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ORIGINAL ARTICLE

Comparison of the Effectiveness of Long Acting Beta 2 Agonist and Long Acting Antimuscuranics with Long Acting Beta 2 Agonist/Long Acting Antimuscuranics Plus Inhaled Corticosteroids in preventing Exacerbations of patients with Chronic Obstructive Pulmonary Disease Targeted by Blood Eosinophils

AQEELA NAEEM[1], ASMA SABIR[2], KANWAL FATIMA KHALIL[3], ASMA AMBREEN[4], SHUMIALA AWAN[5], JAMILA KHAN[6]
[1]*Ex-Postgraduate Trainee, Department of Pulmonology, Fauji Foundation Hospital, Rawalpindi*
[2]*Assistant Professor, Departmentof Pulmonology, POF Hospital Wah Cantt*
[3]*Consultant Respiratory Physician, University Hospital North Durham, UK*
[4,5]*Assistant Professors, Department of Medicine, Fauji Foundation Hospital, Rawalpindi*
[6]*Senior Registrar, Department of Gastroenterology, Wah Medical College, WahCantt*
Correspondence to: Aqeela Naeem, Email: aqeelanaeem@yahoo.com, Cell: 0321-5332171

ABSTRACT

Objective: To compare the efficacy of long acting beta 2 agonist and long acting antimuscuranics with long acting beta 2 agonist/long acting antimuscuranics plus inhaled corticosteroids in preventing exacerbations of chronic obstructive pulmonary disease and its relationship with increased eosinophils level.

Study Design: Randomized control trial

Place and Duration Study: Department of Pulmonology, Fauji Foundation Hospital, Rawalpindi from 7th February 2018 to 6th August 2018.

Methodology: Seventy patients with chronic obstructive pulmonary disease were enrolled. They were divided in two groups; Group A receiving LABA/LAMA combination and Group B receiving LABA/LAMA plus ICS combination. Both groups treatment efficacy was related with increased eosinophils count. Patients were regularly followed and number of exacerbations in the first three months was noted. At the completion of the study, the rate of exacerbations among the 2 groups was compared.

Results: The rate of efficacy in LABA/LAMA and LABA/LAMA plus ICS group was 62.9% and 85.7% respectively. Efficacy was more achieved in LABA/LAMA plus ICS group in patients whose eosinophil count was ≥ 2% up to 90.5% and was 78.6% whose eosinophil count was ≤ 2%.

Conclusion: Treatment with long acting beta 2 agonist/long acting antimuscuranic plus inhaled corticosteroids is more effective in preventing exacerbations of patients with advanced COPD than with long acting beta 2 agonist and long acting antimuscuranic.

Keywords: Chronic obstructive pulmonary disease, Long acting beta 2 agonist, Long acting antimuscuranics, Inhaled corticosteroids, Efficacy, Eosinophilia

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major health problem and is associated with significant morbidity and mortality. Chronic obstructive pulmonary disease is currently the 4th commonest global cause of death in the developed countries affecting 80 million people worldwide and is expected to be ranked 3rd by 2020.[1]

Chronic obstructive pulmonary disease is characterized by persistent airflow limitation associated with airway and alveolar changes in response to noxious substances,[2] affecting 10% of the population over the age of 40years.[3]It is complicated by frequent and recurrent exacerbations characterized by augmentation in patient's symptoms of dyspnea, cough and sputum production, having significant impact on quality of life, lung function and exercise performance requiring unscheduled hospital visits, in-hospital care and medication. Various risk factors are responsible for the exacerbations with smoking being most important. Other causes include respiratory infections, biomass fuel, industrial pollutants, allergens and dietary factors.[4]

Patients with COPD have increased inflammatory markers including eosinophils, C-reactive protein (CRP), fibrinogen and inflammatory cytokines. There is also decline in values of forced expiratory volume (FEV) on spirometry. COPD is highly related with blood eosinophilia which is the hallmark for increased risk of exacerbations.[5]The goal of COPD management is to avoid recurrent exacerbations, improve symptoms and preserve lung function.[6]

