International Journal of Medical Research Professionals
P-ISSN: 2454-6356; E-ISSN: 2454-6364
DOI: 10.21276/ijmrp

IJMRP

Original Research Article

Role of Statin in COPD Patients: Case-Control Study

Pratap Anand[1*], Mitali Nayak[2], Kumar Dudhane[3]

[1*]Assistant Professor, [2]Professor & Head, [3]Senior Resident,
Department of Pulmonary Medicine, Terna Medical College, Nerul, Navi Mumbai, Maharashtra, India.

ABSTRACT

Introduction: In COPD, airway pro inflammatory cytokine levels have been demonstrated to be associated with increased airway obstruction and exaggerated airway inflammatory response. Statins are now becoming recognized as powerful anti-inflammatory agents that exert beneficial effects beyond low-density lipoprotein cholesterol reduction. COPD patients receiving statins obtain a benefit from these therapeutic agents. Clearly, the best medical evidence for the association of statins with improved outcomes for COPD patients. So this study aimed in this study to assess role & anti-inflammatory effects of statin in COPD patients.

Materials & Methods: Case-Control study on 70 COPD Patients out of which 35 cases were on statins receiving treatment for hyperlipidemia, 35 control- not on statins& not hyperlipidemic. All patients were subjected to Pulmonary function (spirometery) pre and at end of study. Sputum induction before and at end of 10 months from starting treatment with statins and determination of leptin, total and differential cell counts, pre and at end of study.

Results: After 10 months from statin intake we found significant decrease of TCC in statin group and also significant decrease of sputum leptin, neutrophils, and COPD exacerbation in the same group, when compared to control group.

Conclusion: We conclude that statins may lower the exacerbation in patients with chronic obstructive lung diseases and may lower the total cell count of inflammatory cells, sputum leptin and neutrophils.

Keywords: COPD, Statin, Spirometery.

***Correspondence to:**

Dr. Pratap Anand,
Assistant Professor,
Department of Pulmonary Medicine,
Terna Medical College,
Nerul, Navi Mumbai, Maharashtra, India.

Article History:

Received: 11-06-2016, **Revised:** 06-07-2016, **Accepted:** 27-07-2016

Access this article online	
Website: www.ijmrp.com	Quick Response code
DOI: 10.21276/ijmrp.2016.2.4.055	

INTRODUCTION

In COPD, airway pro inflammatory cytokine levels have been demonstrated to be associated with increased airway obstruction and exaggerated airway inflammatory response.[1-3] In addition, elevated levels of pro-inflammatory cytokines, including IL-8 and TNF-alpha, have been associated with increased incidence of respiratory infections[4] and worse clinical outcomes including increased mortality and poor health status.[5-8]

Statins, are the inhibitors of 3-hydroxy-3-methyl glutaryl coenzyme A reductase, a potent inhibitors of cholesterol biosynthesis and have greatly improved the management of ischaemic heart disease. Recent studies suggest that direct antithrombotic and anti- inflammatory effects associated with treatment with statins may at least partly account for the reduction of cardiovascular events. In particular, statins reduce high sensitive C reactive protein (hs-CRP), tumour necrosis factor a, and metalloproteinase 9 production.[9] Statins are now becoming recognized as powerful anti-inflammatory agents that exert beneficial effects beyond low-density lipoprotein cholesterol reduction. The anti- inflammatory effects of statins on both pulmonary and systemic inflammation through inhibition of guanosine triphosphatase and nuclear factor-kB mediated activation of inflammatory and matrix remodeling pathways could have substantial benefits in patients with COPD due to the following.1) Inhibition of cytokine production (tumour necrosis factor-a, interleukin (IL)-6 and IL-8) and neutrophil infiltration into the lung.

