A CLINICAL STUDY ON SAFETY AND EFFICACY OF FORMOTEROL AND TIOTPROIM COMBINATION COMPARED TO FORMOTEROL AND TIOTPROIM WITH ROFLUMILAST COMBINATION IN TREATMENT OF MODERATE TO SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS

KAVITHA DEVI M1, SARUMATHY S2, SARATH LAL SASIDHARAN2, MEHANAZ SHAIK2, GOTTIMUKKALA SANDEEP2, VUNNAM RAJASEKHAR2, DAMODHARAN N2*

1Department of Pulmonary Medicine, SRM Medical College Hospital and Research Centre, SRM University, Kattankulathur, Kancheepuram - 603203, Tamil Nadu, India. 2Department of Pharmacy Practice, SRM College of Pharmacy, SRM University, Kattankulathur, Kancheepuram - 603203, Tamil Nadu, India. Email: dharan75@gmail.com

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ABSTRACT

Objectives: The objective of this study is to assess the safety and efficacy of formoterol and tiotropium combination compared to formoterol and tiotropium with roflumilast combination in treatment of moderate-to-severe chronic obstructive pulmonary disease (COPD) patients on inhaled combination therapy.

Methods: A comparative prospective interventional study was carried out in 61 COPD patients who were visiting the pulmonary medicine ward during 6 months (October 2016 to March 2017). The patients were randomized into two groups. Group A patients received a combination of formoterol and tiotropium, whereas Group B patients received roflumilast along with formoterol and tiotropium combination. Spirometry tests were done to both the study population. Forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were noted at the initial visit and after the treatment. All the statistical analyses such as mean and p values were calculated using SPSS 14.0 version software.

Results: The average age group of the study population was 57.63±8.3 years. Comorbid condition such as diabetes mellitus was higher in the study groups. Comparison of spirometry reports before and after drug administration in both groups was done. FEV1 and FVC were found to be statistically significant between the study group (0.001, p<0.05). The average mean change of FEV1 before and after treatment in Group B was found to be improved as compared to Group B (0.66).

Conclusion: Tiotropium and formoterol with roflumilast combination were found to be safe and effective in moderate-to-severe COPD patients.

Keywords: Roflumilast, Tiotropium, Formoterol, Spirometry.
was approved by central drug standard control organization in 2013 for use as concomitant maintenance treatment of severe COPD along with bronchodilators and showed clinically significant improvements in health status of COPD patients.

Since no study has been conducted comparing roflumilast and formoterol-tiotropium combination, in rural south Indian population, we designed a comparative study on efficacy and safety of roflumilast in moderate-to-severe COPD patients.

**METHODS**

A comparative randomized control study was carried out in 61 COPD patients who were visiting the pulmonary medicine ward during 6 months (October 2016 to March 2017). The study has been conducted after getting approval from the Institutional Ethics Committee (Ethics Clearance number: 1060/IEC/2016). The consent was obtained from the hospital authorities, and the informed consent has been collected from the patients. The inclusion criteria were both genders aged more than 40 years, moderate-to-severe COPD patient, current or ex-smokers, with a smoking history, patient with other comorbid conditions. The exclusion criteria were patients with a history of bronchial asthma and other lung diseases, lower respiratory tract infections and pregnancy and lactation. Group A included 30 patients who received a combination of formoterol and tiotropium, whereas Group B patients (n=31) received roflumilast along with formoterol and tiotropium combination. The patient history collection is done during the first visit, and the necessary information regarding patient’s lifestyle, comorbid conditions, medication, medical history, family history, and physical examinations were collected. Basic information regarding the lifestyle modification and medication was given to the patients. The following spirometry test was done to the patients of Group A and Group B. The parameters such as forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were noted at baseline (initial visit) and after the treatment (12th weeks) for both the study population. All the statistical analyses such as mean and p values were calculated using SPSS 14.0 version software.

**RESULTS**

This interventional study has been carried out for 12 weeks in moderate-to-severe COPD patients. The demographic details such as age, smoking history, and comorbid conditions are depicted in Table 1. Table 2 shows the spirometry values before (initial visit) and after the treatment (12th weeks) in Group A and Group B patients.

The following adverse drug reaction such as diarrhea was observed in 10% of patients, weight loss (23.3%), headache (3.3%), back pain (3.3%), insomnia (10%), and decreased appetite (13.3%) were observed in Group B patients treated with roflumilast.

**DISCUSSION**

Medical treatment for COPD is usually aimed at improving the clinical conditions of the patient by improving the value of pulmonary function test and reducing the frequency of exacerbations. Ferguson, roflumilast when used as a concomitant maintenance treatment for severe COPD along with bronchodilators it showed clinically significant improvements in health status of COPD patients [11]. Vincken and Vandevoorde, in earlier studies on COPD patients, concluded that etiology and acute effects of COPD was mostly prevalent in the age group above 60 years and is similar to our study as patients in the age above 60 years were found to be more in both groups [12].

Rodrigo et al., in earlier studies have identified that majority number of patients have a current history of smoking (more than 10 cigarettes per day) [13]. In the present study, the data obtained identified that 32% of patients were former smokers whereas 17% were current smokers and 51% were passive smokers. Barnes and Celli, in earlier studies, have identified that there are significant number of comorbid conditions in COPD patients, and in the present study, there were more number of patients with comorbid disease conditions such as diabetes mellitus and hypertension [14]. Gross and Glembycz in earlier studies, it has been concluded that roflumilast is safe [15]. In the present study, 53.3% patients in the Group B have not reported any adverse drug reactions and 46.7% patients showed mild-to-moderate adverse drug reactions. Fabbi et al., in earlier studies, the FEV1 and FVC values showed significant improvement after the administration of roflumilast once-daily oral tablet along with other bronchodilators [16]. In this study, the FEV1 and FVC values showed an improvement of 60 ml and 10 ml, respectively, at the end of the study which is similar to the above study. Wells et al., in a randomized, placebo-controlled trial of roflumilast study suggests for the first time that administration of roflumilast for 12 weeks can reduce lung inflammation and is beneficial in patients with moderate to severe COPD and is comparable to the present study as there is a significant improvement in spirometry values [17]. Calverley et al., in a REACT study protocol, the data were pooled from 14 randomized, double-blind, placebo-controlled studies of roflumilast in COPD patients, the most frequent adverse events occurring more commonly were diarrhea, weight loss and headache [18]. Currie and Clarke in a new approach to oral treatment has demonstrated that phosphodiesterase 4 (PDE4) inhibitor appear to confer benefit in improving lung function and health-related outcomes, while the oral route of administration may present a compliance and ease of administration over inhaled medication and is relevant to our study as PDE4 inhibitor improves the lung function [19]. Ulrik and Calverley studies suggest that roflumilast is beneficial for maintenance treatment of patients with severe COPD with chronic cough and a history of frequent exacerbations as add-on treatment with long-acting bronchodilators and is relevant to our present study [20]. The study has been conducted only for 12 weeks, and hence, the exacerbations were not assessed in moderate-to-severe COPD patients. Anti-inflammatory properties of the drug have not been evaluated, and the patient’s sample size is limited.
CONCLUSION
Roflumilast was found to be safe and efficacious in moderate-to-severe COPD patients. When compared to the standard treatment, roflumilast, when given as an add-on therapy, has shown significant improvement in pulmonary function tests of patients.

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