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Original Article

Redemptive benefit of atorvastatin in the risk factors of coronary artery disease

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ABSTRACT

Cardiovascular disease, in particular coronary artery disease (CAD), is the principal cause of mortality in developed countries. The classical acute phase protein, C-reactive protein (CRP) is an exquisitely sensitive systemic marker of disease with broad clinical utility for monitoring and differential diagnosis. In recent years, acute phase reactants have been shown to predict future cardiovascular events in individuals with and without established CAD. Atorvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, substantially reduce cardiovascular morbidity and mortality, and recently their anti-inflammatory properties have been investigated. The present study was therefore designed to determine the effects of atorvastatin on CRP in patients with CAD. Ninety two patients with or without or at the risk of CAD were recruited for the study, of which 35 belongs to control (untreated) and 57 were test group, in which, 30 of them received daily with 20 mg/day of atorvastatin and the remaining 27 were untreated. The patients were followed for over a period of 6 weeks. For entire study population, CRP along with lipid profile, SGOT, SGPT, urea and creatinine were measured 1st day and at the end of 6th week of the treatment. For patients with or at risk of CAD, the reduced rate of progression of atherosclerosis associated with intensive atorvastatin treatment, as compared with control is significantly related to greater reduction in the levels of both atherogenic lipoproteins and CRP. This may be important with respect to the early benefits of atorvastatin therapy.

1. Introduction

Cardiovascular diseases (CVD) are the major cause of death and a significant cause of disability in the industrialized world and more recently threaten to pose an increasing health burden on developing nations. Between 1990 to 2020 the proportion of worldwide deaths from cardiovascular disease is projected to increase from 28.9% to 36.3% [1]. Moreover, in terms number of years of life lost, it is projected that cardiovascular disease will jump in ranking from fourth to first, while as a cause of premature death and disability; it will rise from fifth to first [1]. Inflammation plays a key role in the pathogenesis of CVD, acute atherombotic events and atherosclerosis [2, 3]. Circulating levels of several inflammatory markers rise in individuals at risk for atherosclerotic events. In particular C-reactive protein (CRP), a nonspecific acute-phase reactant that is easily and reliable measured has strong predictive power for cardiovascular events. Indeed, measurements of CRP plasma levels add to both the prognostic information gleaned from assay of plasma lipid risk factors and the risk levels estimated by means of Framingham study-based criteria [4]. Many clinical and population studies, with cross-sectional and nested case control designs, proved these inflammatory mediators to be predictors of CVD [5-8]. Most clinical studies report that CRP is an independent predictor of risk

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of atherosclerosis [4], cardiovascular events [9], atherothrombosis [10], hypertension [11] and myocardial infarction [12], even after considering other cardiovascular risk factors such as age, smoking, obesity diabetes, hypercholesterolemia and hypertension.

While improving the understanding of atherosclerotic disease, current insights hold promise for meaningful clinical applications in risk assessment and guidance to targeted therapy. The 3-hydroxy-3-methylgultaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are well-established class of drugs in the treatment of hypercholestrolemia, and members of this class have shown to reduce the risk of cardiovascular morbidity and mortality in patients with or at risk for CAD [13, 14] in several clinical trials. Drug of this class are similar to the precursor of cholesterol HMG-CoA and competitively inhibit HMG-CoA reductase, the last regulated reaction in the synthesis of cholesterol. These compounds act by upregulating low-density lipoproteins (LDL) receptor activity and reducing the entry of LDL into the blood stream. However the statin therapy results in a greater clinical benefit when levels of the inflammatory biomarker CRP is elevated and that statins lower CRP levels in a manner largely independent of LDL cholesterol levels. These findings, along with basic laboratory evidence, have led to the hypothesis that, in addition to being potent lipid-lowering agents, statins may also have anti-inflammatory properties that are important for prognosis and treatment. In the present investigation whether a rapid CRP and lipid profile reduction can be achieved by a short-term therapy using routine lipid lowering statin (Atorvastatin) in patients with CAD.

2. Materials and methods

2.1. Study population

The study population (test group) consisted of 57 patients with a mean age of 61.3±8.4 years. The control group included 35 patients with mean age of 58.7±6.8 years, were included in this study. The combined group both cardiac and non cardiac patients numbering 92 are divided into three groups. Among them 35 were under control and untreated (group A). Further the test group of number 57 divided as two such as atorvastatin treated were 30 (group C) and untreated were 27 (group B).

The present study included the taking of a full medical history, physical examinations, blood chemistry and an electrocardiogram. The diagnosis of CAD and inclusion criteria were based on a history of ischemic chest pain and characteristic ECG changes. Exclusion criteria included body temperature >38.00C, inflammatory diseases (e.g., malignancies), impaired liver functions, renal failure, active cancer and recent major surgery. For all patients, blood was drawn before the initiation of therapy and about 6 week later. No patients were taken statins at the time of enrolment. Other medications remained unchanged during the study period. All patients gave written informed consent before the study.

