Pharmacology

A PROSPECTIVE, COMPARATIVE STUDY OF EFFECT OF ROFLUMILAST IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND ITS EFFICACY IN REDUCING ACUTE EXACERBATIONS.

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ABSTRACT

TITLE: A prospective, comparative study of effect of Roflumilast in COPD and its efficacy in reducing exacerbations
AIM: To study the efficacy of Roflumilast as an add on therapy and to reduce exacerbations in COPD.
OBJECTIVE: To determine whether Roflumilast improves lung function and decreases exacerbation frequency over a period of 6 months in patients with COPD.
METHOD: This was a prospective, comparative, randomized, open label study. Patients attending outpatient department of Thoracic medicine diagnosed with COPD with FEV1/FVC < 0.7 were recruited and divided into 2 groups of 50 patients each. Group 1 was administered with standard treatment consisting of Salmeterol and steroid inhalation, while Group 2 patients were administered Roflumilast 500 microgm once daily as add on therapy. Patients were followed every week and enquired for exacerbations and adverse effects. Lung function tests were performed every month using spirometer.
RESULTS: 24 participants were female and the rest 76 were male. There was improvement seen in lung function tests in Roflumilast group compared to control group. All patients in Roflumilast group reported improvement in symptoms such as cough, breathlessness and increase in sputum production and in quality of life compared to control group. Exacerbation of COPD was seen in 3 patients in Roflumilast group compared to 9 patients in control group. The median time to exacerbation was 4.3 months in Roflumilast group compared to 2.8 months in control group.
Conclusion: Data suggest that roflumilast reduces moderate to severe exacerbations with the benefit most well established in patients with severe disease.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a type of obstructive lung disease characterised by poor air flow and can be present lifelong. It is progressive in nature i.e. gets worse over time [1]. COPD affects about 329 million people every year which is nearly 5% of the global population [2]. It is diagnosed in middle aged or older adults. Both males and females are commonly affected. It is one of the major causes of disability in the world and contributes to the burden of deaths in low and middle income countries. The disease significantly affects health related Quality of life in the world [3].

Smoking is the most common cause and risk factor which lead to development of COPD [4]. Bidi smokers were at higher risk of developing COPD than those who smoked cigarettes [4]. Cooking fuel, kerosene, biomass fuel, firewood also contributed to the development of disease in developing countries. Second hand smoke is a combination of two forms – the smoke exhaled by a smoker and the smoke from lighted end of a cigarette, cigar, pipe or tobacco. Intense and prolonged exposure to fumes, dust, chemicals in workplace also increase risk of COPD in smokers and non smokers [5]. During pregnancy, if women smoke, may increase the risk of COPD in the child. Exposure to these irritants for a long time causes an inflammatory response in the lungs which results in narrowing of airways and in breakdown of lung tissue. Genetic factor Alpha 1-antitrypsin deficiency plays a small role in development of COPD [6].

Acute exacerbation of COPD is defined as increased shortness of breath, cough, and increased production of sputum in a patient diagnosed with COPD. There is sudden worsening of symptoms. triggered by infection, environmental pollutants, and cold temperature.

Diagnosis of COPD is done using Spirometer which determines the severity of airflow limitation [7,8].

The current treatment modalities available for COPD are inhaled bronchodilators, beta2 agonists and anticholinergics. If these drugs are ineffective, then corticosteroids and Methylxanthines are added [9]. Supplemental oxygen is recommended in patients with low oxygen level at rest. Medications are given with a metered dose inhaler with a spacer or via a nebuliser [9]. These measures do not change the progression of underlying disease and do not reduce the rate of hospital admissions [21].

The prognosis of persons affected with COPD is bad as the disease gets worse over time and can lead to death [10]. The number of years living with disability due to COPD is increasing in the world. It can also lead to many comorbid conditions such as cor pulmonale and end stage lung disease leading to respiratory failure, pneumonia, polycythemia and pneumothorax [10,11]. The effects of COPD extend beyond the lungs which includes cardiovascular disease, diabetes mellitus, osteoporosis, and depression [12,13]. Also in COPD, airflow reduction does not improve significantly with bronchodilators, in contrast to asthma [11,14]. Therefore, there is a need for new drug to decrease disease progression, reduce exacerbations and to improve the quality of life in patients with COPD.

Drug Roflumilast is a selective, long acting inhibitor of Phosphodiesterase-4 (PDE-4) which leads to accumulation of cAMP. It has anti inflammatory property and works by decreasing swelling in the lungs and reducing irritation [15]. Also due to its property of changing the internal airflow distribution, it improves efficacy of Steroids and B2 agonists as well [16,17]. Therefore, in this study comparison of effect of standard treatment of COPD with Roflumilast as add on therapy to standard is done.