2) Inhibition of the fibrotic activity in the lung leading to small airways fibrosis and irreversible airflow limitation. 3) Antioxidant and Anti-inflammatory (IL-6 mediated) effects on skeletal muscle.4) Reduced inflammatory response to pulmonary infection. 5) Inhibition of the development (or reversal) of epithelial-mesenchymal transition, a precursor event to lung cancer.[10]

Recently it has been shown that statins can modify the balance of T helper subset 1 (Th 1) and 2 (Th 2) cells by inhibition of Th1 development and augmentation of Th 2 development of CD4+ T cells. In the present observational retrospective study we observed a relation between statin use and frequency of an unusual Th1 subset of T lymphocytes, CD4 +CD28 null, which is often expanded in unstable angina.

So this study aimed to assess role & anti-inflammatory effects of statins in COPD patients.

MATERIALS & METHODS

Study Design:

Case-Control Study.

Study Participants

COPD Patients who attended pulmonary medicine OPD of THRC & affiliated health posts were included in the study.

Study Area

OPD of THRC & affiliated health posts of medical college in Navi Mumbai

Study Duration

One Year.

Study Period

January 2015 to December 2015

Sample Size

70 COPD Patients (35 cases- on statins & receiving treatment for hyperlipidemia, 35 control- not on statin& not hyperlipidemic)

Sampling Method

Convenient sampling.

Inclusion criteria

1. Complete history and clinical examination.
2. Routine haematological investigations-CBC, LFT, RFT, lipid profile.
3. Pulmonary function (spirometery) pre and at end of study.
4. Sputum induction before and at end of 10 months from starting statins and determination of leptin, total and differential cell counts- pre and at end of study.

Exclusion Criteria

1. Any patients whose statin therapy had been interrupted
2. Concomitant diagnosis of congestive heart failure
3. Radiographic evidence of pneumonia/ infection
4. Uncooperative patients.
5. Patients on long-term oral corticosteroids
6. Those with a FEV1, predicted, of <20% or a life expectancy of <1 year.

Sputum Induction[11]

Sputum was induced via inhalation of a hypertonic saline aerosol, generated by an ultrasonic nebulizer. Solutions of sodium chloride 5%, 6 ml divided to three 2 ml were nebulized at room temperature for 7 min each. Subjects then inhaled the hypertonic saline aerosols, thrice, for periods of 7 min each. Following each period of hypertonic saline nebulization, subjects were asked to blow their nose and to rinse their mouth and gargle their throat thoroughly with water. They were then encouraged to cough and expectorate sputum into a sterile plastic container, which was kept in ice. The procedure was terminated after three nebulisation procedures of 7 min each or after a fall in FEV1 of 20% from the baseline value.

Sputum Processing[11]

Sputum was processed within 15 min after termination of the induction. The volume of the whole sputum sample was determined, and an equal volume of 0.1% dithiothreitol was added. The samples were agitated on a vortex mixer in a wide-bore plastic test tube and placed in a shaking water bath for 15 min at 37 C to ensure complete homogenization. The samples were then filtered through 48-mm nylon gauze (Thompson, Ontario, Canada) and agitated on a vortex mixer. A total cell count (TCC) was performed on the filtered sample and viability was checked by means of trypan blue exclusion. The filtered sample was centrifuged for 5 min at 5906g at 48 C. The supernatant was aspirated and stored in Eppendorf tubes at -808 C. The cell pellet was resuspended in fluorescence activated cell sorter (FACS) buffer (0.5% bovine serum albumin in phosphate-buffered saline (pH 7.4 ± 7.6) to a concentration of 0.46106 cells mL_1 and cytospins preparations were performed by putting 100 mL of the cell suspension in the funnels and centrifuging for 5 min at 236g with low deceleration. Two cytospin slides for differential cell counts were stained with May-GruE`nwald Giemsa (MGG). Differential cell counts were performed by counting 300 non squamous cells in each coded MGG cytospin preparation in a blinded fashion by two technicians. The mean of both scores was used for analysis. Absolute cell numbers per milliliter of sputum were calculated by multiplying the cell percentage by the total (non squamous) cell number in the sputum, divided by the volume of the sputum sample in milliliters.

