Original Article

Atorvastatin in Prevention of Cardiovascular Risks Pak Armed Forces Med J 2012; 62 (4): 561-6

EVALUATION OF EFFICACY OF ATORVASTATIN IN PREVENTION OF CARDIOVASCULAR RISKS IN STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS

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ABSTRACT

Objective: To demonstrate the dual cardiopulmonary protective effects of Atorvastatin in COPD patients, which may become the mainstay of therapy in prevention of exacerbation of COPD and cardiovascular events in COPD patients.

Study Design: Quasi experimental study.

Place and Duration of Study: This study was conducted over a period of 6 months (December 2010 to May 2011) with an individual study period of 3 months (90 days), conducted in the Department of Pharmacology & Therapeutics in collaboration with Chest medicine JPMC Karachi.

Subjects and Methods: Thirty five moderate stable COPD with post bronchodilator FEV <80% and post bronchodilator FEV1/FVC <70%, with hsCRP level >3mg/l, were evaluated in a quasi experimental trial. The patients were assigned to give tablet Atorvastatin 20 mg once daily for 12 consecutive weeks. The primary study outcome was to evaluate the reduction in cardiovascular risk by evaluating the improvement in FEV1 and reduction in hsCRP levels. Efficacy was evaluated at days 30, 60 and day 90.

Results: Out of 35 patients only 33 (94%) patients completed the study. At baseline hsCRP level was 6.45±0.30 which decreased to 4.6±0.19 (p<0.05) at day 90. FEV1 at baseline was 2.16±0.07 and at day 90 FEV1 increased upto 2.48±0.06 (p<0.01). This shows that, the Atorvastatin can lead to statistically significant decrease in the hsCRP levels and increase the forced expiratory volume in one second.

Conclusion: This study demonstrated that Atorvastatin effectively decreases the cardiovascular risk by decreasing the systemic inflammation which was indicated by decreasing the hsCRP levels and it can also improve the pulmonary functional capacity in COPD patients.

Keywords: Atorvastatin, COPD, CVD, FEV1, hsCRP, ICS, Pleiotrophic effects.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the inflammatory disease of the lungs characterized by airflow imitation that is not fully reversible[1]. Air flow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gas, primarily cigarette smoking[2].

COPD is leading cause of death and disability worldwide. The rise in morbidity and mortality from COPD will be most dramatic in Asian and African countries over the next two decades, mostly due to progressive increase in the prevalence of smoking[3]. The WHO estimates that 80 million people worldwide have moderate to severe COPD with 5% of all death being attributed to the disease[4] WHO estimated that COPD is currently the 12th most common cause of morbidity and the 6th leading cause of death in the world. By 2020 it is estimated to become the 5th most common cause of disability and 3rd most frequent cause of death just behind coronary and cerebrovascular disease[5,6].

Although these figures are alarming, they are likely to be gross under estimates of the true health and economic burden of COPD because COPD is an important risk factor for other causes of morbidity and mortality, including cardiovascular disease[7]. In Pakistan, the estimated COPD mortality rate is 71 deaths per 100,000 and the fourth highest rate among 25 most population in the world[8].

COPD is no longer being considered a disease only of the lungs. It is associated with a wide variety of systemic consequences, most

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Received: 15 Aug 2011; Accepted: 31 Jan 2012

notably increased risk of cardiovascular diseases, depression, osteoporosis and vascular weakness[9].

It has long been recognized that reduced lung function in COPD is a major risk factor for cardiac death. It has also become clear that cardiac events are the major cause of death for patients with COPD with all stages of disease[10].

COPD patients have increased arterial stiffness, which may explain the epidemiological link between reduced forced expiratory volume in 1 secomd (FEV1) and cardiovascular mortality. Chronic bronchitis and lung function have also been identified as independent predictor of the occurrence of the ischemic heart disease[11].