The pharmacological management in COPD is with bronchodilators that include long acting beta 2 agonist and long acting antimuscuranics and are the standard care of treatment in patients with advanced COPD. The inhaled corticosteroids are also used in the COPD management due to their inflammatory nature. Guidelines recommend use of inhaled corticosteroids in patients presenting with exacerbations despite taking long acting bronchodilators.[7] However, few observations have shown that inhaled corticosteroids are associated with an increased risk of pneumonia.[8] Other treatment options in COPD include smoking cessation, oxygen therapy, pulmonary rehabilitation and surgical intervention.[9]

The association between eosinophilia and COPD exacerbations and that COPD patients with increased eosinophil count are at increased risk of exacerbations and only these are the patients who benefit by adding ICS.[10,11] Blood eosinophil count is the helpful tool in assessing the beneficial effect of adding inhaled corticosteroids to initial LABA/LAMA treatment.[12]In a study by Shawn and colleagues, the annual exacerbation rate in patients with COPD was 64.8% who were in tiotropium plus salmeterol group[13,14] and was reduced to 13.9% in tiotropium/formoterol plus budosenide group in another study conducted by Sang-Do Lee and colleagues.[15]

This study was carried out to compare effectiveness of β-2-agonist plus antimuscuranics and adding inhaled corticosteroids to β-2-agonist acting antimuscuranics. It clarified reduced rate of exacerbations and hospital stay of COPD patients. Likewise, a positive relationship of effectivness of triple therapy with increased eosinophils count was cleared.

MATERIALS AND METHODS

This randomized control trial study type was performed at Department of Pulmonology, Fauji Foundation Hospital Rawalpindi from 1st February 2018 to 31st August 2018. An informed consent was taken from all the participants. A non probability consecutive sampling technique was used for the purpose of data collection. A total of 70 patients were allocated to either of the groups after

randomizing patients by lottery method; group A receiving LABA/LAMA combination and group B receiving LABA/LAMA plus ICS combination. Patients were regularly followed and number of exacerbations in the first three months was noted. At the completion of study, the rate of exacerbations among the 2 groups was compared.

Patients from 40 to 60 years of age both males and females were selected. Patients included were diagnosed case of COPD belonging to group C & D according to GOLD Guidelines, with ≥2 episodes of exacerbations in last 1 year with baseline eosinophil count of ≥2 or ≤2 were included in the study. Patients with comorbities (Hypertension, Diabetes, Ischemic Heart Disease, Congestive cardiac failure and other Obstructive airway disease were excluded from the study. Spirometry was performed at baseline and after improvement with triple inhaler. Modified Medical Research Council (mMRC), OCPD Assessment Test (CAT) score and blood eosinophils count was checked out at baseline.

Data was analyzed using SPSS-19.Effect modifiers like age, gender, eosinophil count, number of episodes of acute exacerbations and smoking status were controlled by stratification.

RESULTS

The mean age of the patients was 53.20±5.75 years of group A and 53.48±4.79 years of group B. There were 2 (5.7%%) male and 33 (94.3%) female patients in group A whereas, 8 males and 27 females were present in group B. The mean number of exacerbation events of patients was 1.17±0.8 in group A and 1.7±1.09 in group B (Table 1).

There were 11 (57.9%) versus 19 (90.5%) patients in both the groups (p-value 0.017) who have >2% eosinophil counts before start of the study. There were 22 patients (62.9%) in LABA/LAMA group who achieved efficacy out of which 11 patients (68.8%) had baseline eosinophil count ≤2 and 11 patients (57.9%) with eosinophil count >2. On the other hand, 30 patients (85.7%) achieved efficacy in LABA/LAMA plus ICS group and of which 11 patients (78.6%) were with eosinophil count ≤2 and 19 patients (90.5%) with eosinophil count >2(Table 2).

