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ORIGINAL ARTICLE

Role of Roflumilast for Improvement of Lung Function in Chronic Obstructive Pulmonary Disease Patients

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Abstract:

Background: *Current pharmacotherapy for chronic obstructive pulmonary disease (COPD) has limited clinical efficacy so that patients often remain symptomatic. Roflumilast an oral, selective phosphodiesterase-4 inhibitor has been shown to improve lung function in COPD patients. General objectives were to evaluate the effect of Roflumilast on improvement of lung function of COPD. Specific objectives was to evaluate the effect of Roflumilast on FEV_1 and to evaluate improvement of symptoms by COPD Assessment Test (CAT)*

Methods: *A single blind, randomized, prospective placebo controlled trial was carried out in the department of Respiratory medicine at National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka. A total number of 130 samples were collected from both inpatient department and outpatient department (OPD). Among them 46 patients in group-A and 50 patients in group-B came to final follow-up. Group-A patients got Roflumilast (0.5 mg single time daily x 3 months) with conventional therapy (Inhaled Tiotropium-18ìg, Salmeterol-50 ìg, and Fluticason-500 ìg) and Group-B patients got placebo with conventional therapy (Inhaled Tiotropium-18 ìg, Salmeterol-50 ìg, and Fluticason-500 ìg). A spirometry and CAT (COPD assessment test) score was performed in each case at the beginning and monthly for consecutive 3 months. Difference of mean FEV1 and CAT-score from baseline between two groups was measure to assess the Roflumilast activity. The primary outcome variable was change in mean FEV_1 and secondary outcome variable was change in mean CAT score from base line.*

Results: *Mean FEV_1 change in 1st visit increase 26.72(±137.15) ml were in group A and decrease 0.84(±3.84) ml were in group B ($p<0.05$) that was statistically significant. Mean FEV_1 change in 2nd visit increase 12.07 (±30.14) ml were in group A and decrease 7.91 (±8.09) ml were in group B ($p <0.05$) that was statistically significant. Mean FEV_1 change in 3rd visit increase*

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11.44(21.36) ml were in group A and decrease 16.25 (±9.88) ml were in group B ($p<0.05$) that was statistically significant. Total difference of mean FEV_1 in two group 27.56 ml at first visit, 19.97 ml at second visit and 27.69 ml at final visit ($p<0.05$) that was statistically significant. Mean CAT change in 1st visit decrease 0.94(±2.07) were in group A and decrease 0.25(±1.52) were in group B ($p<0.05$) that was statistically significant. Mean CAT change in 2nd visit decrease 1.56 (±2.28) were in group A and decrease 0.42(±1.95) were in group B ($p<0.05$) that was statistically significant. Mean CAT change in 3rd visit decrease 2.56 (±2.18) were in group A and decrease 0.23(±2.0) were in group B ($p<0.05$) that was statistically significant. Mean CAT change between two group in 1st visit 0.69, in 2nd visit1.14, in 3rd visit 2.23 ($p<0.05$) that was statistically significant.

Conclusion: *The present study was concluded that COPD patients who received Roflumilast along with conventional therapy (Inhaled Tiotropium-18 ìg, Salmeterol-50 ìg and Fluticason-500 ìg) experienced better lung function evidenced by increased FEV_1 ($p<0.05$) and symptomatic improvement than with conventional therapy (Inhaled Tiotopium-18 ìg, Salmeterol-50 ìg and Fluticason-500 ìg).*

Key wards: *COPD, Roflumilast, Phosphodieste-4 inhibitors.*

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Introduction:

Chronic obstructive pulmonary disease (COPD) is defined as a preventable and treatable lung disease with some significant extra pulmonary effects that may contribute to the severity in individual patients. The pulmonary component is characterized by air flow limitation that is not fully reversible. The air flow limitation is usually progressive and associated with an abnormal inflammatory responds of the lungs to noxious particles and gases.[1]