Systemic inflammation in COPD reflected by elevated c-reactive protien (CRP) levels and impaired pulmonary functions may have additive effects in increasing the risk of cardiac disease[12].

High sensitivity CRP analysis have already been recommended for clinical application in the detection and prevention of cardiovascular disease (CVD)[13]. Since CVD is a major cause of mortality in COPD and CRP is a predictor of acute exacerbation of COPD, hospital admissions and mortality in chronic respiratory failure and seems to be marker of impaired exercise capacity and disease due to respiratory symptoms, routine hsCRP analysis could be of major clinical importance in COPD[14, 15].

Current therapy in COPD (bronchodilators and steroids) relieves symptoms and reduces hospitalizations but does not change the natural history of disease (pulmonary inflammation, systemic inflammation and lung function decline) or outcome (respiratory mortality and cardiovascular mortality). Even steroids have little effects on COPD patients as compared to the asthmatic patients because in COPD there was mainly neutrophilic inflammation and steroids had little effects on neutrophilic inflammation[16] .

Furthermore current therapy may even increase the cardiovascular risk[17]. There is clearly a need for new therapies that directly target the specific inflammatory processes underlying chronic obstructive pulmonary disease and its pulmonary and extrapulmonary manifestations[18].

Recently pleiotropic effects of statins are identified. Pleiotropic effects of statin are anti-inflammatory and immunomodulatory; thus by these pleiotropic effects Atorvastatin may improve the entire outcomes (such as cardiovascular mortalities) and decreases the exacerbation of COPD[19,20].

Patients with COPD die from causes other than respiratory failure. Indeed, in patients with mild to moderate COPD, lung cancer and cardiovascular complications are the leading causes of mortality[21]. Cardiovascular disease is a major cause of mortality and morbidity in patients with COPD. Systemic inflammation plays a major role in the pathogenesis of cardiovascular disease in COPD. Multiple retrospective studies show that the statins beyond its cholesterol lowering effects may be able to decrease the incidences of cardiovascular complications, pneumonia[40], and influenza[41] and even in long term use can decrease the incidences of lung cancer in COPD patients. Current anti inflammatory drugs such as steroids can increase the incidences of pneumonia in COPD patients[42].

The main objective of our study was to evaluate the efficacy of Atorvastatin in reducing the risks of cardiovascular events in COPD patients.

This was a quasi experimental study carried out in Department of Pharmacology and Therapeutic, Basic Medical Sciences Institute, JPMC Karachi in collaboration with Department of Chest Medicine, JPMC, Karachi from Dec 2010 to May 2011. The ethical committee of this institution approved the study protocol.

PATIENTS AND METHODS

A total of 35 patients having diagnosis of stable moderate COPD met the inclusion criteria were enrolled after taking written and informed consent. Patients of both sexes with moderate COPD as indicated by spirometry assay FEV1 < 80% and FEV1/FVC < 70%, with age ranges between 35-65 years and with

hsCRP levels >3mg/l were included in this study. Patients with unstable COPD, history of exacerbations criteria previous 3 months, patients already on Statin therapy, or showing previous statia sensitivity or myopathy or myositis, pregnant or lactating mothers, patients with connective tissue disorders, patients with active or chronic liver disease, patients with evidence of active respiratory tract infections and with documented history of active coronary artery disease are excluded from the study.

During the treatment period patients were assigned to tablet Atorvastatin 20 mg once daily for 12 weeks followed by monthly follow up visits.

At baseline pulmonary function test performed. Impact of therapy on health related quality of life were assessed by BODE index and SGRQ score and impact of therapy on cardiovascular risk were assessed by changes of FEV1 and hsCRP levels from the baseline which were the primary outcomes of this study. The safety and tolerability of drug was assessed by maintaining adverse events at each follow up visits and performed liver function tests (LFT) and creatinine kinase levels at baseline and at the end of study.

