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Effect of statins on the inflammatory biomarkers of COPD

Keywords: cytokines, COPD, Kashmir, hematopoietic system, biomarkers

Abbreviations: BOLD, burden of lung disease; GM-CSF, granulocyte monocyte colony stimulating factor; CRP, primarily C - reactive protein; FEV1, expiratory volume in first second; IEC, institutional ethics committee; ADRs, adverse drug reactions

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Shagufta Parveen, Nasreen Jan, Shaheen Rasool
Department of Pharmacology, Kashmir University, India

Correspondence: Nasreen Jan, Department of Pharmacology, Kashmir University, Tel 9419017365, India, Email nasrenchashoo@yahoo.co.in

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Introduction

The Burden of Lung Disease (BOLD) Study has documented more severe diseases than previously found with a substantial prevalence of (3-11%) of COPD in never smokers.[1] Worldwide prevalence of COPD ranges from 4-6%.[2] In India documented prevalence is up to 4.1% with males (5%) and females (3.2%).[3] Study from Kashmir pointed to a higher prevalence of 7.5% in smokers and 10.5% in people living in poorly ventilated houses.[4] Although most of the available data on the disease are reported from the western world, it is being equally recognized from Asia and Africa.[5] It continues to cause a heavy health and economic burden in US and around the world.[6] Although COPD is characterized primarily by the presence of largely fixed airflow limitation but there is increasing evidence and acceptance that COPD can no longer be defined as a diseases restricted to lungs.[7] The oxidant load derived from the lung (exogenous and endogenous) crosses the endothelium, where in combination with elevated circulating cytokines, it results in systemic inflammation in the vascular system.[8,9] Smoke exposure further initiates the release of other inflammatory cytokines from variety of cells including interleukin 6 (IL6), tumor necrosis factor (TNFα), transforming growth factor (TGF-β1), and granulocyte monocyte colony stimulating factor (GM-CSF).[10] Stimulation of hematopoietic system with the release of polymorph nuclear leucocytes, systemic oxidative stress, activation of coagulation factors and a direct effect on the endothelial function of the peripheral vessels have been attributed to smoking.[11] Recent studies have shown a consistent association between biomarkers of systemic inflammation, primarily C - reactive protein (CRP) and severity of COPD.[12] The link between IL6, CRP and COPD is supported by the population based studies showing an inverse relationship between these biomarkers and forced expiratory volume in first second (FEV1).[13,14] According to GOLD Guidelines, a diagnosis of COPD can be established by a fixed ratio of post bronchodilator FEV1 and FVC below 0.7 measured by spirometery.[15] In summary there is growing evidence that COPD is associated with systemic inflammation that is exaggerated by, but not dependent on cigarette smoking.[16] These observations are consistent with the hypothesis that lung function is not just a barometer to the lung response to airway aero pollutant exposure but also a matter of a more general systemic response.[17] Over the past years, the understanding of COPD has evolved from it being a disease affecting the lungs to it being a complex, heterogeneous and generalized disorder in an aging population.[7] The treatment of COPD is no longer focused exclusively on inhaled therapy but is taking on a multidimensional approach.[7] Recently statins have emerged as a possible disease modifying agent in COPD.[18] Evidence shows that statins possess pleotropic effects in addition to their conventional cholesterol lowering properties including anti-inflammatory, anti-oxidant, anti thrombogenic and vascular functions restoring actions.[19] The rationale for their use in COPD partly derives from the fact that the pathogenesis of COPD involves inflammatory processes[18] and persistent systemic inflammation seems to be present even in patients with stable COPD who do not currently smoke.[9] This study aims at investigating the effect of statins on the biomarkers of inflammation present in COPD.

Aims and objectives

This study was conducted to evaluate the effect of statins on the systemic and lung specific biomarkers of inflammation related to COPD.

