OCTOBER - DECEMBER 2013

MEDICAL CHANNEL

Original Article

COMPARISION OF EFFECTS OF ATORVASTATIN AND BUDESONIDE IN REDUCTION OF CARDIOVASCULAR RISK IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS

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ABSTRACT:

Background: The objective of this study is to demonstrating the duel 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. Cardiovascular disease is a major cause of mortality and morbidity in COPD patients. Systemic inflammation plays a major role in the pathogenesis of cardiovascular disease in COPD. It has, therefore, been suggested that anti-inflammatory agents may prevent cardiovascular disease. it would be plausible that inhaled steroids, such as Budesonide, and by pleiotrophic effects of Atorvastatin can reduce the local inflammation and subsequent cardiovascular morbidity, thus a local effect on the lung resulting in diminished spill-over of inflammation systemically to the cardiovascular system is an attractive hypothesis.

Objective: To assess the impact of Atorvastatin in reducing the cardiovascular risk in COPD patients and compare its effects with current anti-inflammatory agent (Steroids)**.**

Study design: Quasi experimental design.

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

Methodology: 105 patients with moderate stable COPD, with hsCRP level >3mg/lit, were evaluated in an open label, intention to treat clinical trial. The patients were equally divided into 3 groups, Group A were assigned to give Tab. Atorvastatin, Group B were assigned to give Budesonide inhaler 200mcg BD and Group C were assigned to give combination of above therapy 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, was evaluated at day 30, 60 and day 90.

Results: 100 (96%) patients were completed the study. At day 0 there was no significant difference was noted between all treated groups. At day 90 all the parameters were further improved in all treated groups. The mean of hsCRP was 4.61 ± 0.19(28.5%) in Atorvastatin treated group whereas 5.82 ± 0.20(12.9%) in Budesonide treated group and 4.56 ±0.14 (29.2%) and there were highly significant difference were noted between the all treated groups and combination therapy was more effective in decreases the hsCRP.

Conclusion: In conclusion, combination therapy of Atorvastatin with Budesonide effectively decrease the cardiovascular risk by decreasing the systemic inflammation which were indicated by decreasing the hsCRP levels and also improve pulmonary functional capacity in COPD patients.

Key Words: COPD, Budesonide, hsCRP, FEV1, CVD,ICS.

INTRODUCTION

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 peoples worldwide have moderate to severe COPD with 5% of all death being attributed to the disease 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[4,5].

Although these figures are alarming, they are likely to be gross underestimates 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[6]. 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[7].

COPD is not longer being considered a disease only of the lungs. It is associated with a wide variety of systemic consequences, most notably increased risk of cardiovascular diseases, depression, osteoporosis and vascular weakness[8].

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[9].

COPD patients have increased arterial stiffness, which may explain the epidemiological link between reduced FEV1 and cardiovascular mortality. Chronic bronchitis and lung function have also been identified as independent predictor of the occurrence of the ischemic heart disease[10].

Systemic inflammation in COPD reflected by elevated CRP levels and impaired pulmonary functions may have additive effects in increasing the risk of cardiac disease[11]. High sensitive C-reactive protein analyses have already been recommended for clinical application in the detection and prevention of cardiovascular disease[12]. 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 prove to be of major clinical importance in COPD[13].

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 compare to the asthmatic patients because in COPD there was mainly neutrophilic inflammation and steroids had little effects on neutrophilic inflammation[14] .

Furthermore current therapy may even increase the cardiovascular risk[15]. 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[16].

Recently pleiotrophic effects of Statin are identified. Pleiotrophic effects of Statin are anti-inflammatory and immunomodulatory effects; thus by these pleiotrophic effects Atorvastatin may improve the entire outcomes (such as cardiovascular mortalities) along with decreases the exacerbation of COPD[17,18].

MATERIAL AND METHODS

Objective of Study:

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[19].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 shows that the Statin beyond its Cholesterol lowering effects may be able to decrease the incidences of cardiovascular complications, pneumonia[20], and influenza 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.

The main objective of our study was to evaluate the efficacy of Atorvastatin in reducing the risks of cardiovascular events in COPD patients and compare with current therapy of COPD (Inhaled Steroids).

Study design:

This was 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. The ethical committee of this institution approved the study protocol.

Patients

A total 105 patients who 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 static sensitivity or myopathy or myositis, pregnant or lactating mothers, patients with connective tissue disorders, patients with active or chronic liver disease and with documented history of active coronary artery disease are excluded from the study and divided into three groups A, B and C with 35 patients in each group.

