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Effect of atorvastatin on hs CRP, pulmonary function and quality of life in chronic obstructive pulmonary disease - An open labeled randomized control trial

Pharmacology

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ABSTRACT

Objective - Beneficial effects of statins on chronic obstructive pulmonary disease have been projected in many retrospective studies, but prospective studies were lacking. So this study was done to study the efficacy of atorvastatin in improving the high sensitivity C reactive protein (hs CRP levels), pulmonary functions and quality of life in chronic obstructive pulmonary disease patients (COPD). **Method**- This was an open labeled interventional study conducted on 60 stable COPD patients who were having abnormal lipid profile. The patients were randomized into two groups of 30 patients each – one receiving medications for COPD and another receiving 20 mg atorvastatin along with other medications for COPD. The outcome measures were change in hs CRP levels levels, pulmonary function test and health related quality of life after 12 weeks. **Results**- A total of 60 participants with COPD were enrolled for the study and divided into two equal groups of 30 patients. There were 2 and 1 drop outs in atorvastatin and without atorvastatin group. After 12 weeks follow up in the atorvastatin group there was a significant improvement in the levels of hs CRP levels from 4.82 ± 0.77 to 2.81± 0.73 (P<0.05) as compared to other group without atorvastatin (4.34 ± 0.97 to 4.04±0.63). Mean force expiratory value in one sec (FEV1) as percent of predicted value was similar in the atorvastatin and group without atorvastatin after 12 weeks: 54 .2 ±18.1 to 55.6± 17.9 (P = 0.54) and 55.7± 19.1 to 56.1±18.1. (P = 0.58), respectively. Both treatments had similar improvement in St George Respiratory questionnaire total score. No adverse effect was observed in the atorvastatin group. **Conclusions**- Atorvastatin at a daily dose of 20 mg for 12 weeks has a significant beneficial effect on the levels of high sensitivity C reactive protein in COPD patient in comparison with the other group not receiving atorvastatin. There was no effect on the pulmonary function test and quality of life scores. (Trial registration Number - CTRI/2012/11/003162)

KEYWORDS:

Chronic Obstructive Pulmonary Disease, Statins, C- reactive protein

Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease worldwide with a high burden to society. It is characterised by repeated episodes of dyspnoea that require frequent hospitalisation, thereby decreasing the quality of life of patient and increasing the cost of care. Even though it is affecting a large magnitude of population there is lack of effectual therapies for the treatment or limitation of disease process. The study into the pathogenesis of COPD revealed the fact that it involves inflammatory processes. [1] Recently, statins have emerged as a potential disease modifying agent in COPD.[2] Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors that are widely used for their lipid lowering effects. They also possess many pleotropic effects one of which is an anti-inflammatory effect, which may impart beneficial effect in COPD. [3] This postulate is supported by animal studies showing that statins inhibit the progression of emphysema in mice models.[4] Various retrospective studies indicate that statins may have beneficial role in decreasing morbidity and mortality in COPD patients.[5] But there is lack of information on the effects of specific statins in most of the reviewed observational studies. There are studies to support that high sensitivity C reactive protein (hs- CRP) levels are a predictor of COPD morbidity and mortality[6], and statins have been shown to reduce serum levels of CRP.[7] Lipophilic statins like simvastatin and atorvastatin have additional anti-inflammatory potential.[8] Since most of the available data of effect of statin on COPD are based on observational studies, interventional studies were needed to evaluate the therapeutic effect of specific statins in COPD.

Materials and methods

The study was conducted in the Department of Pulmonary medicine in tertiary care teaching hospital in Uttarakhand, over a period of six months from December 2012 to May 2013. It was an open label interventional study conducted on chronic stable COPD patients. Approval for the study was obtained from the hospital's institutional research committee and institutional ethical committee. Patients suffering with COPD in stable condition for 3months, aged between 40-80 years and having abnormal lipid profile (LDL-130-160 mg/dl) were included in the study. The exclusion criteria was history of bronchial asthma, prior exposure to statins, acute exacerbation of COPD for 3months, any active infection, renal disease, hepatic dysfunction and Pregnant and nursing females.