Spirometry Technique[12]

Subject preparation- Patients were advised to preferably avoid the following activities prior to lung function testing:

1. Smoking within at least 1 h of testing
2. Consuming alcohol within 4 h of testing
3. Performing vigorous exercise within 30 min of testing
4. Wearing clothing that substantially restrict full chest and abdominal expansion 5 Eating a large meal within 2 h of testing

Statistician's Remark

Data was analysed by using statistical package SPSS (Version-16). For quantitative variables descriptive statistics were calculated and presented as number & percent. Comparison between groups was done by Chi-Square test. Data was presented as mean ± SD.

Paired t-test was used for comparison within groups. Student t-test was used to compare between two groups. P <0.05 was considered to be statistically significance.

RESULTS

Present study was conducted Department of Pulmonary Medicine, Terna Medical College, Nerul, Navi Mumbai, Maharashtra (India) with aimed to assess role & anti-inflammatory effects of statins in COPD patients.

Table no. 1 shows that there is no significance differences between the two groups regarded to age, pulmonary function, leptin, total, differential cell count in induced sputum and exacerbation 10 months before introduction of statin.

In Table no 2, After 10 months from statin there is significant decrease of total cell count in statin group and also high significance decrease of sputum leptin, neutrophils and exacerbation in the statin group compared to control group.

Table no.3 shows that there is significant decrease of total cell count in statin group pre and at end of study, and high significance decrease of leptin, neutrophils and exacerbation of statin group pre introduction of statin and at end of study.

In Table no 4 shows that In control group there are no significance changes in control group at start and at end of study.

Table 1: Statin and control groups before introduction of statin.

	Statin (n = 35)	Control (n = 35)	P value
AGE	58.39± 7.40	57.54± 6.22	0.375
FEV1 pre	47.31± 9.48	46.64± 10.68	0.883
FEF25pre	58.86± 6.13	56.71± 10.00	0.501
FEF50pre	55.07± 6.73	54.93± 6.15	0.955
FEF75pre	37.50± 6.44	38.14± 5.93	0.796
lePtin pre (pg/ml)	181.29 ± 49.02	182.07 ± 47.85	0.976
TCC 106 cells mL 1	2.6 ± 12.2	2.7 ± 12.9	0.976
Squamous cells%	5 ± 9.1	5.3 ± 8.6	0.422
Neutro% pre	54.14± 10.10	51.71± 8.87	0.575
Macro% pre	38.43± 8.74	38.21± 8.57	0.848
Esino% pre	1.69 ± 1.15	1.51 ± 0.75	0.675
Lymph% pre	7.81± 5.01	8.34 ± 6.80	0.993
Exacerbation pre	5.57 ± 1.45	5.50 ± 1.51	0.909
Intubation pre	10 (28.57%)	07(20.00%)	0.783

Table 2: Statin and control group at the end of study

	Statin (n = 35)	Control (n = 35)	P value
FEV1post	46.08± 9.58	45.33± 10.63	0.768
FEF25post	58.99± 7.19	56.10± 10.32	0.541
FEF50post	52.93± 7.44	51.62± 7.42	0.861
FEF75post	34.78± 6.56	34.14± 5.35	0.756
Leptin post (pg/mL)	92.00± 17.19	170.35 ± 45.46	0.000
TCC 106 cells mL 1 post	2.1 ± 3.21	2.8 ± 9.44	0.05
Squamous cells%	5.8 ± 7.1	6.3 ± 8.6	0.112
Neutro post	30.64± 7.43	54.78± 9.93	0.000
Macro post	35.96± 11.7	37.11± 8.86	0.866
Esino post	1.33 ± 0.69	1.17 ± 0.52	0.283
Lymph post	9.73 ± 3.66	9.51 ± 7.36	0.819
Exacerbation post	2.50 ± 0.76	5.57 ± 1.83	0.000
Intubation post	5 (14.28%)	13(37.14%)	0.180

Table 3: PFT, sputum leptin, total, differential cell count and exacerbation in statin group pre and post introduction of statin.