Study procedure

The study was extended over 12 week's period. During this treatment period Group A patients were assigned to tablet Atorvastatin 20 mg once daily for 12 weeks followed by monthly follow up visits, Group B was assigned to given Budesonide 200mcg 2puffs BD for consecutive 12 weeks and Group C was assigned to given inhaled Budenoside 2puff/BD/day along with Atorvastatin 20mg /OD for 12 weeks.

At baseline pulmonary function test (FEV1, FVC, FEV1/FVC ratio) were 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 LFT and creatinine kinase levels at baseline and at end of study.

Statistical Analysis:

SPSS (statistical Package for Social Sciences) ver 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 ± S.D. for quantitative variables (age, PEFR, FEV1, FVC, FEV1/FVC ratio, Liver function test (LFT), lipid profile, etc). Paired sample Student t-test (paired) was used for comparison of quantitative data from baseline (day-0) to day-30, day-60 and day-90.

RESULTS

In this study, a total of 105 patients of diagnosed COPD patients were enrolled and divided into groups A, B and C. Out of which 5 patients withdrew during treatment period and therefore failed to complete the study. Reason for withdrawal was not came on follow up, so finally statistical analysis was done in remaining patients. Table 1A & 1B shows the baseline characteristics of all treated patients.

When Atorvastatin group was compared with Budesonide and combination therapy group in of reducing the cardiovascular risks by assessing the hsCRP and FEV1 there were significant difference were noted between the all three groups and combination therapy was more effective in reducing the both hsCRP and increases the FEV1. At day 0 there was no significant difference was noted between all treated groups.

At day 30 all the parameters were improved in the all treated groups. The mean hsCRP was 6.15 ± 0.29(4.7%) in Atorvastatin treated group whereas 6.50 ± 0.22(2.6%) in Budesonide treated group and 5.56 ±0.18 (13.6%) in combination therapy group, there was significant difference were noted between all treated groups and combination therapy was more effective in decreases the hsCRP.

At day 60 all the parameters were further improved in all treated groups. The mean hsCRP was 5.24 ± 0.24(18.7%) where as 5.97 ± 0.18(10.7%) in Budesonide treated group and 5.18 ±0.21 (19.5%) in combination therapy group, there was significant difference were noted between the all treated group and combination therapy was more effective in decreases the hsCRP.

At day 90 all the parameters were further improved in all treated groups. The mean of hsCRP was 4.61 ± 0.19(28.5%) in Atorvastatin treated group whereas 5.82 ± 0.20(12.9%) in Budesonide treated group and 4.56 ±0.14 (29.2%) and there were highly significant difference were noted between the all treated groups and there were highly significant difference were noted between the all treated groups and combination therapy was more effective in decreases the hsCRP. As depicted in table 2 and figure 1.

When Atorvastatin group was compared with Budesonide and combination therapy group in comparison of safety profile both biochemically and clinically shows that there were no significant difference were noted between all treated groups both biochemically and clinically. As depicted in table 3A & 3B.

DISCUSSION

COPD is a chronic inflammatory disorder characterized by pro-

TABLE 1A
BASELINE CHARACTERISTICS OF All TREATED PATIENTS

Characteristics	**Group A** (n=33) No. (%)	**Group B** (n=34) No. (%)	**Group C** (n=34) No. (%)	**P-value**
Total patients	**35**	**35**	**35**	**-**
Left out	**02**	**01**	**01**	**-**
Remained in the study	**33**	**34**	**34**	**-**
Gender				
Male	25 (75.8)	25 (73.5)	26 (76.5)	0.958
Female	8 (24.2)	9 (26.5)	8 (23.5)	
Smoking history	26 (78.8)	26 (75.8)	28 (82.4)	0.987
Cough	23 (69.7)	25 (73.5)	26 (76.5)	0.821
Sputum production	13 (39.4)	14 (41.6)	19 (55.9)	0.328
Family history of COPD	17 (51.5)	15 (44.1)	20 (58.8)	0.479
Family history of IHD or hypertension	23 (69.7)	23 (67.6)	26 (76.5)	0.702
History of any comorbodities				
Hypertension	8 (24.2)	9 (26.5)	10 (29.4)	0.891
Diabetes mellitus	3 (9.1)	4 (11.)	4 (11.7)	0.921
Stable IHD	7 (21.2)	2 (5.9)	5 (14.7)	0.189
Disease known since				
< 1year	5 (15.2)	6 (17.6)	7 (20.6)	0.844
1-5 years	19 (57.6)	13 (38.2)	12 (35.3)	0.137
>5 years	9 (27.3)	15 (44.1)	15 (44.1)	0.264

