ORIGINAL ARTICLE

To Compare Reduction in Exacerbation of Severe COPD with Double Inhaled Therapy Plus Roflumilast Vs Double Inhaled Therapy Alone

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ABSTRACT

Objective: To compare the efficacy of double inhaler therapy plus Roflumilast versus double inhaler therapy alone in reducing COPD exacerbations among patients with severe COPD.

Study Design: Quasi experimental study.

Place and Duration of Study: The study was conducted in Pulmonology department Pakistan Institute of Medical Sciences Islamabad, from 1-8-2019 to 1-8-2020.

Materials and Methods: A total of 126 COPD (GOLD stage III and IV) patients, on dual inhaled therapy with Long-Acting Beta 2 Agonists (LABA) and Inhaled Corticosteroids (ICS), who had one or more acute exacerbation in the preceding year were included in the study. Patients were divided into two groups A & B. Group A was assigned dual inhaled therapy plus Roflumilast 500mcg once daily, and Group B, dual inhaled therapy alone. Forced Expiratory volume 1 (FEV1*),* 6 minutes' Walk Distance (6mWD), modified Medical Research Council Scale for dyspnea (mMRC dyspnea scale) and number of acute exacerbations were assessed at baseline, and at one , three, six, nine and twelve months of treatment and compared. SPSS version 21 was used for analyzing the data. Categorical variables were computed as frequency and percentage. Mean and Standard Deviation for numerical variables. Chi square test was used to compare frequencies of categorical variables and independent sample t-test for Mean. Level of Significant was taken at $P \leq 05$.

Results: Twelve months after the start of therapy, group A showed significant improvement in FEV1, 6MWD, mMRC scale and acute exacerbations compared to group B (p values = 008*, 0.001*and 0.04* respectively).

Conclusion: Adding Roflumilast to dual inhaled therapy in severe COPD significantly improves lung functions, patients' functional status and frequency of acute exacerbations

Key Words: *Chronic Obstructive Pulmonary Disease*, *Forced Expiratory Volume, Forced Vital Capacity, GOLD Stage, Inhaler Therapy, Roflumilast.*

Introduction

COPD is a progressive disorder characterized by chronic inflammation of the airways and parenchymal lung destruction, leading to a decline in lung function. The course of COPD is complicated by acute exacerbations. Co morbidities like cardiac failure, hypertension, diabetes mellitus, and pneumonia also effect the clinical course.[1] Recurrent exacerbations are major determinants of reduction in lung function, and increase in morbidity and mortality. Acute exacerbations are defined as sustained worsening of a patient's condition beyond normal day to day variation that require a change in medication and or hospitalization. [1] Roflumilast a highly selective phosphodiesterase-4 (PDE4) inhibitor has been evaluated in the treatment of severe COPD and has revealed improvement in lung functions and reduction in acute exacerbations. PDE4 is a major cyclic-3',5'-adenosinemono-phosphate (cyclic AMP, cAMP)-metabolizing enzyme which is expressed on nearly all immune and pro-inflammatory cells. The increase in intracellular c AMP induced by roflumilast's inhibition of PDE4 is thought to mediate its disease-modifying effects.[2] It is given orally and has a bioavailability of 80%. It has been evaluated in the treatment of COPD in phase III/IV randomized double- blind trials that revealed improvement from baseline in Forced Expiratory Volume in first second (FEV1) and post

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bronchodilator Forced Vital Capacity (FVC).[1,3,4]

In Pakistan the prevalence of COPD is reported to be 2.1% among adults aged more than 40 years. [5] In rural areas of Pakistan, the prevalence of undiagnosed COPD is 31.1% [6] which imposes a significant health burden in Pakistan.

In this study we compared the effect of Roflumilast plus double inhaled inhaler therapy on lung functions, patients' functional status and frequency of acute exacerbations to double inhaled therapy alone in our population.

Materials and Methods

A quasi-experimental study was conducted over a period of one year at Pakistan Institute of Medical Sciences. A total of one hundred and twenty-six (n=126) diagnosed patients of COPD (Gold stage III and IV) who were on regular double inhaled therapy (LABA and ICS) and had one or more exacerbation in the previous year were enrolled. Written informed consent from the patients and approval from the ethics committee of Shaheed Zulfiqar Ali Bhutto Medical University SZAMBU /PIMS was taken prior to enrollment (Letter No. F.1-1/2015/ERBSZABMU/446 Dated 23-7-2019). The sample size was calculated by WHO calculator.

Patients were divided into groups A & B. Group A received dual inhaled therapy plus Roflumilast and Group B received dual inhaled therapy alone. Patients were assessed at baseline and after one month (follow up 1), three months (follow up II), six month (follow up III), nine months (follow up IV) and at twelve months (follow up V) for FEV1, 6mWD, m MRC dyspnea scale 0 to 4 : (0- breathlessness on strenuous exercise only ; 1 shortness of breath on walking fast or uphill; 2, walks slower because of breathlessness or has to stop to catch breath; 3, stops for breath after walking ~ 100 m or after few minutes on the level; and 4, too breathless to leave the house, or breathless when dressing or undressing).[7]

Improvement in m MRC dyspnea scale and number of exacerbations during the treatment year were assessed by detailed history and medical records of admission in ER or hospitalization at 12 months and compared in both groups.