MATERIALS AND METHODS

This was a prospective, comparative, randomized, open label study conducted at Govt Thiruvoteeswarar TB and chest hospital, Otteri, Chennai which belongs to Govt. Kilpauk Medical College between March 2016 and January 2017.
Approval from The Institute Ethics Committee was obtained prior to commencement of the study. The conduct of the study was along the guidelines laid down by ICMR on the conduct of biomedical research.

SAMPLE SIZE

The sample size was calculated using the following formula [18]:

$$n = \frac{2(Z_a + Z_{1-\beta})^{2}\sigma^{2}}{\Delta^{2}}$$

where n is the required sample size, Z_a, Z is a constant (set by convention according to the accepted α error). σ is the standard deviation (estimated) and Δ the difference in effect of two interventions which is required (estimated effect size).

This gives the number of sample per arm in a controlled clinical trial. Let us assume we will accept a $p<0.05$ as acceptable and a study with 80% power; we get the following values: Z_{α} is 1.96 and $Z_{1-\beta}$ is 0.8416. The standard deviation based on data would be approximately 0.35. For Δ, the effect size would be 15%.

A minimum sample size of 100 (50 per group) was required to have 80% chance (alpha error of 0.05) of detecting an improvement in lung function tests in the experimental group. Therefore a sample size of 100 was arrived at.

SCREENING
The study procedure required screening for patients with COPD from those who attended outpatient department of the hospital based on GOLD criteria [19]. Patients (old and newly diagnosed) who satisfied the inclusion criteria and those who were willing to take part in study were recruited. Written informed consent was obtained. A detailed history and clinical examination was performed on the participants.

Diagnosed patients of COPD who were on treatment with Theophylline group of drugs were excluded, as Theophylline group is also a phosphodiesterase inhibitor. Patients were subjected to spirometry test by which their lung function was recorded and persistent airflow limitation was noted. Those patients with FEV1/FVC value of < 0.7, and value after post bronchodilator therapy with <12% change were chosen for the study. In post bronchodilation testing after 30 minutes inhalation of salbutamol and Hydocortisone, there should not be reversal of obstruction or less than 12% change should be seen. This differentiates bronchial asthma from COPD as reversibility is a feature of bronchial asthma.

INCLUSION CRITERIA
1. Patients diagnosed with COPD of any grade based on Gold criteria with H/O at least one exacerbation within last 1 year.
2. Patients of either sex, aged above 30 years

EXCLUSION CRITERIA
1. Patients with co morbid conditions like diabetes, hypertension, tuberculosis, and cardiovascular diseases.
2. Patients diagnosed with asthma,
3. Patients of COPD on treatment with theophylline group of drugs

RANDOMIZATION
A simple randomization method was adopted. Patients were randomised into 2 groups, i.e, Roflumilast drug therapy group and the standard treatment group.

Table 1 :

Group 1 Standard treatment	Group 2 Standard along with Roflumilast
n=50	n=50
Oral Salmeterol 250ug and inhalational Steroid Fluticasone50 ug twice daily 12 hours apart for 6 months.	Oral Roflumilast 500ug along with Salmeterol and inhalational Steroid once daily for 6 months.

Salmeterol 250ug was given orally and steroid Fluticasone 50ug was given by inhalational route. Tablet Roflumilast 500ug, was taken once daily in the morning after food.

PROCEDURE
After recruitment of patients and before initiation of therapy, lung function test was performed using spirometry. It measures lung function, specifically the amount (volume) and/or speed (flow) of air that can be inhaled and exhaled and is helpful in assessing breathing patterns. The patient was asked to take the deepest breath they can, and then exhale into the sensor as hard as possible, for as long as possible, preferably at least 6 seconds.

In both the groups, patients were checked weekly for exacerbations, and were enquired about occurrence of any subjective symptoms, side effects and were examined for any external signs such as rashes, urticaria, and other hypersensitivity features.

If exacerbation occurred, the median time to exacerbation was noted. Lung function tests were done every month, i.e. in the beginning after recruitment, and at the end of 1, 2, 3, 4, 5, and 6 months and changes were noted.

RESULTS
DEMOGRAPHICS
24 participants were female and the rest 76 were male. All patients in Roflumilast group reported improvement in symptoms such as cough, breathlessness and increase in sputum production. They also reported that their breathing was easier than before and there was improvement in quality of life compared to control group.