2.2. Biochemical parameters and Assay

In serum the levels of CRP, lipid profile as well as hepatic enzymes (SGOT and SGPT) and renal markers (urea and creatinine), were obtained in the fasting state in the first day and at the end of 6 week of therapy. All the venous blood samples were drawn into pyrogen-free blood collection tubes without additive. The serum was collected after centrifugation at 3500 rpm for 3 minutes and then stored at -700C until analyzed. CRP was measured by using immunoturbidometry method (RANDOX Laboratories Ltd., United Kingdom). Estimation of total cholesterol (TC) (CPC Pharmaceuticals Pvt Ltd., Spain), serum triglycerides (TG), high-density lipoprotein (HDL) cholesterol, SGOT, SGPT (Raichem, Laboratories Ltd., California) urea (RANDOX Laboratories Ltd., United Kingdom) and creatinine (DiaSys Diagnostic Systems GmbH & Co, Germany) were performed in the fasting venous blood sample using standard commercial kits. The value of low-density lipoprotein cholesterol (LDL), and very low-density lipoprotein cholesterol (VLDL), were calculated using Friedwald's equation.

2.3. Statistical Analysis

Statistical analysis was performed with SPSS 12 statistical software package. Data were recorded on a pre-designed performed and managed on spreadsheet. All the entries were checked for any error. Descriptive statistics for quantitative variables were computed by mean and standard deviation. Means in all groups were compared by Student's t-test. In this study, $p<0.05$ has been considered as statistically significant.

3. Results

Baseline characteristic of the patients are shown in the Table 1 (Age, sex, alcohol consumption, smoking history, diabetes, hypertension, medical conditions and treatment). The baseline mean and S.D. of the effects of atorvastatin on lipid profile, CRP, SGOT, SGPT, urea and creatinine levels are shown in Table 2.

Table 1. Baseline clinical characteristics

Variables	Control (n=35)	Test group(n=57)
Age (years)	58.7±60	61.3±8.4
Sex (male/female)	27/8	42/15
Systemic hypertension (%)	12(34)	45(79)
Diabetes mellitus (%)	10(29)	32(56)
Smoking consumption (%)	7(20)	28(49)
Alcohol consumption (%)	2(5)	13(23)
Oral hypoglycemic (%)	10(29)	26(45)
Insulin (%)	-(0)	3(5)
Aspirin (%)	2(6)	24(42)
Nitrates (%)	-(0)	38(67)
Antihypertensive (%)	10(29)	36(64)
Atorvastatin (%)	-(0)	32(56)

Table 2. Baseline mean levels of CRP, lipid profile, SGOT, SGPT, urea and creatinine

Biochemical Parameters	Control (Group A)			Test Group – Untreated (Group B)			Test Group – Treated (Group C)		
	1st day	6th week	P Value	1st day	6th week	P Value	1st day	6th week	P Value
CRP (mg/dl)	0.63±0.4	0.6±0.4	NS	0.9±0.6	1.8±0.9	0.001	2.1±0.6	1.4±0.4	0.001
TC (mg/dl)	171.1±37.1	171.6±35.6	NS	167±22.8	178.3±30.4	0.001	203.6±38.4	159.3±27.2	0.001
TG (mg/dl)	132.4±51.6	151.6±73.6	0.05	137.2±65	144.7±68.7	NS	164±94.2	140±61.7	0.05
HDL cholesterol (mg/dl	40.2±6.7	44.7±10.4	NS	39.6±6	45.6±9.7	0.01	38.1±5.7	40.6±10.5	NS
LDL cholesterol (mg/dl)	103.8±33.9	96.4±25.9	NS	100.5±21.6	111.8±24.4	NS	134.5±37	94.4±20	0.001
VLDL cholesterol (mg/dl)	26.9±11.34	30.2±14.7	NS	25.5±12	28.8±14.3	NS	32±17.9	32±12.3	NS
SGOT U/L at 37	28.8±12.2	24.8±5.7	NS	25.4±5.2	25.7±5.2	NS	24.4±5.8	29±12.5	0.05
SGPT U/L at 37	30.9±16.3	25.9±6.1	NS	25.1±6.7	25.66±4.8	NS	26.8±7.2	30.1±11.8	NS
Urea (mg/dl)	29.6±13.4	30±12.2	NS	25.6±6.7	31.4±12.8	0.02	23.7±6.2	29.5±12.8	0.02
Creatinine (mg/dl)	1±0.4	1.2±0.5	NS	1.2±0.3	1.4±1	NS	1.0±0.2	1.1±0.4	NS

CRP-C-reactive protein; TC-total cholesterol; TG-triglycerides; NS-not significant; Values are expressed as means and standard deviation.