Inclusion Criteria

Patients of COPD diagnosed by spirometry with FEV_1/FVC ratio less than 70%, and pre- and post-BDT FEV_1 of 30 to 49% of the predicted for Grade III and < 30% for Grade IV), smoking history of 20 pack years or more, at least one exacerbation of COPD in the previous year , on inhaled LABA and ICS regularly for the last one year and no exacerbation in the 4 weeks prior to inclusion in the study were included in the study .

Exclusion Criteria

Patients with less than one exacerbation in the previous year, those not using dual inhaler therapy, who had an acute exacerbation four week prior to enrollment and those with comorbidities like cardiac failure, asthma and bronchiectasis were excluded.

Data Analysis

SPSS version 21 was used for analyzing the data. Categorical variables like gender, symptoms (m MRC Dyspnea Scale,) were computed as frequency and percentage. Mean and Standard Deviation was computed for numerical variables like age, FEV1, FEV1/FVC. Chi square test was used to compare relative frequencies of categorical variables in both groups. Independent sample t-test was used to compare Mean, Level of Significant was taken at *P* ≤05.

Results

The total number of patients was 126, 63 in each group**.** The groups were comparable in age, gender, co-morbidities, COPD stage and baseline parameters of FEV1, FEV1/FVC and 6mWD ,COPD exacerbation in the previous year ,mMRC scale of dyspnea (Table I)

At 12 months after the start of therapy FEV-1 improved in both treatment groups, the improvement was better in Group A. The difference for FEV1 was statistically significant at 9 month (p=0.042*,) and at 12 months (p=0.008*). (Table II). The improvement in 6MWD in Group A was also significant. p=0.001*(Table III). Group A showed 15.9% in improvement in the m MRC scale compared to 4.8 % in Group B with P=0.04*. (Table IV) while 25.4% of patient in Group A showed reduction in acute exacerbations compared to 4.8% Group B P=0.001* (Table IV).

Discussion

The results of this study show that adding Roflumilaast to standard treatment of advanced COPD leads to improvement in lung functions and patients' functional status in addition to reducing the frequency of Acute exacerbations.

Table I: Baseline Characteristics Including Gender, Age, Co-Morbidities , COPD GOLD Stage, Lung Parameters and Number of Acute Exacerbations: n=126

Gender		Groups		Total
		A	B	
Male		41(65.1%)	43(68.3%)	84(66.7%)
Female		22(34.9%)	20(31.7%)	42(33.3%)
TOTAL		63(100.0%)	63(100.0%)	126(100.0%)
Different Age Groups				
40-55 YEARS		26(41.3%)	27(42.9%)	53(42.1%)
56-70YEARS		37(58.7%)	36(57.1%)	73(57.9%)
Mean age (years)		56.6±5.6	56.3±5.1	56.4±5.3
Baseline co Morbidities				
HTN	Present	12(19.0%)	13(20.6%)	25(19.8%)
	Absent	51(81.0%)	50(79.4%)	101(80.2%)
DM	Present	15(23.8%)	17(27%)	32(34%)
	Absent	48(76.2%)	46(70%)	94(74.6%)
IHD	Present	9(14.3%)	8(12.7%)	17(13.5%)
	Absent	54(85.7%)	55(87.3%)	109(86.5%)
Gold Stage				
STAGE III		39(61.9%)	43(68.3%)	82(65.1%)
STAGE IV		24(38.1%)	20(31.7%)	44(34.9%
Baseline Parameters				
FEV1 (ml)	MEAN	1042.3	1034.4	
	STD. DEV	299.1	306.9	
FEV1 (%)	MEAN	35.3	35.2	
	STD. DEV	8.2	8.3	
FEV1/FVC	MEAN	34.1	32.1	
	STD. DEV	14.9	13.4	
6MWD	MEAN	282.6	283.3	
	STD. DEV	112.6	111.9	

Number of Exacerbations During Previous year			
Number of exacerbations	A	B	TOTAL
1	6 (9.5%)	13(20.6%)	19(15.1%)
2	40(63.5%)	30(47.6%)	70(55.6%)
3	10(15.9%)	17(27.0%)	27(21.4%)
4	7(11.1%)	3(4.8%)	10(7.9%)

The improvement in 6MWD was significant at six months and FEV1 at nine months of starting Roflumilast .At twelve months the mMRC scale had improved in the treated group by 10.3% and the frequency the acute exacerbation by 15.9% . It is interesting to note that there was an overall

