, hypertension and smoking the cigarette on level CPR, we accommodated those groups with upper condition and introduce one of them to the physician by using software RA and state the method of allocation to the physician, because he/she will not know containing of the tablets (in the form of medicine A and medicine B)

The population under study

Some persons who were up 21 years old and recently suffer non-ST elevation MI during 24 hours and went to the emergency department of Feiz hospital and/or Chamran hospital (at Isfahan) and were confined to bed in the CCU. They are selected for studying voluntarily.

Inclusion Criteria

1) Having severe MI without elevating ST fragment (according to some definitions that are said). 2) Not having myocardial infarct with Q wave. 3) some persons who are studied and are up 21 years old. 4) The subscription for entering to the investigating plan for the patients who accept the plan voluntarily (subscription would be presented by appendix). 5) Not administering controller drugs 3-Hydroxy 4-methylglotaril co enzyme A redoctase and other drugs for decreasing the cholesterol in the blood at recent one month. 6) Lack of existing history of active hepatic disease. 7) Not belonging to group of untreated patients with glands disease. 8) Not having history of systemic inflammatory disease and/or different cancers. 9) Diagnosing one case that has not sensitiveness to statin 10) under physician's opinion the patient able administer drugs and follows them. 11) The patients don't have certain infectious disease during 30 days. 12) The patients don't suffer cardiogenic shock and swelling pulmonary. 13) His /her hepatic enzymes are not more than 3 times normal level. 14) The patient dose not suffer trauma and some beats lead to injure tissue and swelling undeveloping epithelium. 15) the patient is not pregnant and in lactation's periods.16) the patient dose not history of abnormal renal.

Exclusion Criteria

The patient suffers hepatitis disease during the plan. 2) The patient suffers pancreatic disease during the plan. 3) The patient suffers angioedema during the plan. 4) The patient suffers Rabdomyolis during the plan.

The method of performance

The beginning study: when the physician confirms the patient for purpose of inclusion and exclusion criteria and giving subscription he/she enters to the plan. The patient do following examinations in addition of

treatment and routine examinations: 1) hs-CRP 2) triglyceride cholesterol total, high density lipoprotein, low density lipoprotein (for entering to the study).
Then one of two drugs 20 mg and 80 mg Atorvastatin during the day that Just are determined by A and B codes and based on order of providing them via Random allocation method are administered by a physician (he/she dose not know its containing of tablet) The tablets without considering their dose give to executive assistant and finally monthly the patients are received by them. (The tablets with A, B codes are received by executive assistant). The examinations hs-CRP and lipid profile were done by the laboratory of cardiovascular center (Sedigheye-Tahereh Center). When discharge a patient from the hospital (consider he/she almost 5 to 10 days after entering to the hospital), she/he was examined for hs-CRP and lipid profile.

The end of period of studying

The study continues for considering long-term effects of the drugs in the CCU during 2 months. At the end of 2 months, the patient must do some activities that relate to explore. (According to the upper factors at the part of exploring) and in addition to them, the patient must do following examinations:
HS-CPR 2) TG, Chol.Total, HDL, LDL

The method of analyzing data

The data was entered in SPSS .Mean +SD, changing CRP and lipid profile at 2 groups for studying is measured and at\each level t-test, regression and ANOVA are measured.

Results

In this study, we divided 50 patients with non ST elevation MI to two equal groups: 25 patients treated with low dose atorvastatin and 25 patients treated with high dose atorvastatin and then investigated CRP changes.
After data analysis, following results was gotten.

1) Sex distribution:

According to given results, it was specified that in group treated with 80 mg atorvastatin 12 patients (48%) were males and 13 patients (52%) were females. In group treated with 20mg atorvastatin, 16 patients (64%) were males and 9 patients (36%) were males. With chi-square statistical test, sex distribution was compared in two groups and no meaningful difference was detected (Table 1).

2) Mean age:

According to given results, it was specified that mean age in group treated with 80 mg atorvastatin was 60.1 ± 13.4 years and in group treated with 20mg atorvastatin was 59.6 ± 11.2 years. With t-student statistical test mean age was compared in two groups and no meaningful difference was detected (P = 0.32).

3) Mean CRP:

In this study we compared mean CRP in two atorvastatin groups in three times: at CCU admission, discharge and two months latter, which will discuss in following.