ACUTE EXACERBATIONS
Exacerbation of COPD was seen in 3 patients in Roflumilast group compared to 9 patients in control group. The median time to exacerbation was 4.3 months in Roflumilast group compared to 2.8 months in control group.

Fig 1: Graph showing comparison between exacerbations and median time to exacerbation in Roflumilast group and control group.
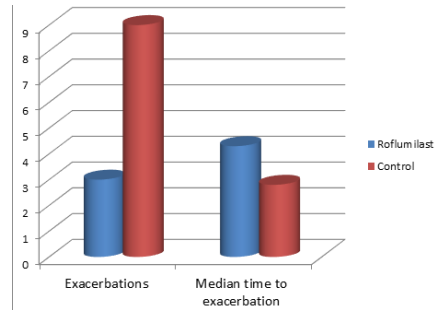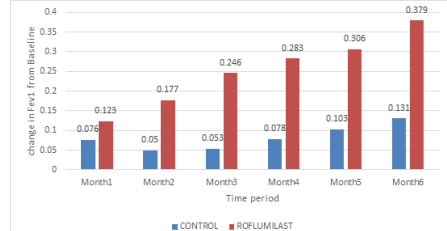

Table:2 Comparison of mean Change in FEV1 at 6 months across study groups (N=100)

Group	Change in FEV1 at 6 months Mean±SD	Mean difference	95% CI		P value
			Lower	Upper	
CONTROL	0.131 ± 0.204	-0.25	-0.34716	-0.14884	0.001
ROFLUMILAST	0.379 ± 0.239				

The mean change in FEV1 at 6 months was 0.131±0.204 in subjects belonging to Control and mean change in FEV1 at 6 months was 0.379±0.239 in subjects belonging to Roflumilast. The mean difference across the group is (-0.25). It is statistically significant.

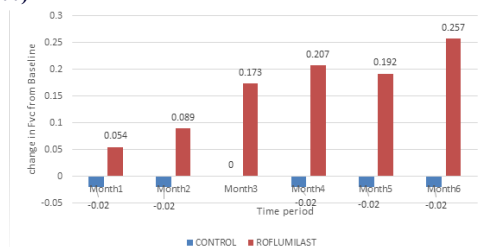Fig 2: Comparison of mean change in FEV1 across study groups (N=80)

B) Forced vital Capacity (FVC)

TABLE:3 Comparison of mean Change in FVC at 6 months across study groups (N=100)

Group	Change in FVC at 6 months Mean±STD	Mean difference	95% CI		P value
			Lower	Upper	
CONTROL	0.02 ± 0.345	0.29	-0.42205	-0.15195	0.001
ROFLUMILAST	0.257 ± 0.253				

The mean change in FVC at 6 months was 0.02±0.345 in subjects belonging to Control and mean change in FVC at 6 months was 0.257±0.253 in subjects belonging to Roflumilast group. The mean difference across the group is (-0.29). It is statistically significant (P Value 0.001).

**Fig 3: Comparison of mean change in FVC across study groups (N=100)**

C)% FEV1 (FV1/FVC)

TABLE :4 Comparison of mean Change in FEV1/FVC at 6 months across study groups (N=100)

Group	Change in FEV1/FVC at 6 monthsMean ±STD	Mean difference	95% CI		P value
			Lower	Upper	
CONTROL	0.101 ± 0.120	-0.04	-0.09127	0.01077	0.120
ROFLUMILAST	0.142 ± 0.108				

The mean change in FEV1/FVC at 6 months was 0.101±0.120 in subjects belonging to Control and mean change in FEV1/FVC at 6 months was 0.142±0.108 in subjects belonging to Roflumilast group. The mean difference across the group is (-0.04). It is statistically not significant (P Value 0.120).

Fig 4: Comparison of mean Change in FEV1/FVC across study groups (N=100)
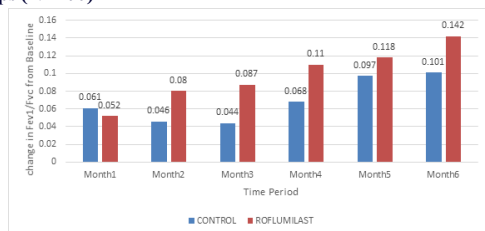
ADVERSE DRUG REACTIONS
Out of 50 patients recruited in the Roflumilast group, 27 patients reported adverse effects such as headache a few hours after ingestion of the drug. A few reported tremors, insomnia, nausea, diarrhoea, dizziness, and clouding of consciousness after intake of drug. The other participants tolerated the drug well. No life threatening or severe reactions to drug occurred.