Materials and methods

After the approval from Institutional Ethics Committee (IEC) of Sheri-Kashmir Institute of Medical Sciences (SKIMS) Srinagar with IEC reference: Protocol 40/2012, the study was conducted at Department of Clinical Pharmacology as a study Centre in collaboration with the Department of General Medicine, Department of Immunology and Molecular Medicine. The study incorporated patients attending SKIMS Srinagar, Kashmir, which is a Tertiary Care Institute. Patients suffering from respiratory ailments visiting Pulmonary Clinic of Department of General Medicine were screened for the study cohort. The study was a hospital based, prospective, double blind, randomized, placebo controlled, parallel group clinical trial with the treatment allocation in three identical groups. A minimum sample size of 172 subjects was calculated for the study based on the expected 9% prevalence of COPD in Kashmir with desired confidence level of 0.05 and margin of error 3%. All patients attending the COPD clinic were screened by a physician, also the site specific co-investigator. Selected participants who after being explained the various aspects of the study summarily and after making them understand the purpose and rights, using their own language whenever necessary, consented to be the participants and signed the formal consent form along with witnesses and investigator. Diagnostic criteria for COPD as outlined by GOLD 201115 were followed. Eligible participants comprised of adults with:

1. Age between 50-70 years irrespective of gender.
2. Clinical diagnosis of COPD as per GOLD criteria.
3. Population likely to have acute exacerbation should have one or more of the following conditions:
4. Be using supplemental O_2,
5. Receiving a course of systemic corticosteroids and/or antibiotics for respiratory problem.
6. Visiting emergency department or being hospitalized for COPD exacerbations within past year.

At the initial visit, complete history, general physical examination and base line investigations along with Spirometery (lung function test) and laboratory investigations of systemic and lung specific biomarkers of inflammation (CRP, IL6, IL8) were performed before intervention and repeated six months after intervention .Analysis of the laboratory markers determined in the study was conducted in the Department of Immunology & Molecular Medicine SKIMS under the supervision of site specific co-investigator. The Human ELISA kit was used for the in-vitro quantitative determination of interleukin-6 (IL-6) and interleukin-8 (IL-8) in human plasma. High sensitivity C Reactive Protein (hsCRP) was measured by ELISA.

Intervention

In addition to conventional treatment of COPD, patients received either treatment A (Test drug Atrovastatin 40mg) or treatment B (Atrovastatin 10mg) or control treatment C (matched placebo) intervention according to pre designed random allocation. Patients were advised to take the single dose orally daily at bed time for a period of six months. The treatment was implemented and supervised jointly by the investigators from Department of General Medicine and Department of Clinical Pharmacology and regular periodic follow ups for drug compliance, any adverse drug effect, hospital admission or deterioration in existing clinical condition within the six months period. At the completion of six months, patients were called for monitoring of outcomes (clinical and laboratory outcomes) as well as any adverse drug reactions (ADRs). The trial drug and placebo in different doses i.e., Atorvastatin 10mg and 40mg was arranged by the co-investigator from Department of General Medicine as a bonfire contribution to the cause of research and development by the Ranbaxy laboratory under its social corporate responsibility programme. The lots of this investigational material were directly received by the interventionist who then was responsible for allocation concealment.

Statistical analytical methods

Categorical variables were analyzed by using the Chi square test and continuous variables were analyzed by using Student's t-test and one way ANOVA. Odds ratio and Confidence interval for COPD and for the effect of age, sex, ethnic group, Body Mass Index, smoking status, education and socioeconomic status were calculated. Multivariate statistics analysis was carried out where ever needed. Analysis was done using standard statistical software's like SPSS and Minitab.