A) Mean CRP in patients at CCU admission:
According to given results it was specified that mean CRP at CCU admission in group treated with 80mg atorvastatin was 7 ± 5.5 and in group treated with 20mg atorvastatin was 7.1 ± 8.3. With t-student statistical test mean CRP was compared in two groups and no meaningful difference was detected (P = 0.55).

B) Mean CRP in patients at discharge:
According to given results it was specified that mean CRP at time of discharge in group treated with 80 mg atorvastatin was 5.3 ± 4.1 and in group treated with 20 mg atorvastatin was 5.7 ± 7.4, therefore it was decreased in both groups but with t-student statistical test it was compared in two groups and no meaningful difference was detected (P = 0.32).

C) Mean CRP in patients two months latter:
Given results in this study showed that mean CRP in patients two month after treatment in group treated with 80 mg atorvastatin was 2.3 ± 4.3 and in group treated with 20 mg atorvastatin was 3.5 ± 5.1. With t-student statistical test it was compared in two groups and meaningful difference was detected (P = 0.02).

Table 1: Comparison sex distribution in two atorvastatin groups' patients

Sex / group	Male		Female		Sum total		P value
	Frequency	Percent	Frequency	Percent	Frequency	Percent	
Atorvastatin 80mg	12	48	13	52	25	100	0.252
Atorvastatin 20mg	16	64	9	36	25	100	

Sum total	28	56	23	44	50	100

Table2: Comparison correlation between decrease serum CRP and LDL levels in two atorvastatin groups patients with Pearson correlation

Pearson correlation group	Pearson Coefficient(R)	P value
All patients without group considering	0.619	< 0.001
Atorvastatin 80 mg	0.186	0.38
Atorvastatin 20 mg	0.247	0.235

Table3: Comparison correlation between decrease serum CRP and LDL levels in two atorvastatin groups patients with logistic regression

Group	Odds ratio	95% CI	P value
All patients without group considering	1.77	1.23-2.55	0.002
Atorvastatin 80 mg	0.72	-	0.151
Atorvastatin 20 mg	0.81	-	0.252

4) Mean serum LDL

In this study we measured mean serum LDL in patients before and two months after treatment that this results was gotten.

A) Mean serum LDL in patients before treatment

Given results in this study showed that mean serum LDL in patients before starting treatment in group treated with 80 mg atorvastatin was 134.2 ± 33.2 and in group treated with 20 mg atorvastatin was 141.07 ± 33.4. With t-student statistical test, these results was compared in two groups and no meaningful difference was detected (P = 0.71).

B) Mean serum LDL in patients after treatment

According to given results it was specified that mean serum LDL in patients after treatment in group treated with 80 mg atorvastatin was 117.5 ± 31.9 and in group treated with 20 mg atorvastatin was 126.4 ± 32.5. With t-student statistical test, this result was compared in two groups and no meaningful difference was detected. (P = 0.77).

5) Pearson correlation and logistic regression

In this study we investigated correlation between decrease CRP and decrease serum LDL with Pearson correlation .In patients without group considering, (in total 50 patients) meaningful correlation was detected, But between decrease CRP and decrease serum LDL in patients in two groups separately no meaningful correlation was detected ($P > 0.05$) (correlation coefficient R: 0.186, 0.247, 0.619 respectively for 80 mg and 20 mg atorvastatin and total patients) (Table 2).

We also investigated this correlation between decrease CRP and serum LDL with logistic regression. It was specified that logistic regression was meaningful only in total patients ($P = 0.002$), but not for the high dose atorvastatin group or the low dose atorvastatin group alone ($P > 0.05$).odds ratio and more information are in table 3.

Discussion

CRP is a highly sensitive marker of inflammation and tissue damage, and levels can rise to more than 500 mg per liter in a variety of acute or chronic inflammatory conditions.[6] In contrast, base-line CRP levels are roughly divided into population thirds of less than 1 mg per liter, 1 to 3 mg per liter, and more than 3 mg per liter.[7] Increased baseline concentrations of hs-CRP are strongly associated with mortality and heart failure across the ACS spectrum.[8] In a recent meta-analysis of 22 studies, Danesh et al reported the relative risk for coronary heart disease to be 50% higher for those with CRP levels in the highest third of the respective study populations compared to those with levels in the lowest third.[9]

Statins have been recognized to have anti-inflammatory and antioxidant properties[10] and it has been suggested that these so-called 'pleiotropic' effects may account for some of the benefits of statins beyond LDL-C lowering alone.[11,12]

Regarding statins effects on inflammatory markers especially hs-CRP and therefore cardiovascular outcome in patients with NON ST ELEVATION MI, this study was done with this general purpose: Determination and Camparison C-reactive protein changes level in patient with non st elevation MI receiving high dose and low dose atorvastatin.