After taking written informed consent, 60 patients were randomized into two groups – group 1 receiving only the medications for COPD and Group 2 receiving 20 mg atorvastatin along with other medications for COPD. At baseline the patients were evaluated with physical examination, pulmonary function test, blood test and health related quality of life questionnaire. The pulmonary function test included total lung capacity, inspiratory lung capacity and force expiratory value in one sec (FEV_1). The haematological and biochemical investigation included serum hemoglobin, complete lipid profile and serum hs –CRP (done by ELISA). The quality of life was assessed with COPD related St George's Respiratory Questionnaire (SGRQ).[9] It is a validated self administered questionnaire which provides an overall measure for quality of life with subscale scores in three areas: Symptom, activity and impact of disease on daily life. SGRQ scores range from 0-100, a score of zero represents no quality of life impairment while 100 mean maximal impairment. The questionnaire was interpreted in the local language of the patient to facilitate the understanding while administering it. The minimum clinically important difference (MCID) was four points in SGRQ total score.[10] The patient were followed up monthly and again reevaluated after 12 weeks. The patients were actively monitored for any adverse effects with the help of checklist.

Statistical Methods

GraphPad InStat 3 was used for statistical analysis. All statistical calculations were done by paired t-test and unpaired t-test. A P value of < 0.05 was considered statistically significant.

Results

A total of 69 patients were screened for the study. Seven patients were excluded due to prior use of statins and 2 other were having renal

disease (Fig 1). The demographic and baseline clinical characteristics of the participants in both the groups are shown in Table 1. Out of 60 patients 25% were women. The patients had a mean age of 60.5±8.4 years and FEV1 that was 41.95±11.5% of the predicted value, and a smoking history of 34 .44±17.73 pack-years. There were no significant differences between the two groups with respect to any characteristics at baseline. Follow-up visit information was not available for 3 of the 60 participants (5%), so 28 patients in the atorvastatin group and 29 in the no atorvastatin group were included in the primary analysis.

Figure 2 shows the change in the hs CRP levels at weeks 0 and 12 in both treatment groups. In Group I there was no significant change in hsCRP levels after 12 weeks (4.34 ± 0.97 to 4.04±0.63). In the Group II (atorvastatin group) there was a significant change in the levels of hs CRP from 4.82 ± 0.77 to 2.81± 0.73 (P<0.05).

Both the groups had similar significant improvement in SGQR quality of life score as shown in Figure 3. In group I the scores were reduced from 46 ± 16.1 to 40 ± 15.2 (P value <0.05) and in group II the scores were reduced from 47± 14.8 to 40 ± 15.1 (P value <0.05) which indicates improvement in quality of life. Figure 3 shows the change in the FEV1 (% predicted value) at weeks 0 and 12 in both treatment groups. In Group I, the increase in the FEV1 (% predicted value) was from 54 .2 ±18.1 to 55.6± 17.9 whereas in group II it was 55.7± 19.1 to 56.1±18.1. The change in FEV1 was not significant in the intragroup and intergroup comparison.

There was significant reduction in the serum levels of LDL in Group II (receiving atorvastatin) after 12 weeks (142.7± 10.19 to 101 ± 30.4. P value <0.01) as compared to group I (140.3 ±9.19 to 141.5 ± 10.19. (P value 0.863). There was no adverse effect reported in both the groups.

Discussion

This randomized controlled open labeled study was conducted to evaluate the effect of 20 mg atorvastatin on FEV1, hs CRP and quality of life in patients with COPD. Our results demonstrated that 20 mg of daily atorvastatin had no effect on the lung function and disease specific quality of life in patients with moderate to severe COPD. But there was statistically significant decrease in the hsCRP levels with the use of atorvastatin. There was no difference in the adverse drug reaction in both the groups. These data clearly indicate that daily use of 20 mg atorvastatin for duration of three months has no role in improvement of pulmonary function and health related quality of life but has significant improvement of hs CRP levels.