3.1. Effect of atorvastatin therapy on CRP and lipid profile

As shown in the Table 2 there was no significant change in the level of CRP in group A. There was a significant increase in CRP level was observed in group B. Moreover, mean levels of CRP decreased as 33.3% mg/dl (Table 3) was observed in treatment group (group C) after administration of atorvastatin. There was no significant change in the lipid profile in group A were found in the present study at 1st day and the end of 6th week. There were significant increases in the TC, TG and HDL cholesterol and slight increase in the mean levels of LDL cholesterol were noted in group B. However, as shown in Table 2 dose of 20 mg/day atorvastatin induced significant reductions in TC (-21.7%) and LDL cholesterol (-30%) at the end of the 6th week compared with data obtained from group A and group B. A less significant change was observed in mean TG level (-14.6%) compared with that of reduction of TC and LDL cholesterol. There was no significant increase in the mean HDL cholesterol (6.5%) level from baseline to data available from 6th week of atorvastatin therapy in group C.

3.2. Effect of atorvastatin on hepatic enzymes and renal safety parameters

The present study also measured serum hepatic enzymes including, SGOT and SGPT in all patients from each group at 1st day and the end of 6th week. There were no significant different within and between the group A and B. There was a minor elevation of SGOT and SGPT were observed in some patients in group C following atorvastatin therapy. These elevations are not clinical significant and measuring hepatic enzymes once together with CRP, lipid profile after starting therapy is probably sufficient for the patients. There were no significant changes in urea and creatinine within and among groups.

Table 3. Changes in mean CRP and lipid profile levels (mg/dl) in patients with coronary artery disease after 6-week of atorvastatin therapy (20 mg/day)

Duration	CRP	TC	TG	HDL cholesterol	LDL cholesterol
1st day	2.1±0.6	203.6±38.4	164±94.2	38.1±5.7	134.5±37
6th week	1.4±0.4	159.3±27.2	140±61.7	40.6±10.5	94.4±20
%change	-33.3%	-21.7%	-14.6%	6.5%	-30%

4. Discussion

Over the past decade, HMG-CoA reductase inhibitors have emerged as one of the most effective means of reducing risk for CVD. Several large randomized, controlled trials have demonstrated that statins statistically significantly reduce risk for CVD in both primary and secondary prevention settings [15-18]. Most studies focused on the efficacy of statins in patients with elevated circulating levels of LDL cholesterol. More recently, however, there has been growing interest in the possibility that some of the clinical benefits of statins are due to so called pleiotropic effects that are not directly related to their lipid-altering effects [19, 20].

Based upon the data presented, atorvastatin seems unique in its ability to preferentially lower those components most elevated within each dyslipidemic category: TC, LDL cholesterol and TG. This result suggests that atorvastatin primarily reduces the lipid fraction most available, rather than targeting only one lipid fraction. Statins have biological effects beyond LDL cholesterol

level reduction, including antiproliferative effects on smooth muscle cells, restoration of endothelial activity, antithrombotic effects, antioxidant effects, and anti-inflammatory effects, which have been identified in a number of experimental settings [21-24]. CRP especially has been shown to be an important independent risk factor, which is additive to the TC/HDL cholesterol related risk [25] and it is also a strong prognostic marker for 90-day outcome in acute coronary syndrome [26]. Measures to decrease CRP are therefore promising interventions to decrease cardiovascular risk.

The present study shows changes in CRP levels with atorvastatin use. Many clinical trials have shown that statin treatment reduced plasma levels of CRP. Ridker et al [27] have shown that 5 years of therapy with pravastatin decreases CRP levels significantly and improves clinical outcome as compared to a placebo group where CRP levels tended to increase [27]. Indeed, the PRINCE study has demonstrated that pravastatin reduces CRP levels at both 12 and 24 weeks in a LDL cholesterol-independent manner [28]. Moreover, it seems that atorvastatin exerts a more potent effect on the reduction of CRP than pravastatin, as demonstrated by the ARBITER study [29]. This result has been confirmed by the REVERSAL study, which confirms that atorvastatin induces a greater reduction in CRP levels that pravastatin [30], and seems also to be more potent that simvastatin [31]. In 2005, the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial again clearly demonstrated that CRP is a marker of cardiovascular risk in primary and secondary prevention [32].

The observation that CRP levels are extensively reduced through treatment with atorvastatin at 6 weeks may be of particular interest in view of new data on early intervention with statins in acute coronary syndromes. These data show a significant benefit for early statin treatment as compared to controls with conventional, non-invasive therapy. Whether this clinical benefit is due to an improvement of endothelial function or plaque stabilization, either via lowering of lipids or via reduction of inflammatory processes remains, to be elucidated. Since recent data indicate [33] that endothelial dysfunction can be improved through statin therapy within days, it is conceivable that chronic inflammation can consecutively be improved within a short period.

5.Conclusion

Atorvastatin significantly decreases CRP concentrations after 6 weeks of therapy. Patients who have low CRP levels after atorvastatin therapy have better clinical outcomes than those with higher CRP levels. Strategies to lower cardiovascular risk with atorvastatin should include monitoring CRP as well as cholesterol. The results of this study will provide important information on how to maximize the therapeutic benefits of atorvasstatin in a broader range of patients at risk for cardiovascular morbidity and mortality. Of course, data from large, randomized, prospective trials are required to substantiate these findings.

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