Various studies investigated and Camparison effects of intensive (high) dose and low dose statin on CRP and atherosclerosis.

In one study, Paul M Ridker and his colleagues compared the effect of intensive statin therapy (80 mg of atorvastatin orally per day) and moderate statin therapy (40 mg of pravastatin orally per day) on the serum LDL and CRP level and the risk of recurrent coronary events after acute coronary syndromes among 3745 patients with acute coronary syndromes.[13] With regard to CRP, the median levels were similar in the atorvastatin and pravastatin groups at randomization (12.2 and 11.9 mg per liter, respectively; $P = 0.60$), but they were significantly lower in the atorvastatin group than in the pravastatin group at 30 days (1.6 vs. 2.3 mg per liter, $P < 0.001$), 4 months (1.3 vs. 2.1 g per liter, $P < 0.001$), and the end of the study (1.3 vs. 2.1 mg per liter, $P < 0.001$). Although the levels of both LDL cholesterol and CRP were reduced by statin therapy at 30 days, the correlation between the achieved values was small ($r = 0.16$, $P = 0.001$), and Patients who had low CRP levels after statin therapy had better clinical outcomes than those with higher CRP levels, regardless of the resultant level of LDL cholesterol.

In another study, double-blind, randomized active control multicenter trial performed at 34 community and tertiary care center in USA comparing the effect of intensive lipid lowering regimen consisting of 80 mg atorvastatin and moderate regimen consisting 40 mg pravastatin on serum CRP and LDL level.[14] Baseline mean CRP levels in group with intensive regimen was 2.8 mg/l and in group with moderate regimen was 3 mg/l. after 18 months, mean CRP level in group with intensive regimen was 1.8mg/l with -%36.4 change from Baseline and in group with moderate regimen was 2.9 mg/l with -%5.2 change from Baseline .significant difference in the reduction in CRP were observed.

In another study 502 patients were enrolled at 34 U.S. centers and were randomly assigned to receive moderate treatment (40 mg of pravastatin orally per day) or intensive treatment (80 mg of atorvastatin orally per day).[15] Baseline mean CRP levels in group with intensive treatment were 2.8 mg/l and in group with moderate treatment were 3 mg/l .after 18 month fallow up mean CRP levels in group with intensive treatment were 1.8 mg/l and in group with moderate treatment were 2.8 mg/l. There were greater reductions in LDL cholesterol, and CRP levels in the atorvastatin group than in the pravastatin group. There was no correlation between LDL and CRP levels changes. The slower rate of progression in atherosclerosis was seen in group with intensive treatment than moderate treatment.

Given results in our study shows that:

First: both high dose and low dose atorvastatin in patients at discharge from hospital cause decreasing serum hs-CRP and no meaningful difference was detected.

Second: two month after treatment, high dose atorvastatin decrease mean hs-CRP to lower level in comparison to low dose atorvastatin and meaningful difference is detected

Comparison CRP changes at discharge and two month latter in two group showed that high dose atorvastatin don't cause significant difference in CRP levels at short term but at long term, it cause significant difference in CRP level and even below critical level.(3 mg/l).

Comparison this result with other studies shows that in Paul M Ridker study[13] significant difference were observed in mean CRP level in all plasma samples that obtained from patients in two groups at 30 days, 4 months and end of the study (24 months), in contrast in our study, at discharge no significant difference was detected in mean CRP level in two groups despite significant changes after two months. Perhaps this can explain in some by the time of discharge from hospital for our patients that are on average less than 2 weeks (We Considered mean time of discharge almost 5 to 10 days after entering to the hospital). In other studies,[14,15] there is any referred to mean CRP at short term, but at long term, as our study, there is significant difference in mean CRP level between two groups.