Results

Patients (n=172) clinically diagnosed as COPD, fulfilling the GOLD criteria of COPD, between the age 40- 70 years of age, irrespective of gender and smoking status were randomized into treatment allocation groups A, B and C. Number of patients was matched as far as possible for age and gender in three treatment allocation groups. In our study the role of statins in COPD patients has been investigated with respect to the levels of inflammatory markers associated with the disease The levels of various biomarkers pre and post intervention were compared across the study groups (Table 1). ANOVA shows pre CRP concentration across the three study groups A (5003.93, 3551) B (5889.88, 3882) & C (5938.07, 3870) are comparable ($p>0.05$). Post intervention hsCRP concentration across the three groups A, B and C were (3752.04 3058, 4449.22, 4188, 5220.61, 3986). On comparing decrease in levels post intervention although not significant ($p>0.05$) is maximum in group A followed by group B and least in group C (Table 2). The respective mean IL6 levels in Groups A, B and C before intervention were observed as 303.44±58.8, 250.86±62.1 and 265.21±55.6 ($p>0.05$). After the intervention for six months changes observed in the levels across the three groups (A, B and C 57.17±93.0,78.44±17.9,141.34±14.9) revealed statistically significant difference among the three groups ($p<0.05$). Post Hoc test for multiple comparison done by least significant difference (LSD) test as shown in Table 3 revealed that the Pre intervention comparison of IL6 levels across the three groups revealed statistically no significant difference ($p>0.05$), but there was a statistically significant difference in the post intervention means IL6 levels between group A and group C ($p<0.05$). Also there was a statistically significant differences in the post intervention mean IL6 levels between group B and group C ($p< 0.05$), however mean IL6 levels of group A and group B did not differ significantly (>0.05) post intervention (Table 4). Post Hoc test for multiple comparison done by least significant difference (LSD) test as shown in Table 5 revealed that Pre intervention comparison of IL8 was significantly high in group A and C as compared to group B ($p<0.05$, $p< 0.05$), and there was a statistically significant difference in the post intervention means IL8 levels between group A and group C ($p < 0.05$) as well. On making comparison between group B and group C, a statistically significant differences in the post intervention mean IL8 levels was observed between the two groups ($p< 0.05$), however the mean IL8 levels of group A and group B did not differ significantly ($p > 0.05$) post intervention.

Table 1 Comparison of pre and post intervention C reactive protein levels across the study groups

Group	No. of patients	Mean±SD		95% CI for mean			
				Lower bound		Upper bound	
		Pre CRP	Post CRP (ng/ml)	Pre CRP	Post RP	Pre CRP	Post CRP
A	54	5003.93±551.58	3752.04±358.22	3936.91	2833.25	6070.94	4670.83
B	49	5889.88±882.18	4449.22±188.60	4576.34	3032.00	7203.43	5866.44
C	60	5938.07±870.61	5220.61±986.36	9878.03	4110.80	6998.12	6330.42
Overall	172	5608.96±740.48	4514.93±782.19	4967.39	3866.19	6250.54	5163.66

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Table 2 Comparison of pre and post intervention IL6 levels across the study groups

Group	No. of patients	Mean±SD		95% CI for mean			
				Lower bound		Upper bound	
		Pre IL6	Post IL6 pg/ml	Pre IL6	Post IL6	Pre IL6	Post IL6
A	54	303.44±58.58	57.17±93.00	105.58	29.23	501.30	85.12
B	49	250.86±62.19	78.44±17.91	26.80	41.93	474.91	114.95
C	69	265.21±55.68	141.34±14.95	110.50	101.26	419.91	181.42
Overall	172	274.26±66.94	95.84±14.04	168.44	101.26	380.08	181.42

Table 3 Post hoc test for comparison of IL6 levels pre and post intervention among three study groups

Dependent variable	(I) Groups	(J) Groups	Mean difference (I-J)	Std. error	Sig.	95% Confidence interval lower upper bound	
Pre IL6	Group A	Group B	52.58333	138.92470	.706	-222.2626	327.4292
		Group C	38.23291	126.49472	.763	-212.0218	288.4876
	Group B	Group A	-52.58333	138.92470	.706	-327.4292	222.2626
		Group C	-14.35043	134.70474	.915	-280.8477	252.1468
	Group C	Group A	-38.23291	126.49472	.763	-288.4876	212.0218
		Group B	14.35043	134.70474	.915	-252.1468	280.8477
Post IL6	Group A	Group B	-21.26667	26.63934	.426	-73.9694	31.4361
		Group C	-84.16838(*)	24.25584	.001	-132.1557	-36.1811
	Group B	Group A	21.26667	26.63934	.426	-31.4361	73.9694
		Group C	-62.90171(*)	25.83014	.016	-114.0036	-11.7999
	Group C	Group A	84.16838(*)	24.25584	.001	36.1811	132.1557
		Group B	62.90171(*)	25.83014	.016	11.7999	114.0036