Statin group	Pre (n = 35)	Post (n = 35)	P Value
FEV1	45.21± 9.88	45.08± 9.78	0.971
FEF25	57.86± 6.33	57.99± 7.28	0.920
FEF50	52.07± 6.53	52.93± 7.84	0.962
FEF75	34.50± 6.54	34.78± 7.46	0.966
Leptin (pg/mL)	176.29 ± 49.02	90.00± 16.19	0.000
TCC 106 cells mL 1	2.6 ± 12.2	2.1 ± 3.21	0.05
Neutro	53.14± 10.10	31.64± 7.43	0.000
Macro	38.43± 8.74	36.96± 11.7	0.412
Esino	1.69 ± 1.15	1.16 ± 0.52	0.116
Lymph	8.81 ± 5.01	9.83 ± 3.66	0.213
Exacerbation	6.57 ± 1.45	2.50 ± 0.76	0.000
Intubation	10 (28.57%)	5 (14.28%)	0.187

Table 4: PFT, total and differential cell count and exacerbation in control group pre and at end of study.

Control group	Pre (n = 35)	Post(n = 35)	P value
FEV1	45.64± 10.68	44.23± 10.53	0.584
FEF25	56.71± 10.00	55.10± 10.12	0.340
FEF50	54.93± 6.15	52.62± 7.22	0.833
FEF75	35.14± 5.93	34.14± 5.35	0.375
Leptin (pg/mL)	184.07 ± 47.85	178.29 ± 45.46	0.11
TCC 106 cells mL 1	2.6 ± 12.9	2.8 ± 9.44	0.915
Neutro	53.71± 8.87	51.78± 9.93	0.221
Macro	38.21± 8.57	37.11± 8.86	0.132
Esino	1.41 ± 0.75	1.06 ± 0.52	0.263
Lymph	8.64 ± 6.80	9.51 ± 7.36	0.082
Exacerbation	5.50 ± 1.51	5.57 ± 1.83	0.720
Intubation	07(20.00%)	13(37.14%)	0.423

DISCUSSION

Within the last few years, it has been suggested that the anti-inflammatory properties of statins[9] may lead to their utility in the treatment of other diseases in which inflammation plays a role in pathogenesis.[10] Statins might have a place in the treatment of COPD. This anti-inflammatory effects of statin proved in several studies[13], who found statin use reduce of the frequency of CD4+ CD28 T lymphocytes in patients with unstable angina and confirm an association between statin use and reduced concentrations of hs-CRP. CD4+ CD28 null T cells. And[14] who using a retrospective cohort design, 854 consecutive patients (mean age 70.8 years; 51.5% female) with a diagnosis of COPD exacerbation were included in the study at discharge from a Norwegian teaching hospital and found that Treatment with statins was associated with improved survival after chronic obstructive pulmonary disease exacerbation, while inhaled corticosteroids appeared to increase the survival benefit associated with statin use. Results of our study were in line with a previous study[15] in which 1687 patients (mean age 70.6 years) were followed, including 596 statin users and 1091 non-users, and conclude Statin use is associated with a 30% reduction in all-cause mortality at 3–4 years after first admission for COPD, irrespective of a past history of cardiovascular disease and diabetes.

Also we agreed with[16] who make Medline, Excerpta Medica Database, Papers First, and the Cochrane collaboration and Cochrane Register of controlled trials were searched. Randomized controlled trials (RCTs), observational cohort studies, case-control studies, and population-based analyses were considered for inclusion. And conclude that the current literature collectively suggests that statins may have a beneficial role in the treatment of COPD. However, the majority of published studies have inherent methodological limitations of retrospective studies and population-based analyses. There is a need for prospective interventional trials designed specifically to assess the impact of statins on clinically relevant outcomes in COPD.

CONCLUSION

So we conclude that statin may lower the exacerbation in patients with chronic obstructive lung diseases and may lower the total cell count of inflammatory cells, sputum leptin and neutrophils.