TABLE 1B
BASELINE CHARACTERISTICS OF ALL TREATED PATIENTS

Characteristics	Group A (n=33) Mean± SEM	Group B (n=34) Mean± SEM	Group C (n=34) Mean± SEM	P-value
Age (years)	54.7 ± 0.98	56.8 ± 0.68	55.6 ± 0.72	0.176
Smoking, Pack/year	28.9 ± 1.63	28.1 ± 1.43	26.2 ± 1.33	0.403
MMRC Dyspnoea score	2.82 ± 0.13	2.88 ± 0.11	2.85 ± 0.12	0.188
History of exacerbation				
in last 6 months	1.2 ± 0.17*	1.8 ± 0.11	1.6 ± 0.11	0.006 **
Peak expiratory flow rate	162 ± 3.88	165 ± 2.01	164 ± 3.14	0.739
BMI (Body Mass Index)	20.0 ± 0.39	19.9 ± 0.35	20.3 ± 0.19	0.781
FEV1	2.16 ± 0.07	2.12 ± 0.05	2.18 ± 0.03	0.613
FVC	3.57 ± 0.11	3.51 ± 0.08	3.54 ± 0.05	0.263
FEV1/FVC ratio %	0.59 ± 0.01	0.60 ± 0.01	0.59 ± 0.01	0.095
Resting heart rate/ min	73.2 ± 0.62	75.6 ± 0.57*	73.8 ± 0.56	0.016 *
Lipid profile				
Total Cholesterol	189 ± 5.14	194 ± 5.05	192 ± 5.16	0.877
Triglyceride	117 ± 3.76	119 ± 3.16	113 ± 3.23	0.056
LDL	124 ± 3.22	128 ± 3.02	128 ± 3.03	0.631
HDL	29 ± 0.88	31.6 ± 0.92	31.8 ± 0.96	0.204
LFT (Liver function test)				
SGPT	31.0 ± 0.79	30.7 ± 0.79	31.2 ± 0.81	0.901
Alkaline phosphates	145 ± 2.78	147 ± 2.81	141 ± 3.15	0.286
Bilirubin Total	0.56 ± 0.02	0.58 ± 0.02	0.59 ± 0.02	0.458
Bilirubin Direct	0.21 ± 0.02	0.23 ± 0.02	0.25 ± 0.02	0.388
Creatinine kinase	94.7 ± 3.29	96.5 ± 3.36	97.3 ± 3.24	0.861

***=p-value<0.05, significant difference between the all three groups**
****=p-value<0.01, highly significant difference between the all three groups**

TABLE 2A
COMPARISON OF REDUCTION IN CARDIOVASCULAR RISKS BY ASSESSING THE C - REACTIVE PROTEIN AND FORCED EXPIRATORY LEVEL IN ONE SECOND LEVELS (FEV1) IN ALL TREATED COPD PATIENTS

	Group A (n=33) Mean ± SEM	Group B (n=34) Mean ± SEM	Group C (n=34) Mean ± SEM	p-value
Reduction in C-reactive protein levels				
Day – 0	6.45 ± 0.36	6.68 ± 0.26	6.44 ± 0.27	0.812
Day – 30	6.15 ± 0.29(4.7%)	6.50 ± 0.22(2.6%)	5.56 ±0.18(13.6%)	0.031*
Day – 60	5.24± 0.24(18.7%)	5.97 ± 0.18(10.7%)	5.18 ±0.21(19.5%)	0.036 *
Day – 90	4.61± 0.19(28.5%)	5.82 ± 0.20(12.9%)	4.56 ±0.14(29.2%)	0.001 **
Improvement in FEV1 levels				
Day – 0	2.16 ± 0.07	2.12 ± 0.05	2.18 ± 0.03	0.613
Day – 30	2.25± 0.06(4.2%)	2.24 ± 0.05(5.7%)	2.28 ± 0.06(4.6%)	0.861
Day – 60	2.35 ± 0.06(8.8%)	2.31 ± 0.04(9%)	2.47 ± 0.04(13%)	0.378
Day – 90	2.48± 0.06(14.9%)	2.40 ±0.04(14.2%)	2.60±0.04(19.3%)	0.020*