Statistical Analysis:

SPSS (statistical Package for Social Sciences) version 11.5 was used for data feeding and analysis. Frequencies and percentages were calculated for qualitative variables (gender, smoking history, sputum production, family history, etc.) while mean and standard deviation (SD) for quantitative variables (age, FEV1 and hsCRP). Paired sample t-test was used for comparison of quantitative data from baseline (day-0) to day-30, day-60 and day-90. A p-value <0.05 was considered as significant.

RESULTS

Total 35 COPD patients were selected for treatment. Two patients withdrew during treatment period and therefore failed to complete the study. Reason for withdrawal was non compliance.

Avereage age of patients was 54.7±0.98 years. Twenty five (75.8%) were males. Base line chracteristics were described in table-1.

Patients given tab Atorvastatin alone for 90 days revealed overall reduction in cardiovascular risks as assessed by hsCRP and FEV1 levels, mean FEV1 which was 2.16±0.07, where as hsCRP was 6.45±0.36 at the start of the study. At day 30 FEV1 was increased by 42% while hsCRP was decreased by 4.7%. But this change was insignificant as compared to baseline.

At day 60 all the parameters further improved mean of 8.8% increased was observed in FEV1 which was significant (p<0.001), whereas mean hsCRP was decreased by 18.8% which was highly significant (p<0.001).

As compared to baseline, mean FEV1 was increased by 14.8% at day 90 which was highly significant (p<0.001). Whereas mean hsCRP was decreased by 28.5% which was also highly significant (p<0.001) (table-2).

DISCUSSION

Coronary artery disease is the most common cause of death in COPD patients, estimated to affect between 20-50%. Reduced FEV1 is a powerful marker for CAD and mortality from CVD. It is striking that reduced FEV1 ranks second only to smoking, just above blood pressure, social class and cholesterol as predictor for CVD related mortality in COPD patient in both males and female[22].

The multiple prospective epidemiological studies show that CRP predicts the increased myocardial infarction, stroke, sudden cardiac death. CRP levels of 1, 1 to 3 and > 3 mg/l corresponds to low, moderate and high risk groups for future cardiovascular events[23]. Individuals with LDL cholesterol below 130 mg/dl, who have CRP levels 3 mg/l represent a high risk group often missed in clinical practice. The addition of CRP to standard cholesterol may thus provide simple method to improve global prediction of cardiovascular risk[24].

Melbye et al. shows a strong link between bronchial airflow limitation and the circulating CRP levels in an elderly population. Measuring CRP may be useful part of the diagnostic work-up in COPD patients[25].

Table-1: Baseline characteristics of Atorvastatin treated patients (n=33)

Characteristics	Frequency (Percentages)
Smoking history	26 (78.8)
Cough	23 (69.7)
Sputum production	13 (39.4)
Family history of COPD	17 (51.5)
Family history of ischemic heart disease or hypertension	23 (69.7)
History of any comorbodities	
Hypertension	8 (24.2)
Diabetes mellitus	3 (9.1)
Stable ischemic heart disease	7 (21.2)
Disease known since	
< 1year	5 (15.2)
1-5 years	19 (57.6)
>5 years	9 (27.3)

Table-2: Description of C - reactive protein and FEV1 at different times in Atorvastatin treated patients (n=33)

	Mean ± SEM	*p*-value
Improvement in FEV1 levels		
Day – 0	2.16 ± 0.07	-
Day – 30	2.25 ± 0.06	0.332 NS
Day – 60	2.35 ± 0.06	0.043 *
Day – 90	2.48 ± 0.06	0.001 *
Reduction in C-reactive protein levels		
Day – 0	6.45 ± 0.36	-
Day – 30	6.15 ± 0.29	0.518 NS
Day – 60	5.24 ± 0.24	0.007 *
Day – 90	4.61 ± 0.19	0.001 *

NS- Insignificant
* - Significant

Impaired lung function is a strong predictor of cardiovascular death, both independent of and additive with the risk conferred by smoking. It has also been proposed that coronary artery disease in patients with COPD results in part from spillover of pulmonary derived inflammatory cytokines (e.g. IL-6, TNF-α)[26].