In this study, to sum up we comprised serum LDL changes in two group patients. Serum LDL was decrease in both groups after treatment but no meaningful difference was detected (P = 0.77).

With Pearson correlation and logistic regression, there was correlation between the percent reductions in LDL cholesterol and in CRP levels only for the total patients (P<0.001 and P = 0.002), not for the high dose atorvastatin group alone or the low dose atorvastatin group alone (P > 0.05).

In other studies, as in our study, there wasn't any correlation between percent reductions in LDL cholesterol and in CRP levels in each group alone and indicated that statin effect on reduce CRP is separated from their lipid lowering effect and is due to their anti inflammatory effects.[11-13,15,16]

In all other studies, it is identified that Intensive lipid-lowering therapy with high dose atorvastatin per day in patients with CHD provides significant clinical benefit beyond that afforded by treatment with low dose atorvastatin per day.[17,18] Elevated levels of inflammatory markers, particularly C-reactive protein, indicate an increased risk of coronary heart disease[19] and it is identified that high dose statins cause greater reduction in CRP level compare to low dose statins and thus reduce progression of coronary atherosclerosis and improve cardiovascular mortality and morbidity.[13,14,17,20]

Conclusion

Serum CRP level can be used to assessing cardiovascular outcome. Because greater reduction in serum CRP by high dose statins, more widely use of high dose statins is advised in patients with history of CHD, also we advise other studies to investigate cardiovascular outcome in this patients.

Reference

1. Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T ,et al. Heart Disease and Stroke Statistics—2006 Update: A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2006; 113(6): e85-151.
2. Houslay ES, Sarma J, Uren NG. The effect of intensive lipid lowering on coronary atheroma and clinical outcome. Heart 2007; 93(2): 149-51.
3. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005; 352(16): 1685–95.
4. Jialal I. Contemporary Scientific Insights: Role of Biomarkers of Inflammation in Cardiovascular Disease/Atherosclerosis. Crit Pathw Cardiol 2006; 5(4): 191-210.
5. LIAO JK. Statins: potent vascular anti-inflammatory agents. Int J Clin Pract Suppl 2004; (143): 41-8.
6. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest 2003; 111(12): 1805-12.
7. Tall AR. C-Reactive Protein Reassessed. N Engl J Med 2004; 350(14): 1450-2.
8. Scirica BM, Morrow DA, Cannon CP, de Lemos JA, Murphy S, Sabatine MS, et al. Clinical Application of C-Reactive Protein Across the Spectrum of Acute Coronary Syndromes. Clin Chem 2007; 53(10): 1800-07.
9. Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med 2004; 350(14): 1387–97.
10. Patel TN, Shishehbor MH, Bhatt DL. A review of high-dose statin therapy: targeting cholesterol and inflammation in atherosclerosis. Eur Heart J 2007; 28(6): 664-72.
11. Davignon J. Beneficial cardiovascular pleiotropic effects of statins. Circulation 2004; 109(23 Suppl 1): III39–43.
12. Liao JK. Effects of statins on 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibition beyond low-density lipoprotein cholesterol. Am J Cardiol 2005; 96(5A): 24F–33F.
13. Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, et al. C-Reactive Protein Levels

and Outcomes after Statin Therapy. N Engl J Med 2005; 352(1): 20-8.
14. Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA 2004; 291(9): 1071-80.
15. Nissen SE, Tuzcu EM, Schoenhagen P, Crowe T, Sasiela WJ, Tsai J, et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med 2005; 352(1): 29-38.
16. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C - reactive protein and Low-Density Lipoprotein Cholesterol Levels in the Prediction of First Cardiovascular Events. N Engl J Med 2002; 347(20): 1557-65.
17. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, et al. Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease. N Engl J Med 2005; 352(14): 1425-35.
18. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary syndromes. N Engl J Med 2004; 350(15): 1495-504.
19. Pai JK, Pischon T, Ma J, Manson JE, Hankinson SE, Joshipura K, et al. Inflammatory Markers and the Risk of Coronary Heart Disease in Men and Women. N Engl J Med 2004; 351(25): 2599-610.
20. Packard C. Improving outcomes through statin therapy; a review of ongoing trials. Eur Heart J Suppl 2004; 6(supplement A): A28-A31.