- ****= p<0.01, highly significant difference between the all three groups**
- ***= p<0.05 , significant difference between the all three groups**
- **Percentage changes in parenthesis**

FIGURE 1

COMPARISON OF REDUCTION IN CARDIOVASCULAR RISKS BY ASSESSING THE C – REACTIVE PROTEIN IN ALL TREATED COPD PATIENTS

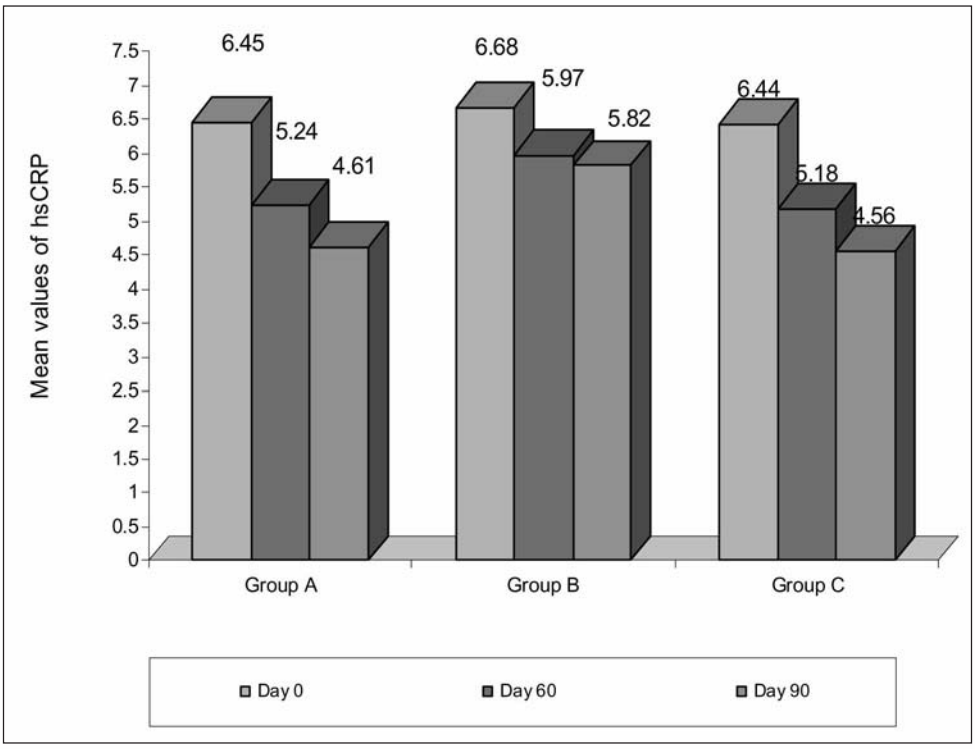


TABLE 3A
COMPARISION OF BIOCHEMICAL SAFETY PROFILE IN ALL TREATED GROUPS

Variables	Group A (n=33) Mean ± SEM	Group B (n=34) Mean ± SEM	Group C (n=34) Mean ± SEM	p-value
Baseline				
SGPT	31 ± 0.79	30.7 ± 0.79	31.2 ± 0.81	0.901
Alkaline phosphatase	145 ± 2.78	147 ± 2.81	141 ± 3.15	0.286
Bilirubin total	0.56 ± 0.02	0.58 ± 0.02	0.59 ± 0.02	0.458
Bilirubin direct	0.21 ± 0.02	0.23 ± 0.02	0.25 ± 0.02	0.388
Creatinine kinase	95 ± 3.29	96.5 ± 3.36	97.3 ± 3.24	0.861
Day 90				
SGPT	33 ± 0.59	32.1 ± 0.92	32.6 ± 0.71	0.702
Alkaline phosphatase	147 ± 2.33	149 ± 2.57	145 ± 2.78	0.544
Bilirubin total	0.61 ± 0.02	0.64 ± 0.02	0.60 ± 0.02	0.339
Bilirubin direct	0.27 ± 0.03	0.26 ± 0.03	0.26 ± 0.02	0.955
Creatinine kinase	98 ± 3.17	97.3 ± 3.26	99.2 ± 2.80	0.906