Atorvastatin in HMG-reductase inhibitor, not only have a proven role in treating cardiovascular disease patients, primarily through their cholesterol lowering ability, but also possess anti-inflammatory and immunomodulatory effects postulated to be beneficial to patients with COPD[27].

Atorvastatin in patients, cholesterol lowering agents with newly recognized, broad anti-inflammatory and immunomodulatory properties, as they suppress the innate immune response in vitro by inhibiting neutrophil migration, oxidative stress, NF-k B-activation, proinflammatory mediator release, expression of matrix metalloproteinases[28].

Evidence from both human and animal studies has shown that statins have strong immune-modulating effects in both the systemic[29] and pulmonary circulation[30], which may have useful anti-inflammatory actions in COPD[31,32].

There is data to show that CRP levels are a predictor of COPD morbidity and mortality, and statins have been shown to reduce serum levels of CRP. COPD patients with high baseline CRP levels (in a stable condition) could therefore be a subgroup to benefit most from statin treatment not just in regard to attenuated

lung function decline, but also improved mortality. The recently published JUPITER study showed that rosuvastatin significantly reduced the incidence of major cardiovascular events in apparently healthy persons without hyperlipidemia but with elevated CRP levels. However, besides the anti-inflammatory action, other possible effects of statins, e.g. anti-oxidant action, may be partially responsible for the apparent beneficial effect in COPD patients[2].

Lee et al. compared the pravastatin to placebo and evaluated the effect of therapy on exercise capacity and CRP levels. The study found a 54% increase in exercise capacity and decrease in hsCRP levels in patients who received 40 mg of pravastatin compared to placebo over a 6-month follow-up period. Furthermore, there was a correlation between the increase in exercise time and the decrease in CRP[33].

Albert et al. showed in their randomized controlled trials that pravastatin reduced CRP level at both 12 and 24 weeks in a largely independent manner, this was consistent with our study because Atorvastatin can significantly decrease the hsCRP levels in our patients. This data provide evidence that statins may have anti-inflammatory effects in addition to lipid lowering effects[34].

Mentecucoo et al. show the statins inhibited CRP induced chemokines secretion, ICAM-1 up regulation and migration in human adherent monocytes, through the inhibition of HMG-COA reductase ERK ½ pathway. This pathway could represent a very promising target to reduce CRP induced activities in monocyte-mediated diseases, such as atherosclerosis[35].

Plenge et al., demonstrated in their study that the Statins even may lowers hsCRP by 14 days, independent of its effects on LDL cholesterol[36].

Statin therapy in COPD was associated with a 54% increase in exercise tolerance. This increase correlated with a reduction in hsCRP and IL-6 suggesting a reduction in systemic inflammation mediated this clinically important end-point. Statin therapy also attenuates the decline in lung function[37, 38].

Very little research has been published that examines the effect of statins on lung function. A recent abstract published for the Chest 2006 conference examined the effects of statin use on lung function in 485 elderly subjects who were current or former smokers. This abstract reported reduced decline in FVC for statin users compared with nonusers[39].

Multiple retrospective studies show that the statin beyond its cholesterol lowering effects may be able to decrease the incidence of cardiovascular complications, pneumonia[40], and influenza[41] and even in long term use can decrease the incidences of lung cancer in COPD patients.. Current anti inflammatory drugs such as steroids can increase the incidence of pneumonia in COPD patients[42].

CONCLUSION

This study demonstrated that the Atorvastatin had dual cardiopulmonary protective effects by decreasing the systemic inflammation which was indicated by statistically significant decrease in hsCRP levels and decrease in pulmonary component of inflammation was indicated by improvements of pulmonary functional capacity in COPD patients. Thus Atorvastatin can be used as the adjuvant therapy in COPD patients.

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