*The mean difference is significant at the 0.05 level

Table 4 Comparison of pre and post intervention IL8 levels across the study groups

Group	No. of patients	Mean±SD		95% CI for mean			
				Lower bound		Upper bound	
		Pre IL8	Post IL8 pg/ml	Pre IL8	Post IL8	Pre IL8	Post IL8
A	54	3081.20±222.52	948.77±150.40	2443.52	633.20	3718.87	1264.35
B	49	2076.66±182.09	994.88±184.90	1406.02	593.97	2747.31	1395.80
C	69	3037.01±229.54	2012.82±286.54	2388.47	1431.92	3685.56	2593.72
Overall	172	2792.02±298.14	1377.27±168.21	2414.99	1096.28	3169.05	1658.26

Mean concentration of IL8 before and after intervention observed in three study groups A, B and C are 3081.20±222.5, 2076.66±182.0 and 3037.01±229.5 and 948.77±150.4, 994.88±184.9, 2012.82±286.5 respectively

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Table 5 Post hoc test for comparison of IL8 levels; pre and post intervention

	(I) Groups	(J) Groups	Mean difference (I-J)	Std. error	Sig.	95% Confidence interval	
						Lower bound	Upper bound
Pre IL8	Group A	Group B	1004.53333(*)	485.36037	.040	44.3059	1964.7608
		Group C	44.18077	441.93383	.921	-830.1325	918.4940
	Group B	Group A	-1004.53333(*)	485.36037	.040	-1964.7608	-44.3059
		Group C	-960.35256(*)	470.61712	.043	-1891.4123	-29.2929
	Group C	Group A	-44.18077	441.93383	.921	-918.4940	830.1325
		Group B	960.35256(*)	470.61712	.043	29.2929	1891.4123
Post IL8	Group A	Group B	-46.11111	350.67245	.896	-739.8746	647.6524
		Group C	-1064.04915(*)	319.29682	.001	-1695.7397	-432.3586
	Group B	Group A	46.11111	350.67245	.896	-647.6524	739.8746
		Group C	-1017.93803(*)	340.02047	.003	-1690.6279	-345.2482
	Group C	Group A	1064.04915(*)	319.29682	.001	432.3586	1695.7397
		Group B	1017.93803(*)	340.02047	.003	345.2482	1690.6279

*The mean difference is significant at the 0.05 level

Discussion

Inflammation is considered central to the pathogenesis[20] of COPD and statins have been shown to possess a diverse range of pleotropic effects including anti-inflammatory actions and recent evidence suggests statins reduce pulmonary inflammation.[21–23] It is expected that they may also suppress the inflammation associated with cigarette smoke and ameliorate the associated structural and functional abnormalities in the lungs of COPD patients.[22,24] Considering this fact the present study besides focusing on the clinical outcomes, laboratory outcomes of inflammation like hsCRP, IL6 and IL8, which have been shown to be affected by statins have been assessed as the primary outcomes of this study. Patients in the present study have shown significantly increased levels of these inflammatory markers (hsCRP, IL6 and IL8) associated with their disease at the onset of study which after six months intervention with statins were markedly brought down in the test groups as compared to controlled group. Levels of hsCRP in patients who received 40 mg daily of the test drug for a period of six months have shown decrease in the levels although statistically insignificant ($p>0.05$). However, patients who received 10 mg of statins although appear to experience a beneficial effect but the difference in the size of effect is less compared to group A (Table1). It will be inferred from these observations that the beneficial effects of statins on the concentration of hsCRP consistently are more seen at higher doses than at lower doses.