Table 1: Demographic information of the patients (n=70)

Characteristics	LABA/LAMA (n=35)	LABA/LAMA/ICS (n=35)
Age (years)	53.20±5.75	53.48±4.79
Gender		
Male	2 (5.7%)	8 (22.9%)
Female	33 (94.3%)	27 (77.1%)
Current smoker	8 (11%)	10 (14%)
Pack-years of smoking	16 (22.8%)	20 (28.8%)
COPD exacerbation in the past 12 months	1.7±0.8	1.7±0.9
MMRC Grade (3-4)	55 (78%)	60 (85%)
Moderate or severe	68 (44%)	68 (43.9%)

Table 2: Comparison of efficacy according to eosinophil count in both groups

Eosinophil count	Efficacy	Treatment given		P value
		LABA/LAMA	LABA/LAMA/ICS	
≤ 2	Yes	11 (68.7%)	11 (78.6%)	0.544
	No	5 (31.3%)	3 (21.4%)	
> 2	Yes	11 (57.9%)	19 (90.5%)	0.017
	No	8 (42.1%)	2 (9.5%)	

Table 3: Comparison of efficacy according to number of exacerbation events in both groups

No. exacerbation events	Efficacy	Treatment given		P value
		LABA/LAMA	LABA/LAMA/ICS	
≤ 2	Yes	21 (84%)	30 (96.8%)	0.096
	No	4 (16%)	1 (3.2%)	
> 2	Yes	1 (10%)	-	0.512
	No	9 (90%)	4 (100%)	

On comparing the efficacy of treatment, group B has efficacy of 85.7% compared to 62.9% in group A. Later on the final outcome regarding the number of exacerbation events during the study was stratified and Frequency and percentage of efficacy among both the groups was 21 (84%) and 30 (96.8%) respectively (p-value 0.096)[Table 3].

DISCUSSION

Our study found that efficacy was more achieved in LABA/LAMA plus ICS group in patients whose eosinophil count was ≥ 2%, upto 90.5% as compared to 78.6% whose eosinophil count was ≤ 2%. Furthermore, efficacy achieved in triple inhaler group was more compared to double inhaler group regardless of eosinophil count. We also found that none of the patient reported with exacerbation in group B with high eosinophil counts at baseline. The goal of COPD management is to avoid recurrent exacerbations, improve symptoms and preserve lung functions. The pharmacological management with bronchodilators can be achieved by long acting beta 2 agonists (LABA) and long acting antimuscuranics (LAMA).These drugs when given in combination have a better outcome than either given alone. The use of inhaled corticosteroids (ICS) add up to the benefit with combination therapy.[16]

During past few years, much research work has been done in comparing the effectiveness of triple therapy i.e. LABA/LAMA plus ICS with LABA/LAMA in COPD management and reduction of exacerbations. Studies have shown an association between eosinophilia and COPD exacerbations and that COPD patients with increased eosinophil count are at increased risk of exacerbations and only these are the patients who benefit by adding ICS.[13] Triple therapy has a beneficial effect in COPD by improving lung function, health status and reducing the risk of exacerbations.[17] An association between ICS treatment and eosinophils level was seen indicating reduced exacerbations rate in patients, as noted in the studies conducted by Harries and colleagues where the positive association was found.[18,19]

In a study by Shawn and colleagues, the annual exacerbation rate in patients with COPD was 64.8% who were in tiotropium plus salmeterol group[14] and was reduced to 13.9% in tiotropium/formoterol plus budosenide group. Same results were seen in another study conducted by Sang-Do Lee and colleagues.[15]

CONCLUSION

The study concludes that treatment with long acting beta 2 agonist/long acting antimuscuranic plus inhaled corticosteroids is more effective in preventing exacerbations of patients with advanced COPD than with long acting beta 2 agonist and long acting antimuscuranic. It also reveals that efficacy was better in patients with blood eosinophil count of ≥2% who were receiving triple therapy. This means that addition of inhaled corticosteroids to LABA/LAMA in patients with eosinophilia ≥2% is beneficial in terms of reduction in rate of exacerbations.

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