DISCUSSION & CONCLUSION
Acute exacerbation of COPD requires increased use of medications and hospitalization. Also, there are no guidelines for treatment of exacerbations in hospitalized patients. In COPD, airflow reduction does not improve significantly with

bronchodilators, in contrast to asthma. Therefore, a better drug was needed to reduce exacerbations in COPD. Very few studies have been done in India. Therefore, this prospective, comparative study of effect of Roflumilast in COPD and its efficacy in reducing exacerbations was carried out.

The findings of our study show that roflumilast prevented moderate and severe exacerbations and improved lung function in patients with severe chronic obstructive pulmonary disease and chronic bronchitis who continued to have exacerbations despite inhaled combination therapy.

Roflumilast, a PDE4 inhibitor is an anti-inflammatory agent rather than a bronchodilator. Also due to change in internal airflow distribution, it improves efficacy of Steroids and B2 agonists. Previous studies conducted in countries outside India (REACT study) have shown that Roflumilast reduces the frequency of exacerbations in COPD [17].

Most of the patients recruited were men, who constituted 76 of 100 patients and all were chronic smokers with a history of smoking for approx 15 years or more. This indeed proves that smoking is the most common risk factor for COPD. Among women who were recruited, most of them had a history of exposure to smoke from burning biomass for cooking. This is in correlation with previous studies conducted [22].

There was significant improvement seen in lung function of FEV1and FVC in patients who were recruited in the group where Roflumilast was given as add on therapy. Roflumilast produced a sustained improvement in post-bronchodilator FEV1 of 0.25% compared with standard. This change is compatible with previous studies done by Herbert et al, Hohlfeld et al [28]. The improvement in lung function in mean variation of FEV1and FVC from base line in Roflumilast group compared to control group were statistically significant. The mean change in Fev1/Fvc at 6 months was not statistically significant. This may be attributed to the low sample size.

The patients recruited in Roflumilast group experienced reduction in symptoms such as cough, breathlessness and sputum production compared to control group. They reported that they could breathe easier implications and justifies the decision to target at-risk patients with COPD. The study shows that Roflumilast reduced the time to 1st exacerbation and also postponed the episodes of exacerbation. The result obtained is in correlation to previous studies [19,20]. Roflumilast saw significant reduction in the incidence of exacerbations in patients who had frequent COPD exacerbations (≥2) in the year prior to treatment.

There were some adverse reactions reported by patients on intake of Roflumilast drug which was of a higher percentage compared to the patients in control group. This also led to dropouts. The most common adverse drug reactions were insomnia, nausea, headache, tremor, dizziness, clouding of consciousness and sweating. This was attributed to potential of Roflumilast to reduce blood sugar. This has been seen in some studies done in animals (Volet et al) and is a prospective, promising drug for diabetics as an oral hypoglycaemic agent [29]. More studies are required in humans to prove this. Most of the reactions were tolerable and patient adherence was good. There were no life threatening or severe reactions witnessed. The anticipated adverse effects such as suicidal tendency and depression which were reported in previous studies by Stephen et al in Europe [26] were not observed.

Based on our study findings Roflumilast, has a definite role in treatment and prevention of exacerbations in COPD due to its anti inflammatory properties. Thus, Roflumilast as part of a combination regimen with long-acting bronchodilators and inhalational corticosteroids appears to be a reasonable treatment option for patients with severe to very severe COPD associated with a history of exacerbations. Further studies are required to be done in a large number of patients.

REFERENCES
1. Vestbo, Jorgen (2013). "Definition and Overview". Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Global Initiative for Chronic Obstructive Lung Disease. pp. 1–7.
2. BD 2015 Disease and Injury Incidence and Prevalence, Collaborators. (8 October 2016). "Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015."Lancet. 388 (10053): 1545–1602. doi:10.1016/S0140-6736(16)31678-6.
3. Chronic obstructive pulmonary disease (COPD) Fact sheet N°315". WHO. January 2015. Retrieved 4 March 2016.
4. Rennard, Stephen (2013). Clinical management of chronic obstructive pulmonary disease (2nd ed.). Informa Healthcare. p. 23.
5. Goldman, Lee (2012). Goldman's Cecil medicine (24th ed.). Elsevier/Saunders. p. 537. ISBN 978-1-4377-1604-7.
6. Foreman MG, Campos M, Celedón JC (July 2012). "Genes and chronic obstructive pulmonary disease". Med. Clin. North Am. 96 (4): 699–711 doi:10.1016/j.mcna.2012.02.006
7. Vestbo, Jørgen (2013). "Management of Exacerbations" (PDF). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Global Initiative for Chronic Obstructive Lung Disease. pp. 39–45.
8. Dhar, Raja (2011). Textbook of pulmonary and critical care medicine. New Delhi: Jaypee Brothers Medical Publishers. p. 1056. ISBN 978-93-5025-073-0.

