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

Dissertation submitted to

THE TAMIL NADU DR. MGR MEDICAL UNIVERSITY

CHENNAI

In partial fulfilment of the regulations for the award of the degree of

M.D. PHARMACOLOGY

Branch VI

GOVT. KILPAUK MEDICAL COLLEGE AND HOSPITAL

CHENNAI – 10

MAY 2018

CERTIFICATE

This is to certify that this dissertation titled "**A PROSPECTIVE, COMPARATIVE STUDY OF EFFECT OF ROFLUMILAST IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND ITS EFFICACY IN REDUCING EXACERBATIONS"** is the bonafide original work done by **Dr.D.Thamizh Vani**., Post graduate in Pharmacology, under my overall supervision in the Department of Pharmacology, Govt. Kilpauk Medical College and Hospital, Chennai, in partial fulfilment of the regulations of The Tamil Nadu Dr.M.G.R. Medical University for the award of **M.D Degree in Pharmacology (Branch VI).**

Dr.RAMACHANDRA BHAT,M.D.,   **Dr.VASANTHAMANI,M.D.,D.G.O**

Professor & HOD   The Dean

Department of Pharmacology   Govt. Kilpauk Medical College and

Govt. Kilpauk Medical College and   Hospital

 Hospital   Chennai – 10.

Chennai – 10.

CERTIFICATE

This is to certify that this dissertation titled "**A PROSPECTIVE, COMPARATIVE STUDY OF EFFECT OF ROFLUMILAST IN CHRONIC OBSTRUCTIVE LUNG DISEASE AND ITS EFFICACY IN REDUCING EXACERBATIONS**" is the bonafide original work done by **Dr.D.Thamizh Vani**., Post graduate in Pharmacology, under my overall supervision and guidance in the Department of Pharmacology, Govt. Kilpauk Medical College and Hospital, Chennai, in partial fulfilment of the regulations of The Tamil Nadu Dr.M.G.R. Medical University for the award of **M.D Degree in Pharmacology (Branch VI).**

Dr.MALAR SIVARAMAN, M.D.

Professor

Department of Pharmacology

Govt. Kilpauk Medical College and Hospital

Chennai – 600010.

DECLARATION

I solemnly declare that this dissertation titled "**A PROSPECTIVE, COMPARATIVE STUDY OF EFFECT OF ROFLUMILAST IN CHRONIC OBSTRUCTIVE LUNG DISEASE AND ITS EFFICACY IN REDUCING EXACERBATIONS",** is the bonafide work done by me at the Department of Pharmacology, Govt. Kilpauk Medical College and Hospital, Chennai, under the supervision of **Dr. RAMACHANDRA BHAT, M.D**., Professor and HOD of Pharmacology, and guidance of **DR.MALAR SIVARAMAN, M.D**., Professor, Department of Pharmacology and **DR.NALINI JAYANTHI**, **M.D.,** Superintendant, Department of Thoracic Medicine, Govt. Thiruvoteeswarar TB and Chest Hospital, Chennai. This dissertation is submitted to The Tamil Nadu Dr.M.G.R. Medical University, Chennai in partial fulfilment of the University regulations for the award of Degree of M.D.Pharmacology (Branch VI) examinations to be held in May 2018.

Place : Chennai

Date :

Dr.D.Thamizh Vani

ACKNOWLEDGEMENT

Kilpauk Medical College and Hospital, and my fellow post graduates for their help and their valuable support.

This acknowledgement would be incomplete if I did not thank my family for their blessings and good wishes.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

COPD   -   Chronic Obstructive Pulmonary Disease

DALY   -   Daily affected life years

TGF-β   -   Transforming growth factor beta

α1AT   -   Alpha one Antitrypsin

MMP   -   Matrix metalloproteinase

IL   -   Interleukin

TNF - α   -   Tumour necrosis factor alpha

CD-8   -   Cluster of differentiation 8

IP -10   -   Inducible protein-10

mTOR   -   mammalian target of rapamycin

Ig   -   Immunoglobulin

FEV1   -   Forced Expiratory Volume in one second

FVC   -   Forced vital capacity

PEF   -   Peak expiratory flow rate

PI   -   Protease inhibitor

SNP   -   Single nucleotide polymorphism

GOLD   -   Global initiative of lung disease

pCO2   -   partial pressure of carbon dioxide

PDE4   -   Phosphodiesterase 4

IV   -   Intravenous

CT   -   Computed tomography

LVRS   -   Lung Volume Reduction Surgery

DLCO   -   Diffusion Capacity of lung for Carbon monoxide

NIPPV   -   Non invasive positive pressure ventilation

PEEP	-	Positive end expiratory pressure
cAMP	-	cyclic Adenosine monophosphate
IAD	-	Internal airflow distribution
CYP	-	Cytochrome P
PFT	-	Pulmonary function test
BD	-	Bronchodilator
HHIP	-	Hedgehog interacting protein