Table II: Comparison of FEV1 In Both Groups Overtime

FEVI (ml)	Groups	Mean	SD	P-value t-test
Baseline	A	1042.3	299.1	0.984
	B	1043.4	306.9	
Follow up 1	A	1072.4	295.2	0.721
	B	1053.3	307.1	
Follow up 2	A	1084.1	297.5	0.634
	B	1058.4	307.5	
Follow up 3	A	1094.7	299.1	0.616
	B	1067.6	306.2	
Follow up 4	A	1175.1	318.1	0.042*
	B	1070.1	308.5	
Follow up 5	A	1219.4	277.4	0.008*
	B	1079.3	305.5	

Table III: Comparison of 6MWD in both Groups Overtime

6mWD (m) At:	Group	Distance in meters	SD	P value t-test
Baseline	A	282.6	112.6	0.969
	B	283.3	111.9	
Follow up 1	A	322.1	112.1	0.132
	B	291.9	112.4	
Follow up 2	A	331.1	112.9	0.118
	B	299.3	114.2	
Follow up 3	A	356.6	114.3	0.013*
	B	305.4	114.5	
Follow up 4	A	363.5	109.2	0.016*
	B	314.8	113.8	
Follow up 5	A	395.1	111.2	0.001*
	B	323.4	112.8	

Table IV : Comparison of Improvement in Mmrc Scale and Acute Exacerbation in Two Groups at 12 Months

Improvement in exacerbations	A	B	Total	P value Chi sq test
Present	16 25.4%	3 4.8%	19 15.1%	0.001*
Absent	47 74.6%	60 95.2%	107 84.9%	
Improvement: mMRC Dyspnea Scale	Groups		Total	P-value chi-square-test
	A	B		
Present	10	3	13	0.040*
	15.9%	4.8%	10.3%	
Absent	53	60	113	
	84.1%	95.2%	89.7%	

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improvement in the all the parameters in both groups. Possibly because of a more supervised treatment and regular follow-ups.

Our results are comparable with other studies. In the REACT study Martinez FJ et al investigated the role of Roflumilast in decreasing the number of exacerbations of COPD [3].The study showed that the exacerbations were 13·2% lower in the Roflumilast group than in the placebo group. Rennard SI et al in their analysis of two randomized, double-blind, placebo-controlled trials comprising of 2686 patients showed that Roflumilast significantly decreased exacerbations by 14.3% compared with placebo.[8]

In a meta-analysis of six randomized controlled trials, Roflumilast was found to be superior to placebo in patients of severe COPD patients already on ICS/LABA combinations in improving FEV_1 as well as COPD exacerbation rate.[9]

In RE(2)POND a 52-week, phase 4, double-blind, placebo-controlled trial, Roflumilast failed to significantly reduce moderate and/or severe exacerbations in the overall population .But there was a reduction in rate of moderate to severe exacerbations per patient per year by 8.5 %. Roflumilast also improved lung function significantly.[9]

It is of interest to note the result of studies using inhaled corticosteroid fluticasone with long acting B2 agonist Vilantrol and monoclonal antibodies to IL5 in the reduction of exacerbations in a subset of patient COPD with high eosinophilc count.[10,11,12,13]

Similarly a differential response to Roflumilast was observed in subgroup of COPD patients who were older > 65 years, had comorbidities and Chronic bronchitis or bronchiectasis.[14]

We did not categorize our patients according to the type of cellular response (eosinophilc or neutrophilc) or phenotype .It would be interesting to see whether Roflulmilast was effective in a specific subgroup of COPD, or the effect was irrespective of the nature of inflammatory response and presence of comorbidities.

Albert RK et al found that adding azithromycin 250 mg daily to usual treatment of COPD patients for one year decreased the frequency of acute exacerbation, but was associated with slight increase in hearing loss and colonization with macrolide resistant microorganism.[15]

A retrospective observation study comparing the results of chronic azithromycin to Roflumilast however showed better out comes for Azithromycin.[16]

The role of pulmonary rehabilitation and assistance to remove secretions and ciliary functions also contribute to improvement in quality of life for COPD patients.[17,18]

We a did not study the side effect profile of Roflumilast. Zeng et al[19] observed the incidence of diarrhea, headache, nausea, weight loss, back pain, loss of appetite, and insomnia was notably higher in the Roflumilast group than in the placebo group. But overall safety profile has been found to be satisfactory and no increase in five-year mortality was reported in a review of the database cohort.[20]

A holistic approach to COPD management aiming at optimal bronchodilator and anti-inflammatory therapy supported by pulmonary rehabilitation and measures to reduce the frequency of acute exacerbations with medicine like roflumilast would improve the overall outlook for COPD.

Our study has several strengths. in addition to assessing the effect on COPD exacerbation we also studied the effect on indicators of functional status like 6mWD and mMRC dyspnea grades. We assessed the patients at multiple follow up visits that enabled us to monitor changes in lung functions and other functional parameters over the period of one year.

One of the limitations of our study ~~is~~ a relatively small sample size.

Conclusion

Adding Roflumilast to standard therapy for COPD reduces the frequency of acute exacerbations and improves lung functions.

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CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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DATA SHARING STATMENT

The data that support the findings of this study are available from the corresponding author upon request.