Current estimates suggest that 80 million people worldwide suffer from moderate to severe diseases. In 2005 COPD contributed to more than 3 million death (5% death globally) but by 2020 it is forecast to represent the third most important cause of death worldwide[1]. The anticipated rise in mortality and morbidity from COPD will be greatest in Asia and African countries as a result of their increasing tobacco consumption. Burden of COPD in Bangladesh is prevalence in more than 40 years of age is 21.24% and prevalence in general population is 4.3%. Total burden of COPD patient is about 6 million.[2]

An exacerbation of COPD is defined as an event in the natural course of the disease characterized by change in the patient's baseline dyspnoea, cough, and or sputum that is beyond normal day-to-day variation, is acute in onset, and may warrant change in regular medication in a patient with underlying COPD.[3]

The most common causes of an exacerbation are infection of the tracheobronchial tree and air pollution[1], but the cause of about one-third of sever exacerbations cannot be identified. The role of bacterial infection is controversial, but recent investigations with newer research techniques have begun to provide important information. Bronchoscopic studies have shown that at least 50% of patient's have bacteria in high concentrations in their airways during exacerbations. Exacerbations affect the quality of life and prognosis of patients with COPD[4]. In addition; exacerbations of COPD have serious negative impacts on patient's quality of life, lung function and socioeconomic cost. Thus, prevention, early detection, and prompt treatment of exacerbation may impact their clinical progression by ameliorating the effects on quality of life and minimizing the risk of hospitalization.[3]

Phosphodiesterase-4, a member of PDE enzyme super family that inactivate c-AMP & c-GMP, is the main PDE isoenzyme occurring in cells

involved in inflammatory-airway diseases.[5] Roflumilast (phosphodiesterase-4 inhibitors) is an oral, potent & selective inhibitor of PDE4, and has a half-life compatible with once-daily dosing.[6] Preclinical studies have shown that Roflumilast inhibits the release of mediators from activated inflammatory cells.[3] and a clinical study found a significant reduction in the absolute number of neutrophils and eosinophils in induced sputum compared with placebo.[7]

The principal action of Roflumilast (phospho-diesterase-4 inhibitors) is to reduce inflammation through inhibition of breakdown of intracellular cyclic AMP. The PDE-4 inhibitor, Roflumilast, has been approved for use in COPD patient. It is a once daily oral medication has been shown to improve FEV1 in patients treated with salmeterol or tiotropium. In patient with stage III: severe COPD or stage IV: very severe COPD, Roflumilast reduces exacerbations treated with oral glucocorticosteroid also seen when Roflumilast is added to long acting broncho-dilators.[3]

Materials and Methods:

This is a single blind, randomized, prospective placebo controlled trial that was carried out in the department of Respiratory medicine at National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka, during the period from July 2012 to June 2013. A total number of 130 samples were collected from both inpatient department and outpatient department (OPD). COPD patients after inclusion and exclusion criteria, sample patients were divided in to two groups. Group-A contain Roflumilast and Group-B contain placebo.

Among them 46 patients in group-A and 50 patients in group-B came to final follow-up. Group-A patients got Roflumilast (0.5 mg single time daily x 3 months) with conventional therapy (Inhaled Tiotropium-18 µg, Salmeterol-50 µg, and Fluticason-500 µg) and Group- B patients got placebo with conventional therapy (Inhaled Tiotropium-18 µg, Salmeterol-50 µg, and Fluticason-500 µg). A spirometry and CAT (COPD assessment test) score was performed in each case at the beginning and monthly for consecutive 3 months. Prior to the commencement of the study, the research protocol was approved by the ethical committee of NIDCH.

This trial was with initial screening of patients that included 4-weeks intensive investigation and management phase (run-in period), followed by a baseline, monthly for 3 months follow-up phase to determine the better improvement of the lung function, CAT score change of COPD patients.

The study was hospital based clinical trial which comprised of:

- Run-in phase- for confirmation of diagnosis and evaluation of eligibility
- After 3 months follow-up phase-management of COPD by conventional treatment (Inhaled Triotopium-18mic.gm, Salmeterol-50mic.gm, and Fluticason-500mic.gm) along with either Roflumilast or Placebo to see the effect of the drugs.

