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Redeeming Measure of Atorvastatin in the Risk Factors of Cardiovascular Disease

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Abstract: The present study was designed to determine the effect of atorvastain on C-reactive protein (CRP) in patients with Cardiovascular diseases (CVD). One hundred and fifteen patients with or without CVD were recruited for the study, of which 75 belongs to control (untreated) and 40 were test group (treated) and received daily with 10 mg day^{-1} of atorvastatin. The patients were followed for over a period of 3 months. For entire study population, CRP along with lipid profile, SGOT and SGPT were measured 1st day and at the end of 3rd month of the treatment. There was greater reduction in the levels of both atherogenic lipoproteins and CRP were found in test group when compare with control. These findings suggest that statin-mediated anti-inflammatory effects may contribute to the ability of atorvastatin to reduce risk for CVD.

Key words: Inflammation, C-reactive protein, cardiovascular disease, statins

INTRODUCTION

Cardiovascular disease (CVD) is a substantial public health problem and is the leading cause of morbidity and mortality in the industrialized world over the past few decades. The most important known risk factors for developing this disease are dislipoproteinemia (Raos and Strujie, 2002), hypertension (Singh and Mehta, 2003), diabetes (Folsom et al., 2003), obesity (Grundy, 2002) and smoking (Critchley and Capewell, 2003). Nevertheless, these factors only explain two thirds of all cardiovascular events (Pahor et al., 1999) and therefore in the last year there has been a great scientific interest in the search of new markers and risk factors that could be associated and responsible for this pathology. Atherosclerosis is considered to be a multifactorial disease driven by inflammatory reactions and a common clinical manifestation of this process is coronary artery disease (CAD). CAD is associated with altered levels of several acute phase proteins including C-reactive protein (CRP), which has a variety of physiological functions in the initial inflammatory response consistent with an important role in non-specific defense mechanisms (Baumann and Gauldie, 1994). Most clinical studies report that CRP is an independent predictor of risk of atherosclerosis (Libby

and Ridker, 2004), cardiovascular events (Black et al., 2004), atherothrombosis (Pepys and Hirschfield, 2001), hypertension (Sesso et al., 2003) and myocardial infarction (Ridker et al., 2002), even after considering other cardiovascular risk factors such as age, smoking, obesity, diabetes, hypercholesterolemia and hypertension.

Statin, a 3-hydroxy-3-methylgultaryl coenzyme A (HMG-CoA) reductase inhibitors, represent a well established class of drugs that effectively lower serum cholesterol levels and are widely used for the treatment of CVD (Ridker et al., 1999; Jackson, 2000; Miller et al., 2001; Plenge et al., 2002; Li and Chen., 2003). When the treatment groups of both primary and secondary prevention trials are compared, the reduction in cardiovascular events is mainly proportional to the reduction in low-density lipoprotein (LDL) cholesterol levels (Azar et al., 2001; Treasure et al., 1995). 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

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that are important for prognosis and treatment. If so, then the level of CRP achieved as a result of statin therapy may have clinical relevance analogous to that of the LDL cholesterol levels achieved through the use of statin therapy. In the present investigation whether a reduction of CRP and lipid profile can be achieved by a three month therapy using routine lipid lowering statin (atorvastatin 10 mg day^{-1}) in patients with CVD.

MATERIALS AND METHODS

Patients: The study population (test group-treated) consisted of 40 patients with a mean age of 61.9±6.1 years, admitted to the Ramakrishna Hospital Cardiac Care Unit. The control group (untreated) included 75 patients with mean age of 58.3±7.2 years, who entered to the hospital for one day health check program were included in this study.

The present study included the taking of a full medical history, physical examinations, blood chemistry and an electrocardiogram. The diagnosis of CVD and inclusion criteria was based on a history of ischemic chest pain and characteristic ECG changes. Exclusion criteria included body temperature >38.0°C, inflammatory diseases (e.g., malignancies), impaired liver functions and recent major surgery. In evaluating the physical and laboratory findings of the subjects, hypertension was measured by using the right arm of a seated subject, after atleast 5 min of rest, with a mercury sphygmomanometer with the optimal cuff-size for the subject's arm circumferences. The first and fifth Korokoff sounds were recorded to determine the systolic and diastolic BP respectively. All patients gave written informed consent before the study.

Biochemical parameters and assay: In serum the levels of CRP, lipid profile and liver markers (SGOT and SGPT), were obtained in the fasting state in the first day and at the end of third month of therapy. 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 min and then stored at -70°C 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 and SGPT (Raichem Laboratories Ltd., California), were performed in the fasting venous blood sample. The value of LDL cholesterol and very low-density lipoprotein cholesterol (VLDL), were calculated using Friedwald's equation.

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 the two groups were compared by Student's t-test. In this study, $p < 0.05$ has been considered as statistically significant.

RESULTS

Table 1 presents the characteristic of the patients. In Table 2, there was a less significant increase in CRP level was observed in control group. Moreover, mean levels of CRP decreased as 38.8% mg dL^{-1} was observed in test group after administration of atorvastatin. There were no significant increases in the TC, TG and LDL cholesterol and a significant increase in the mean levels of HDL cholesterol was noted in control group. However, as shown in Table 2 dose of 10 mg day^{-1} atorvastatin induced significant reductions in TC ($p < 0.001$), TG ($p < 0.01$) and LDL cholesterol ($p < 0.001$) at the end of the 3rd month compared with data obtained from test group. There was a significant increase in the mean HDL cholesterol ($p < 0.02$) level from baseline to data available from 3rd month of atorvastatin therapy in test group.