- **Values expressed as Mean ± SEM**
- **P-value was non significant**

TABLE 3B
COMPARISON OF CLINICAL SAFETY PROFILE IN ALL TREATED COPD PATIENTS

Adverse Events	Group "A" n (%)	Group "B" n (%)	Group "C" n (%)
Muscle pain			
Day – 30	7 (21.2)	3 (8.8)	6(17.6)
Day – 60	4(12.0)	1(2.9)	3(9.0)
Day – 90	1(3.0)	-	3(9.0)
Sore throat			
Day – 30	1 (3.0)	6(17.6)	7(20.5)
Day – 60	3(9.0)	4(11.7)	2(5.8)
Day – 90	-	2(5.8)	1(2.9)
Hoarseness of voice			
Day – 30	-	-	-
Day – 60	-	-	4(11.7)
Day – 90	-	2(5.8)	2(5.8)
Bone pain			
Day – 30	5 (15.2)	4(11.7)	4 (11.7)
Day – 60	1(9.0)	3(8.8)	2(2.9)
Day – 90	-	1(2.9)	-
Retrosternal burning			
Day – 30	-	-	-
Day – 60	2(6.0)	6(17.6)	6(17.6)
Day – 90	1(3.0)	4(11.7)	5(14.7)
Others			
Day – 30	3(9.0)	5(14.7)	5(14.7)
Day – 60	1(3.0)	3(8.8)	3(2.9)
Day – 90	-	2(5.8)	2(5.8)

gressive expiratory airflow limitation that is not fully reversible it is highly prevalent chronic lung condition, affecting 10% of adults over the age of 40 years[21] . COPD affects other end organs including the cardiovascular and the musculoskeletal system, making it a multi component and multisystem disease[22].

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[23].

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[24].

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[25].

Glucocorticoids have potent anti-inflammatory effects and therefore are of theoretic benefit in patients with COPD[26]. Furthermore, the anti-atherogenic properties of corticosteroids have been demonstrated in several animal studies[27,28].

In 2004, Sin and colleagues reported that ICS therapy may provide a similar CRP benefit for those patients with respiratory disease. The authors performed a randomized, double-blind, placebo-controlled trial involving 41 patients with mild-to-moderate COPD to examine the effects of ICS therapy on systemic inflammation. The withdrawal of ICS therapy increased baseline CRP levels by 71%, while a return to ICS therapy for 2weeks reduced CRP levels by 50%. No significant changes were observed with placebo. An additional 8 weeks of ICS therapy was associated with CRP levels that were lower than those at baseline (29% reduction).Interestingly, 2 weeks of prednisone therapy reduced CRP levels by a comparable amount (63%) to that of ICS therapy, even though the ICS dosage (fluticasone,500 µg bid) was thought to be too low to mimic the effects of therapy with systemic corticosteroids[29].

Albert et al. shows 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 decreases the hsCRP levels

in our patients. These data provide evidence that Statin may have anti-inflammatory effects in addition to lipid lowering effects[30]. Inhaled corticosteroids may reduce CRP production indirectly by downregulating the expression of IL-6[31]. Previous studies indicate that IL-6 is a major signaling cytokine for CRP expression by hepatocytes.Importantly persistent therapy with inhaled corticosteroids attenuates IL-6 expression in patients with COPD[32].

The combination of the a HMG-CoA reductase inhibitors and a Glucocorticoids given separately, sequentially or simultaneously may potentiate the effects of either component and also produce a better effect than conventional COPD treatments. The therapeutics effect may be observed with regard to the fast decline in the lung function that is a hallmark of COPD, and effects may be observed regarding the systemic inflammation that is also characteristics of COPD. The most preferred combinations are Atorvastatin/ Budesonide and Rouvastatin/ Budesonide [33].

Combined therapy of Statin with inhaled steroids has more favorable effects on all outcomes in resent study as compare to the either treatment alone. This was consistent with the study conducted by Moneechatesuwan et al. (2010) as they evaluated that either addition of Statin enhances anti-inflammatory effects of steroids in asthmatic patients. They concluded that a Statin enhances the anti-inflammatory effect of inhaled steroids in asthma and this was mediated through the alteration of indoleamine 2, 3-dioxygenase (IDD) activity in macrophages[34].

Both the study drugs were generally well tolerated and not associated with any serious adverse effects and most of the adverse effects noted were self limited, this was in agreement with the study conducted by Roberts et al.,(2007)[35] and Morice et al.,(1996)[36].

CONCLUSION

In conclusion, combination therapy of Atorvastatin with Budesonide effectively decreases the cardiovascular risk by decreasing the systemic inflammation which were indicated by decreasing the hsCRP levels and also improve pulmonary functional capacity in COPD patients.

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