- 130 patients with COPD (defined by specific criteria) were reviewed and if inclusion and exclusion criteria fulfilled, were properly informed and were registered for the study and data were collected.
- During the run-in phase, each subject was evaluated with history and symptoms regarding the presentation. They were examined and certain baseline investigations were done. Patient's age, smoking history, past medical history, current medications were asked. Patients were asked about the cough, sputum production, dyspnoea, wheezing, haemoptysis, and chest pain.
- Each subject were evaluated for the symptoms and signs, the diagnosis were confirmed then with appropriate investigations, Spirometry, in addition to the other necessary baseline investigation (including CBC with ESR, Serum bilirubin, Serum creatinine, Chest X-ray PA view, sputum for AFB, ECG etc.).
- Lung function test in the form of Spirometry, CAT score was done at screening phase and also at baseline before starting trial.

- Patients then subjected to randomize into 'Group – A' and 'Group – B'.

Group A: Patients were treated with Roflumilast, 0.5mg, daily for 3 months in association with conventional treatment (Inhaled Tiotropium-18μg, Salmeterol-50 μg, and Fluticason-500 μg).

Group B: Patients were treated with placebo, daily for 3 months in association with conventional treatment (Inhaled Tiotropium-18 μg, Salmeterol-50 μg, and Fluticason-500 μg).

- After diagnosis medications were provided to the patients and were asked to take regularly.
- All patients were assessed at monthly for 3 months by Spirometry, CAT score and compared with the baseline values to see the outcomes.
- Finally 46 patients in group-A and 50 patients in group-B came to final follow-up, 19 patients in group-A and 15 patients in group-B lost in follow-up. In group-A 15 patients had lost to follow up, 01 patient die and 03 patients stop drug due to GI upset, in group-B 14 patients had lost to follow up and 01 patient die.
- All the information was properly documented in the prescribed forms.

Observation and Results:

A total number of 130 samples were collected, among them 46 patients in group-A and 50 patients in group-B came to final follow-up. In the study mean age 57.66(±9.17) years were in Group A and 56.81(±9.19) years were in Group B. male were predominant, 60(92.85%) were in Group A and 61(93.85%) were in Group B. Mean height in Group A were in 159.95(±7.44) cm and 159.69(±7.79) cm in Group B. Mean weight 52.26(±14.21) kg were in Group A and 52.36(±13.92) in group B. Majority 62(95.38%) smoker were in Group A and 64(98.46%) smoker in Group B. ($p>0.05$) that was not statistically significant. The results were shown in Table-1.

In the study mean FEV_1 change in 1st visit increase 26.72(±137.15) ml were in group A and decrease 0.84(±3.84) ml were in group B ($p<0.05$) that was statistically significant. Mean FEV_1 change in 2nd visit increase 12.07 (30.14) ml were in group A and decrease 7.91 (±8.09) ml were in group B ($p<0.05$) that was statistically significant. Mean FEV_1 change in 3rd visit increase 11.44(21.36) ml were in group A and decrease 16.25 (±9.88) ml were in group B ($p<0.05$) that was statistically significant. Total difference of mean FEV_1 in two group 27.56 ml at first visit, 19.97 ml at second visit and 27.69 ml at final visit ($p<0.05$) that was statistically significant. The results were shown in Table-2 and Fig-I.

Table-I

Distribution of the study population according to base line characteristics.

Characteristics	Group A (case)	Group B (Control)	P value
Age in years(Mean ±SD)	57.66(±9.17)	56.81(±9.19)	0.60
Sex (%)			
Male	60(92.85%)	61(93.85%)	1.0
Female	05(7.69%)	04(6.15%)	
Height (cm)	159.95(±7.44)	159.69(±7.79)	0.84
Weight (kg)	52.26(±14.21)	52.36(±13.92)	0.97
Smoking status (%)			
Smoker	62(95.38%)	64(98.46%)	0.61
Nonsmoker	03(4.62%)	01 (1.54%)	