Table 1: Baseline clinical characteristics

Variables	Control (n = 75)	Test group (n = 40)
Age (years)	58.3±7.2	61.9±6.1
Sex (male/female)	47/28	29/11
Systemic hypertension (%)	12 (16)	28 (70)
Diabetes mellitus (%)	16 (21)	24 (60)
Smoking consumption (%)	17 (22)	18 (45)
Alcohol consumption (%)	12 (16)	8 (20)
Oral hypoglycemic (%)	16 (21)	20 (50)
Insulin (%)	Nil (0)	4 (10)
Aspirin (%)	12 (16)	16 (40)
Antihypertensive (%)	12 (16)	28 (70)
Atorvastatin (%)	Nil (0)	40 (100)
Other lipid lowering drugs (%)	19 (25)	Nil (0)

Table 2: Changes in mean CRP and lipid profile levels in patients with CVD after 3 months of atorvastatin therapy (mean±SD)

Parameters	Control (untreated)		Test group (treated)	
	1st day	3rd month	1st day	3rd month
C-reactive protein	0.5±0.30	0.7±0.40	1.8±0.50	1.1±0.30
Total cholesterol	169.1±32.0	175.6±31.6	205.8±39.5	169.6±23.9
Triglycerides	136.1±56.4	150.2±74.2	177.1±85.9	142.2±49.3
HDL cholesterol	40.3±6.30	45.0±9.60	38.2±5.70	42.1±9.80
LDL cholesterol	101.6±29.6	101.1±25.4	133.0±41.0	96.2±21.4
VLDL cholesterol	27.1±11.3	30.0±14.8	35.4±17.2	28.4±9.90
SGOT	26.3±6.10	25.0±5.10	25.5±7.60	28.5±12.7
SGPT	26.7±5.10	25.5±5.10	27.4±7.20	30.1±13.0

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 3rd month. There were no significant different control group and there were a minor elevation of SGOT and SGPT were observed in some patients in test group 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.

DISCUSSION

In primary and secondary prevention, statins have shown great efficacy in reducing cardiovascular events and deaths. Since the results of Scandinavian Simavastatin Survival Study (4S) were first reported over 10 years ago, many other trials have corroborated the beneficial effects of this class of drugs (Scandinavian Simavastatin Survival Study (4S) Group, 1994; Shepherd *et al.*, 1995; Ridker *et al.*, 1999; Sever *et al.*, 2003).

Based upon the data presented, most atherogenic lipoprotein were reduced to a greater extent in the intensive treatment group. This result suggests that atorvastatin (10 mg day^{-1}) primarily reduces the lipid fraction most available, rather than targeting only one lipid fraction. Numerous long-term, placebo-controlled clinical trials involving 50,000 individuals with an average follow-up of about 5 years have conclusively demonstrated that statins reduce the risk of morbidity and mortality from CVD across a wide range of cholesterol levels (Shepherd *et al.*, 2002). The typical reduction in LDL cholesterol from the doses used in these pivotal trials was 25-35%, with a reduction in relative risk of CVD from 24-37% (Schwartz *et al.*, 2001; Heart Protection Study Collaborative Group, 2002; Sever *et al.*, 2003; Colhoun *et al.*, 2004).

The present study shows changes in CRP levels with atorvastatin use. This reduction of CRP by atorvastatin has increased awareness of anti-inflammatory effects of statins and the possible contribution of such an effect to the rapid clinical efficacy of the treatment in cardiovascular patients. Ridker *et al.* (1999) 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. Indeed, the Pravastatin Inflammation/CRP Evaluation (PRINCE) study has demonstrated that pravastatin reduces CRP levels at both 12 and 24 weeks in

a LDL cholesterol-independent manner (Albert *et al.*, 2001). Moreover, it seems that atorvastatin exerts a more potent effect on the reduction of CRP than pravastatin, as demonstrated by the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) study (Taylor *et al.*, 2002). This result has been confirmed by the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study, which confirms that atorvastatin induces a greater reduction in CRP levels that pravastatin (Nissen *et al.*, 2004) and seems also to be more potent that simvastatin (Wiklund *et al.*, 2002). 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 (Ridker *et al.*, 2005).

It has been demonstrated that patients with CAD and abnormalities of serum lipid and CRP level often have endothelial vasodilator dysfunction, which may contribute to cardiovascular events (Treasure *et al.*, 1995; Schrott *et al.*, 1997; Reed *et al.*, 1995). The LDL cholesterol reduction by statin appears to be a sufficient explanation for the benefits seen in those studies. *In vitro* studies have shown that LDL cholesterol and, in particular, its oxidized derivative, are injurious to the endothelium. Furthermore, decreasing LDL cholesterol level with statin in patients with CAD has been associated with beneficial effect on coronary endothelium by decreasing inflammatory marker (Schrott *et al.*, 1997). Since recent data indicate (Tsunekawa *et al.*, 2001) 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.

CONCLUSION

Atorvastatin significantly decreases CRP and lipid profile levels over time in treated patients as compared to untreated. Atorvastatin decrease CRP level independently of their anti-lipid effects. This shows, atorvastatin may alters the pathogenesis of cardiovascular disease rapidly, such that the effect on cardiovascular events is apparent after three months of initiation of therapy and may more beneficial in minimizing the cardiovascular risk.

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