REFERENCES

1. GOLD 2011, global initiative for chronic obstructive lung disease, Access from www.goldcopd.org.

2. Yoshida T, Tuder RM: Pathobiology of cigarette smoke-inducedchronic obstructive pulmonary disease. Physiol Rev 2007, 87(3):1047-82.

3. Chung KF: Cytokines in chronic obstructive pulmonary disease. Eur Respir J Suppl 2001, (34):50s-59s.

4. Yende S, Tuomanen EI, Wunderink R, Kanaya A, Newman AB, Harris T, de Rekeneire N, Kritchevsky SB: Preinfection systemic inflammatory markers and risk of hospitalization due to pneumonia. Am J Respir Crit Care Med 2005, 172(11):1440-46.

5. Keatings VM, Cave SJ, Henry MJ, Morgan K, O'Connor CM, Fitz Gerald MX, Kalsheker N: A polymorphism in the tumor necrosis factor-alpha gene promoter region may predispose to a poor prognosis in COPD. Chest 2000, 118(4):971-5.

6. Banerjee D, Khair OA, Honeybourne D: Impact of sputum bacteria on airway inflammation and health status in clinical stable COPD. Eur Respir J 2004, 23(5):685- 91.

7. Sethi S, Muscarella K, Evans N, Klingman KL, Grant BJ, Murphy TF: Airway inflammation and etiology of acute exacerbations of chronic bronchitis. Chest 2000, 118(6):1557-65.

8. Stockley RA: Lung infections. Role of bacteria in the pathogenesis and progression of acute and chronic lung infection.Thorax1998, 53(1):58-62.

9. B.R. Kwak, F. Mulhaupt, F. Mach, Atherosclerosis: anti-inflammatory and immunomodulatory activities of statins, Autoimmun. Rev. 2 (2003) 332–8.

10. R.P. Young, R. Hopkins and T.E. Eaton. Pharmacological actions of statins: potential utility in COPD. Eur Respir Rev 2009; (18): 114, 222–32.

11. S.R. Rutgers, W. Timens, H.F. Kaufmann, Th.W. van der Mark, G.H. KoeE` ter, D.S. Postma, Comparison of induced sputum with bronchial wash, bronchoalveolar lavage and bronchial biopsies in COPD, Eur. Respir. J. 15 (2000) 109–15.

12. M.R. Miller, R. Crapo, J. Hankinson, V. Brusasco, F. Burgos,R. Casaburi, A. Coates,

P. Enright, C.P.M. van der Grinten, P. Gustafsson, R. Jensen, D.C. Johnson, Seris ATS/ERS task force: standerdization of lung function test, in: V. Brusasco, R. Crapo, G. Viegi (Eds.), Number 1

in this Series General considerations for lung function Testing, Eur. Respir. J. 26 (2005) 153–61.
13. S. Brugaletta, L.M. Biasucci, M. Pinnelli, G. Biondi-Zoccai, G. Di Giannuario, G. Trotta,
G. Liuzzo, F. Crea, Novel anti-inflammatory effect of statins: reduction of CD4+CD28 null T lymphocyte frequency in patients with unstable angina, Heart 92(2006) 249–50.
14. V. Søyseth, P.H. Brekke, P. Smith, T. Omland, Statin use is associated with reduced mortality in COPD, Eur. Respir. J. 29(2007) 279–83.
15. C.M.M. Lawes, S. Thornley, R. Young, R. Hopkins, R. Marshall, W. Cheuk, G. Jacksone, Statin use in COPD patients is associated with a reduction in mortality: a national cohort study, Prim Care Respir. J. 21 (2012).
16. S. Janda, K. Park, J.M. FitzGerald, M. Etminan, J. Swiston, Statins in COPD a systematic review, Chest 136 (2009) 734–43.

Source of Support: Nil.

Conflict of Interest: None Declared.

Cite this article as: Pratap Anand, Mitali Nayak, Kumar Dudhane. Role of Statin in COPD Patients: Case-Control Study. Int J Med Res Prof. 2016; 2(4):219-23.