Group - A = Roflumilast
Group - B = Placebo
P value reach from Chi square test

Table-II

Comparison of the effects of roflumilast on primary outcome variables between two groups at the end of the study

FEV_1 change	Group A Mean (±SD) ml	Group B Mean (±SD) ml	Mean difference ml	P value
1st visit	-26.72(±137.15)	0.84(±3.84)	27.56	0.02[s]
2nd visit	-12.07 (30.14)	7.91 (±8.09)	19.97	0.04[s]
3rd visit	-11.44(21.36)	16.25 (±9.88)	27.69	<0.001[s]

Group - A = Roflumilast
Group - B = Placebo
P value reaches from unpaired t-test. P value reaches from paired t-test
s = significant

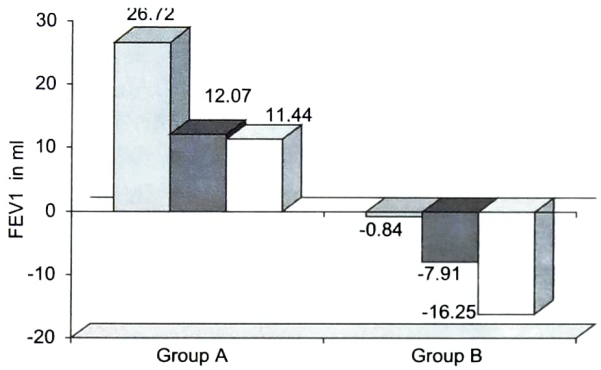

Fig.-1: *Bar diagram showing comparison of the effects of Roflumilast on primary outcome variables between two groups at the end of the study.*

In the current study mean CAT change in 1st visit decrease 0.94(±2.07) were in group A and decrease 0.25(±1.52) ml were in group B (pÂ0.05) that was statistically significant. Mean CAT change in 2nd visit decrease 1.56 (±2.28) were in group A and decrease 0.42(±1.95) were in group B (p<0.05) that was statistically significant. Mean CAT change in 3rd visit decrease 2.56 (±2.18) were in group A and decrease 0.23(±2.0) were in group B (p<0.05) that was statistically significant. . Mean CAT change between two group in 1st visit 0.69, in 2nd visit1.14, in 3rd visit 2.23 (p<0.05) that was statistically significant. The results were shown in Table-3 and Fig-II

Table-III

Comparison of the effects of roflumilast on secondary outcome variables between two groups at the end of the study (CAT SCORE)

CAT score change	Group A Mean (±SD)	Group B Mean (±SD)	Mean difference	P value
Cat 1st visit	0.94(±2.07)	0.25(±1.52)	0.69	0.04[s]
CAT 2nd visit	1.56 (±2.28)	0.42(±1.95)	1.14	0.01[s]
CAT 3rd visit	2.56 (±2.18)	0.23(±2.0)	2.23	0.005[s]

Group - A = Roflumilast . Group - B = Placebo
P value reaches from unpaired t-test.
P value reaches from paired t-test
s = significant

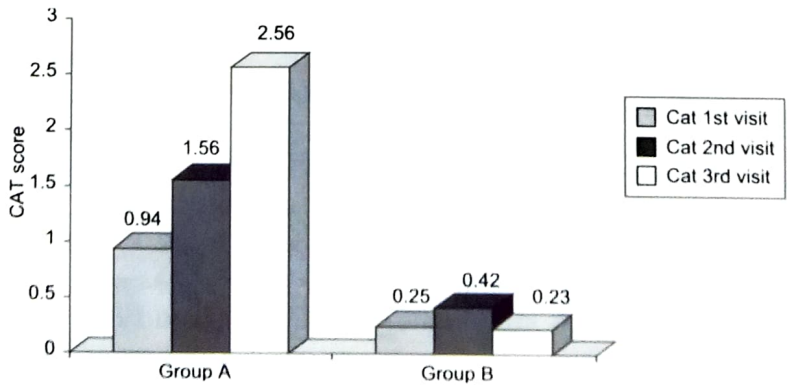

Fig.-2: *Bar diagram showing comparison of the effects of roflumilast on secondary outcome variables between two groups at the end of the study.*