We preferred to use atorvastatin in our study as it is easily accessible and affordable in India. Moreover being a lipophillic agent it is postulated to have greater anti-inflammatory potential. [11] It has a dose dependent anti- inflammatory effect ranging from 10 - 80 mg dose[12] and therefore a dose of 20mg atorvastatin was selected to minimize dose related adverse effects. [13] In our study there was no effect on the pulmonary function with the use of 20 mg atorvastatin. This was in concurrence with other randomized controlled trials where similar results were demonstrated with the use of statins. [14,15] Randomized control trials failed to reciprocate the inverse relationship of hs CRP and pulmonary function as postulated by many cross sectional studies. The most plausible reason for this could be that the shorter duration of follow up in these studies as compared to the longitudinal trials where the patients were followed up till 8-9 years. [16-19] Other factor which could contribute to lack of effect can be relatively lower dose of 20mg used in this study. Moreover in our study only moderate-to-severe COPD patient were included and therefore the feasibility of the beneficial effect of statins in patient with less severe impairment could not be evaluated.

Our study has revealed that there was a significant decrease in the levels of hs-CRP with 3 months of 20 mg/day atorvastatin therapy. These findings were consistent with few other studies which have demonstrated decrease in hs CRP levels in patients with COPD with the use of statins. [14,20,21] In contrast to our study one study has reported statistically non-significant change in hsCRP levels after the use of 40 mg/ day simvastatin for 3 months in patients with COPD. [22] Similarly two other studies also reported no effect on the serum levels of inflammatory markers including hs CRP with simvastatin. [23,24] This could be attributed to small sample size and short treatment period in these studies.

In our study SGRQ scores had similar improvement in both group I not receiving atorvastatin and group 2 receiving atorvastatin (decrease of 7 point vs 5 point; P value >0.05). These results are in contrast of a recent study which reported a significant improvement in SGRQ with mean SGRQ decreased by 12 points after treatment with 40mg/day atorvastatin for 12 weeks (P=0.012) as compared with placebo. [21] The major limitation of this study was a small sample of patient (n=18) as compared to our study sample. Similarly another study has also reported improved asthma quality of life with short-term treatment with atorvastatin in mild asthmatic smokers. [25] Since ambiguous results are available for the effect of atorvastatin on SGRQ scores in COPD patients, further research on larger groups and the effects of longer term intervention on clinical outcomes are needed.

To conclude our study demonstrated a significant decrease in serum hs CRP levels in COPD patient with the use of 20 mg/ day atorvastatin for 12 weeks. But our study didn't reveal any significant effect on other clinical outcomes like pulmonary functions or quality of life. The major limitation of our study was that it was an open labeled study, had small sample size and was of short duration. Since many other studies has demonstrated a favourable effect on the clinical outcomes like pulmonary functions and quality of life, further large scale randomized placebo control clinical trials are required to assess the beneficial effect of statins on COPD.

Table 1. Demographic profile and baseline characteristic of the patients assigned to both the groups

	Patients receiving treatment for COPD Group 1 (n=30)	Patients receiving treatment for COPD and 20 mg /day Atorvastatin Group 2 (n=30)
Age (Mean± S.D.)	61.2 ± 8.5	59.9 ± 8.25
Gender distribution (M:F)	22:8	23:7
COPD severity staging Moderate Severe	27 (90) 3 (10)	25 (83.3) 5 (16.7)
Duration of the disease	12 ± 10	11 ± 9
Smoking history (pack years)	33.45(19. 14)	35.43 (16. 32)
FEV1 after bronchodilator use (% of predicted value)	1.24 ± 0.28 (41.7± 11)	1.28 ± 0.25 (42 .2 ±12)
FEV1/FVC	43.9 ± 11.1	44.2 ±13.5
Hb (g/dl)	10.43±0.52	10.37±0.73
SGQR- Total score (Mean± S.D.)	46 ± 16.7	47 ± 16.5
BDI Score	6.3± 1.5	6.1± 1.8
LDL cholesterol	135.7± 2.19	134.3 ± 3.19
Hs CRP (mg/l)	4.82 ± 0.77	4.34 ± 0.97
Pre study medications for COPD Inhaled glucocorticoids and long-acting beta2-agonist Long-acting muscarinic antagonist and long-acting beta2-agonist Inhaled glucocorticoids, long-acting muscarinic antagonist, and long-acting beta2-agonist Theophylline	7 4 19 4	7 3 20 5