Raised levels of representative pro inflammatory cytokines, IL6, CRP have been shown to be associated with low FEV125.[25] During the last decade, several studies investigating the systemic manifestations of the COPD have reported enhanced levels of circulating inflammatory mediators such as acute phase reactants and cytokines. Scholls and colleagues demonstrated increased levels of CRP in patients with stable COPD.[26] Certain meta-analyses have shown that patients of COPD have higher serum concentration of CRP than healthy controls and that the serum concentration might be an indicator of disease severity.[26,27] Taking hsCRP as primary outcome in the study as a marker of inflammation in the patients of COPD is because of its low cost of measurement and convenience in the procedure besides it may be the marker of disease progression. Such evidence might help physicians to stratify patients with COPD in terms of their risk of disease progression so that early intervention strategies are implemented to modify the risk. Only few studies have evaluated the effect of statins on the inflammatory markers on bases of severity and analyzed the CRP levels only. One or two studies have compared simvastatin 40 mg to placebo in patients with COPD and evaluated CRP levels as the primary outcome.[28–30]

To validate the beneficial effects of statins on the inflammatory markers associated with the COPD and thereby modify the clinical course, the present study has distinctly compared outcome of both acute phase reactants like CRP as well as cytokines IL6 and IL8 with the six months statin therapy. Additionally the effect was compared with two different dosages of the test drug. So far it was not possible to locate any study in which all the features were combined together. Besides assessing the clinical end points, present study has determined the effect of statins on the various inflammatory mediators like IL6, IL8 besides CRP which are now considered key determinants in the pathogenesis of COPD. Pre intervention concentration of IL6 of the patients although very high in comparison to normal levels were comparable across the three study groups (Table 2, $p>0.05$). However statin therapy for a period of six months have significantly lowered the levels in the test groups (A vs B; $p>0.05$) when compared with controls or group C (A vs C; $p<0.05$), (B vs C; $p< 0.05$, Table 3).Within the two test groups A and B, different dosages of the drug (40mg and 10mg) has not much changed the effect between the two groups. Somewhat similar observations were revealed when IL8 concentrations were compared pre and post statin therapy across the three respective groups. Mean concentration of IL8 in group A and C was significantly higher than group B before intervention. However, with six months statin intervention, change in the levels was highly significant in group A as compared to group C ($p<0.05$). Similar results were observed in group B where again significant change in levels was seen when compared with control group ($p<0.05$; Table5). Overall improvement in levels of the inflammatory markers involved in COPD has been observed by the intervention. From the above

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observations we conclude that statin therapy for a prolonged period seems to be beneficial overall for improving the clinical as well as laboratory parameters in COPD. It was also observed that throughout the course of study, it generally did not evoke any adverse effect in participants. Symptoms of acid peptic diseases at the initiation of treatment reported by one patient was reported to PvPI center of SKIMS.

Conclusion

This study was carried out with the main focus to analyze the effect of statins on levels of inflammatory markers in COPD in Kashmiri population ethnically different from the rest of the country. The study may hopefully contribute and substantiate importance and rationale of adding statins to the existing treatment options of COPD. Froude that COPD is associated with increase in certain inflammatory markers and a significant reduction in their levels by the six month therapy with statins is associated with the improvement in the clinical course of the disease. Like other few studies, the results of present study have conferred that statins have significant additional benefits in COPD where elevated levels of various inflammatory mediators is a feature and statins target the pulmonary inflammation only. Present study reveals that statins have a significant beneficial effect not only on CRP but also on other important markers of inflammation. Therefore, statins may represent a new and much needed additional treatment strategy in the patients of COPD especially in our setup where the climatic as well as socio-economic conditions have proven to add to the number of patients and additionally worsen the condition of those already suffering from the disease.

Conflicts of interest

The authors declare that they have no conflict of interest.

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