Discussion:

Current pharmacotherapy for chronic obstructive pulmonary disease (COPD) has limited clinical efficacy so that patients often remain symptomatic. Roflumilast an oral, selective phosphodiesterase-4 inhibitor has been shown to improve lung function in COPD patients. We therefore investigated whether Roflumilast would improve lung function in COPD patients along with conventional therapy. A total number of 130 patients with stable COPD were chosen from both outpatients and inpatients department (OPD) of National Institute of Diseases of the Chest and Hospital. Among them Group-A patients got Roflumilast and Group- B patients got placebo along with conventional therapy. Among them 46 patients in group-A and 50 patients in group-B total 96 patients came to final follow-up. In group-A 15 patients had lost to follow up, 01 patient die and 03 patients stop drug due to GI upset, in group-B 14 patients had lost to follow up and 01 patient die.

The main reason for withdrawal was presence of adverse events of drugs during treatment period and majority of adverse events occurred in the first 4 weeks of Roflumilast treatment, an increased frequency of oropharyngeal candidacies, worsening dyspnoea, experiencing an exacerbation, non-compliance, and failure to return. Different studies observed that disease severity, co-morbidity, and study duration, contributed to the high withdrawal rate.[8-10] Patients were also actively withdrawn from the study and not subsequently followed-up due to GI upset. Two patients died during the study, one patient died from acute respiratory failure during the placebo run-in phase and one patient receiving Roflumilast died during the treatment period from pneumonia with acute respiratory failure.

In this current study it was observed that mean age 57.66(±9.17) years were in Group A and 56.81(±9.19) years were in Group B, the mean age was more than 60 years observed by Calverley et al,[9] Lee et al,[11] Fabbri et al,[12] which were higher than the current study. It is stated that the higher age range may be due to increased life expectancy in their study patients.

The patients were predominantly male in the whole study patients, male were 60(92.85%) in Group A and 61(93.85%) in Group B, Male female ratio 9.15:1 which indicate that the disease incidence was higher in male patients, which closely resembles with Jennings et al,[13] Peinado et al,[14] Barnes et al,[15] studies where all these authors found male predominant in their study patients. Baseline and demographic characteristics of the patients were similar between two groups. Among the baseline clinical characteristics of the study population, 58(89.23%) cough were in Group A and 64(98.45%) were in Group B, 58(89.23%) sputum were in Group A and 64(98.45%) were in Group B, 41(47.69%) Dyspnoea were in Group A and 50(76.92%) were in Group B, 12(18.46%) wheeze were in Group A and 07(10.77%) were in Group B, 34(52.31%) loss of weight were in Group A and 39(60.0%) were in Group B, loss of appetite 55(84.62%) were in Group A and 61(93.85%) were in Group B and tachypnoea 58(89.23%) were in Group A and 64(98.46%) were in Group B, where ($p>0.05$) not statistically significant.

Our data demonstrate that Roflumilast significantly increased pre bronchodilator FEV_1 compared with placebo along with conventional therapy (Inhaled Tiotropium-18 ìg, Salmeterol-50 ìg, and Fluticason-500 ìg). Similar improvements occurred with Roflumilast in reduce symptoms in COPD patients in comparison to conventional therapy (Inhaled Tiotopium-18 ìg, Salmeterol-50 ìg and Fluticason-500 ìg). Improved lung function was observed within 4 weeks of Roflumilast treatment and these benefits were maintained throughout the study.