Figure 1 . Consort flow chart for the study

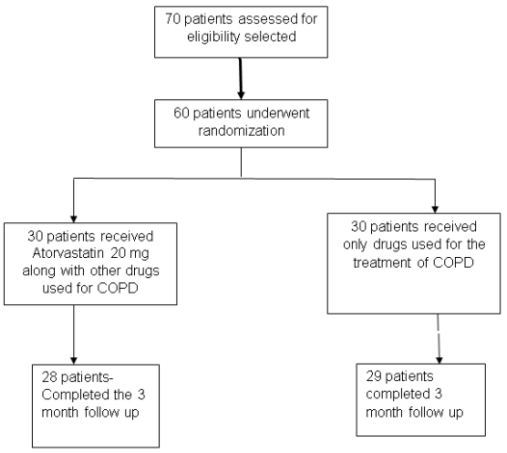
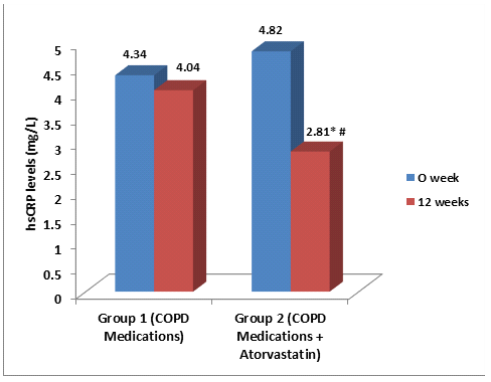
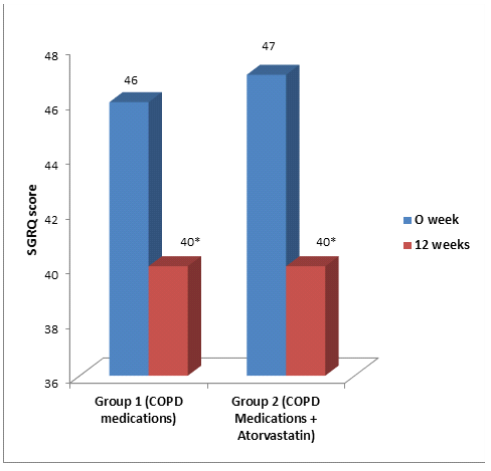