9. Palange, Paolo (2013). ERS Handbook of Respiratory Medicine. European Respiratory Society. p. 194. ISBN 978-1-84984-041-5.
10. Lötvall, Jan (2011). Advances in combination therapy for asthma and COPD. Wiley. p. 251. ISBN 978-1-119-97846-6.
11. Barnes, Peter. Asthma and COPD: basic mechanisms and clinical management(2nd ed.). Academic. p. 837. ISBN 978-0-12-374001-4.
12. Young, Vincent B. Blueprints medicine (5th ed.). Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 69. ISBN 978-0-7817-8870-0
13. Qaseem, Amir; Wilt, TJ; Weinberger, SE; Hanania, NA; Criner, G; et al American College Of Physicians; American College of Chest Physicians; American Thoracic Society; European Respiratory Society (2011). "Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease: A Clinical Practice Guideline Update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society". Annals of Internal Medicine. 155. doi:10.7326/0003-4819-155-3-201108020-00008.
14. National Institute for Health and Clinical Excellence. Clinical guideline 101: Chronic Obstructive Pulmonary Disease. London, June 2012.
15. Mammen MJ, Sethi S (2012). "Macrolide therapy for the prevention of acute exacerbations in chronic obstructive pulmonary disease". Pol. Arch. Med. Wewn. 122 (1–2): 54–9. PMID 22353707.
16. Herath, SC; Poole, P (Nov 28, 2013). "Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)." Cochrane Database Syst Rev. 11: CD009764. doi:10.1002/14651858.CD009764.pub2.
17. Simoens, S; Laekeman, G; Decramer, M (May 2013). "Preventing COPD exacerbations with macrolides: a review and budget impact analysis". Respiratory medicine. 107 (5): 637–48. PMID 23352223. doi:10.1016/j.rmed.2012.12.019.
18. Barr RG, Rowe BH, Camargo CA. Barr, R Graham, ed. "Methylxanthines for exacerbations of chronic obstructive pulmonary disease". doi:10.1002/14651858.CD002168.
19. Poole, P; Chong, J; Cates, CJ (29 July 2015). "Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease."Cochrane Database Syst Rev. 7 doi : 10.1002/ 14651858. CD001287 .pub5.
20. COPD Working, Group (2012). "Long-term oxygen therapy for patients with chronic obstructive pulmonary disease (COPD): an evidence-based analysis". Ontario health technology assessment series.
21. Bradley JM, O'Neill B, Bradley, Judy M, et al. "Short-term ambulatory oxygen for chronic obstructive pulmonary disease". doi:10.1002/14651858.CD004356.pub3.
22. Ekström, Magnus; Ahmadi, Zainab; Bornefalk-Hermansson, Anna; Abernethy, Amy; Currow, David (2016-11-25). "Oxygen for breathlessness in patients with chronic obstructive pulmonary disease who do not qualify for home oxygen therapy". doi:10.1002/14651858.CD006429.pub3.
23. Chapman, Stephen. Oxford handbook of respiratory medicine (2nd ed.). Oxford University Press. p. 707. ISBN 978-0-19-954516-2.
24. Blackler, Laura. Managing chronic obstructive pulmonary disease. p. 49. ISBN 978-0-470-51798-7.
25. Jindal, Surinder K (2013). Chronic Obstructive Pulmonary Disease. Jaypee Brothers Medical. p. 139. ISBN 978-93-5090-353-7.
26. Reduction of exacerbations by the PDE4 inhibitor roflumilast - the importance of defining different subsets of patients with COPD, Stephen I Rennard DOI: 10.1186/1465-9921-12-18
27. The glucose-lowering effects of the PDE4 inhibitors roflumilast and roflumilast-N-oxide in db/db mice, Vollert s et al., 2012 Oct;55(10):2779-2788. doi: 10.1007/s00125-012-2632-z.
28. Roflumilast: a review of its use in the treatment of COPD Int J Chron Obstruct Pulmon Dis. 2016; 11: 81–90
29. Roflumilast : risk of suicidal behaviour From:Medicines and Healthcare products Regulatory Agency 29 January 2013
30. Risk factors for chronic obstructive pulmonary disease: Results of the FARIECE study Aguirre.K.A.Guzmán-Guillen.M.E.Álvarez-Serrano J.R.Vintimilla-Maldonado.