In this current study shows mean FEV_1 change in 1st visit increase 26.72(±137.15) ml were in group A and decrease 0.84(±3.84) ml were in group B, in 2nd visit mean FEV_1 increase 12.07 (30.14) ml were in group A and decrease 7.91 (±8.09) ml were in group B and in 3rd visit mean FEV_1increase 11.44(21.36) ml were in group A and decrease 16.25 (±9.88) ml were in group B ($p<0.05$) that was statistically significant. Total difference mean FEV_1 in two group 27.56 ml at first visit, 19.97 ml at second visit and 27.69 ml at final visit ($p<0.05$) that was statistically significant. In this current study it was observed

that mean CAT change in 1st visit decrease 0.94(±2.07) were in group A and decrease 0.25(±1.52) were in group B, in 2nd visit decrease 1.56 (±2.28) were in group A and decrease 0.42(±1.95) were in group B, in 3rd visit decrease 2.56 (±2.18) were in group A and decrease 0.23(±2.0) were in group B ($p<0.05$) that was statistically significant. Mean CAT change between two group in 1st visit 0.69, in 2nd visit1.14, in 3rd visit 2.23 ($p<0.05$) that was statistically significant.

Lee et al[11] reported that, the mean post-bronchodilator FEV1 increased at the final scheduled visit by 52 mL for patients receiving Roflumilast but decreased by 27 mL for placebo. A statistically significant between treatment differences of 79 mL demonstrated the superiority of Roflumilast for improving post bronchodilator FEV1 in patients with COPD ($P < 0.0001$). Differences in post bronchodilator FEV1 between Roflumilast and placebo treated patients were observed after 4 weeks of treatment and remained to the end of the study. The difference from baseline in mean FEV1 between Roflumilast and placebo groups was 81 mL (95% confidence interval) CI: 48–114 mL; $P< 0.0001$) at week 4, 61 mL (95% CI: 24–99 mL; $P < 0.0007$) at week 8, and 97 ml (95% CI: 55–138 ml; $P < 0.0001$) at the final scheduled visit. The present study also shows significant difference between group's baseline to 4 weeks, 8 weeks and final visit. That study result is higher than my study result because they include moderate to severe COPD patients but my study population was only with severe COPD patients. *Calverley et al[9] study also support this result, they found* the pre-specified primary endpoints were achieved and were similar in magnitude. In a pooled analysis, pre-bronchodilator FEV_1 increased by 48 ml with roflumilast compared with placebo ($p<0·0001$).

In two double-blind, multicentre studies done by *Fabbri et al.*[12] in an outpatient setting, after a 4-week run-in, patients older than 40 years with moderate-to-severe COPD were randomly assigned to oral Roflumilast 500 ìg or placebo once a day for 24 weeks, in addition to salmeterol (M2-127 study) or tiotropium (M2-128 study). The primary endpoint was change in pre-bronchodilator FEV1. The pre-bronchodilator FEV_1 increased significantly in patients in the Roflumilast groups in both studies; similar improvements were noted in post bronchodilator FEV_1 and in pre bronchodilator and post bronchodilator FVC. The pre bronchodilator changes in FEV_1 were similar in patients with different characteristics (e.g. disease severity, sex, rescue use of short acting bronchodilators, and current smoking status). The sensitivity analysis confirmed the robustness of the results for FEV_1 with respect to the effect of differential dropouts and missing data.

In patients with severe COPD treated with Roflumilast improves lung function and some clinically relevant symptomatic outcomes. These results confirm the conclusions drawn from the findings of previous randomized clinical trials in which Roflumilast was efficacious in patients with severe COPD. The improvement in pre-bronchodilator FEV1 suggests that the beneficial effect of Roflumilast on lung function is additive to that achieved with bronchodilators, an effect that is probably not primarily due to smooth muscle relaxation but to other mechanisms. Roflumilast specifically inhibits PDE4, which is mainly expressed in inflammatory cells. Thus, additional studies are needed to investigate the mechanism of improvement in lung function provided by Roflumilast in patients given long-acting bronchodilators.

Conclusion:

The present study was concluded that COPD patients who received Roflumilast along with conventional therapy (Inhaled Tiotropium-18 ìg, Salmeterol-50 ìg and Fluticason-500 ìg) experienced better lung function evidenced by increased FEV_1 ($p<0.05$) and symptomatic improvement than with conventional therapy (Inhaled Tiotopium-18 ìg, Salmeterol-50 ìg and Fluticason-500 ìg).

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