Fig 2.Serum in hs CRP levels



* P value <0.05 in comparison to 0 week
# P value <0.05 in comparison to group 1

Fig 3. SGRQ quality of life score in patients with COPD



* P value <0.05 in comparison to 0 week

Reference

1. Barnes PJ, Shapiro SD, Pauwels RA: Chronic obstructive pulmonary disease: molecular and cellular mechanisms. Eur Respir J 2003, 22:672-688.
2. Hothersall E, McSharry C, Thomson NC. Potential therapeutic role for statins in respiratory disease. Thorax 2006;61: 729-34.
3. Davignon J, Leiter LA: Ongoing clinical trials of the pleiotropic effects of statins. Vasc Health Risk Manag 2005, 1:29-40.
4. Takahashi S, Nakamura H, Seki M, et al. Reversal of elastaseinduced pulmonary emphysema and promotion of alveolar epithelial cell proliferation by simvastatin in mice. Am J Physiol Lung Cell Mol Physiol 2008; 294:L882–L890
5. Janda S, Park K, FitzGerald M, Etiminam M, Swiston J. Statins in COPD : A Systematic Review. Chest 2009;136:734-43.
6. Dahl M, Vestbo J, Lange P, Bojesen SE, Tybjaerg-Hansen A, Nordestgaard BG: C-reactive protein as a predictor of prognosis in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2007, 175:250-255.
7. Prasad K: C-reactive protein (CRP)-lowering agents. Cardiovasc Drug Rev 2006, 24:33-50.
8. Kiener PA, Davis PM, Murray JL, Youssef S, Rankin BM, Kowala M: Stimulation of inflammatory responses in vitro by lipophilic HMG-CoA reductase inhibitors. Int Immunopharmacol 2001, 1:105-118.
9. Meguro M, Barley EA, Spencer S, Jones PW. Development and validation of an improved COPD-specific version of the St George's Respiratory Questionnaire. Chest 2006;132: 456-463.
10. Jones PW. St. George's Respiratory Questionnaire: MCID. COPD 2005; 2: 75–79.
11. Kiener PA, Davis PM, Murray JL. Youssef S, Rankin BM, Kowala M. Stimulation of inflammatory responses in vitro by lipophilic HMG Co A reductase inhibitors. Int. Immunopharmacol 2001;1:105-118.
12. Bonnet J, Mcpherson R, Tegudi A, Simoneau D, Nozza A, Martineau P et al. Comparative effects of 10-mg versus 80-mg Atorvastatin on high-sensitivity C-reactive protein in patients with stable coronary artery disease: results of the CAP (Comparative Atorvastatin Pleiotropic effects) study. Clin Ther 2008 Dec;30(12):2298-313.
13. Golomb BA, Evans MA. Statin Adverse Effects: A Review of the Literature and Evidence for a Mitochondrial Mechanism. American journal of cardiovascular drugs : drugs, devices, and other interventions. 2008;8(6):373-418.
14. Lee TM, Lin MS, Chang NC: Usefulness of C-reactive protein and interleukin-6 as predictors of outcomes in patients with chronic obstructive pulmonary disease receiving pravastatin. Am J Cardiol. 2008, 101: 530-535.
15. Criner G, Connett J, Aaron SD, et al. Simvastatin for the prevention of exacerbations in moderate to severe COPD. N Engl J Med. 2014; 370(23):2201–2210
16. Aronson D, Roterman I, Yigla M, Kerner A, Avizohar O, Sella R, Bartha P, Levy Y, Markiewicz W: Inverse association between pulmonary function and C-reactive protein in apparently healthy subjects. Am J Respir Crit Care Med. 2006, 174: 626-632.
17. Fogarty AW, Jones S, Britton JR, Lewis SA, McKeever TM: Systemic inflammation and decline in lung function in a general population: a prospective study. Thorax. 2007, 62: 515-520.
18. Shaaban R, Kony S, Driss F, Leynaert B, Soussan D, Pin I, Neukirch F, Zureik M: Change in C-reactive protein levels and FEV1 decline: a longitudinal population-based study. Respir Med. 2006, 100: 2112-2120.
19. Alexeeff SE, Litonjua AA, Sparrow D, Vokonas PS, Schwartz J. Statin use reduces decline in lung function: VA Normative Aging Study. Am J Respir Crit Care Med 2007;176:742-7.
20. Agarwal R, Zaheer MS, Ahmad Z, Akhtar J. The relationship between C reactive protein and prognostic factors in chronic obstructive pulmonary disease. Multidisciplinary Respiratory Medicine. 2013; 8:63
21. Kaczmarek P, Sładek K, Skucha W, Rzeszutko M, Iwaniec T, Dziedzina S, Szczeklik A. The influence of simvastatin on selected inflammatory markers in patients with chronic obstructive pulmonary disease. Pol Arch Med Wewn. 2010; 120 (1-2): 11-18
22. John ME, Cockcroft JR, McKeever TM, et al. Cardiovascular and inflammatory effects of simvastatin therapy in patients with COPD: a randomized controlled trial. International Journal of Chronic Obstructive Pulmonary Disease. 2015;10:211-221.
23. Balaguer C, Peralta A, Rios A, Iglesias A, Valera JL, Noguera A, Soriano JB, Agusti A, Sala- Llinas E., Effects of simvastatin in chronic obstructive pulmonary disease: Results of a pilot, randomized, placebo-controlled clinical trial. Contemporary Clinical Trials Communications 2016; 2: 91-96.
24. Mroz RM, Lisowski P, Tycinska A, Bierla J, Trzeciak PZ, Minarowski L, et al. Anti-inflammatory effects of atorvastatin treatment in chronic obstructive pulmonary disease-A controlled pilot study. Journal of Physiology and Pharmacology 2015; 66 (1):, 111-128
25. Braganza G, Chaudhuri R, McSharry C, et al. Effects of short-term treatment with atorvastatin in smokers with asthma - a randomized controlled trial. BMC Pulm Med 2011; 11: 16.