INTRODUCTION

Introduction

Chronic obstructive pulmonary disease (COPD) is a type of obstructive lung disease which is characterised by poor air flow for a long term. It lasts for years and can be present lifelong. The disease makes it hard for the person to breathe. 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 [27,28]. Prevalence of COPD in India accounts to about 30 million people [2]. It occurs in people above 40 years old i.e. 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 [3]. COPD is the cause of about 2.9 million deaths every year and this number is progressing every year [2]. It forms the third leading cause of death in the world. Low and middle income countries contribute to the burden of deaths due to COPD. In India, mortality due to COPD occurs in 102.3/100,000. In the world COPD contributes to 6740,000 DALYs out of 27,756,000 [2]. The disease thus 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]. Likelihood of developing COPD increases with the overall exposure of smoke. Bidi smokers were at higher risk of developing COPD than those who smoked cigarettes [4]. Other types of smoke like marijuana, cigar, water pipe smoke are also risk factors. Cooking fuel, kerosene, biomass fuel, firewood also contributed to the development of disease. Poorly ventilated cooking fires leads to indoor air pollution and is the common cause of disease in developing countries. Second hand smoke is

the cause of COPD in about 20% of cases [5]. Second hand smoke is also called environmental tobacco smoke. It is a combination of two forms of smoke that is formed due to burning of tobacco – 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. People who live in large cities have a higher rate of developing COPD as compared to people living in rural areas [7]. Genetic factor plays a small role in development of COPD. Alpha 1- antitrypsin deficiency is the only clearly inherited risk factor. This contributes to about 1 – 5% of cases [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 [8]. It is triggered by infection, environmental pollutants, and cold temperature. Those with severe disease have more frequent exacerbations and lung function deteriorates at a faster rate [9].

Diagnosis of COPD is done using Spirometer in persons presenting with the clinical symptoms. Spirometry determines the severity of airflow limitation [12,13].

The current treatment modalities available for COPD are inhaled bronchodilators which is the primary medication. The two major types are beta2 agonists and anticholinergics. Both long acting and short acting forms are available [15]. In mild

disease, short acting form is recommended whereas long acting form is used in severe disease and in maintenance therapy [16]. They reduce shortness of breath and exercise limitation and result in an improved quality of life. If these drugs are ineffective, then corticosteroids are added [17]. Methylxanthines are used as a second line agent if not controlled by other measures [18]. 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 [19]. Reducing risk factors like stopping smoking is a must. Pulmonary rehabilitation which is a program of exercise, disease management and counseling, may improve quality of life [20]. Though these measures may reduce the duration of symptoms, improve exercise capacity, reduce risk of exacerbation, they 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 [22,23]. Other complications of the disease include pneumonia, polycythemia and pneumothorax [40,41]. The effects of COPD extend beyond the lungs. Multiple comorbidities may occur with COPD which includes cardiovascular disease, diabetes mellitus, osteoporosis, depression, and pneumonia [80]. Increased use of medications and hospitalisation is needed in acute exacerbation. 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 selected in this study for COPD and to reduce acute exacerbations for the following reasons. Roflumilast is a selective, long acting inhibitor of Phosphodiesterase-4 (PDE-4) which leads to accumulation of cAMP (cyclic adenosine monophosphate) [24]. It has anti inflammatory property and has gained approval for use in severe COPD for preventing exacerbations. It works by decreasing swelling in the lungs and reducing irritation [25]. Also due to its property of changing the internal airflow distribution, it improves efficacy of Steroids and B2 agonists as well [26,27]. Therefore, in this study comparison of effect of standard treatment of COPD with Roflumilast as add on therapy to standard is done.

REVIEW OF

LITERATURE

REVIEW OF LITERATURE

In the past, COPD was referred to as "chronic airflow obstruction" and "chronic obstructive lung disease." Dr. William Briscoe is thought to be the first person to use the term COPD at the 9[th]Aspen Emphysema Conference in 1965. It was also during the 1960's when the term FEV1 was first used to measure expiratory flow. The history of COPD started a long time ago. In 1821, René Laënnec, the doctor who invented the stethoscope, discovered emphysema as a part of COPD. Because smoking during the early 1800s was not common, Laënnec identified environmental and genetic factors as the primary causes of COPD. While Laënnec is correct in identifying environmental and genetic factors as causes of COPD, it is well-known today that smoking is one of the leading causes of COPD [86].

Years later in 1846, John Hutchinson invented the spirometer, and Robert Tiffeneau, a respiratory medicine pioneer, built on Hutchinson's invention about 100 years later. Tiffeneau created a complete diagnostic instrument for COPD, and the spirometer, which measure vital lung capacity, is still an essential device in diagnosing COPD today [87].

Chronic obstructive pulmonary disease (COPD) is defined as a state of disease which is characterized by airflow limitation that is not reversed fully. COPD includes emphysema and chronic bronchitis. Emphysema is an anatomically defined condition characterized by destruction and enlargement of the lung alveoli while chronic bronchitis is a clinical condition with chronic cough and sputum production [29]. It

also comprises of small airways disease, where the small bronchioles are narrowed. COPD is said to be present only if chronic airflow obstruction occurs. Chronic bronchitis without chronic airflow obstruction is not included within COPD. COPD affects >10 million people and is the third leading cause of death in the United States [30].

PATHOGENESIS

The major physiologic change in COPD is airflow limitation which can result from both small airway obstruction and emphysema. Small airways may become narrow due to hyperplasia of cells and accumulation of mucus. This then leads to fibrosis formation. Airway fibrosis occurs due to activation of transforming growth factor β (TGF-β) whereas parenchymal inflammation and emphysema is due to lack of TGF-β [12]. Four interrelated events contribute to the dominant paradigm of the pathogenesis of emphysema. They are: (1) Chronic exposure to cigarette smoke leads to inflammatory and immune cell recruitment within the terminal air spaces of the lung. (2) Elastolytic and other proteinases are released by inflammatory cells. This leads to damage of the extracellular matrix of the lung. (3) Structural cell death of endothelial and epithelial cells occurs directly through oxidant-induced cigarette smoke damage and senescence as well as indirectly through proteolytic loss of matrix attachment. (4) Air space enlargement occurs due to ineffective repair of elastin and other extracellular matrix components which results in pulmonary emphysema [34].

THE ELASTASE: ANTIELASTASE HYPOTHESIS

Elastin is the principal and highly stable component of elastic fibers which makes up the extracellular matrix. This is critical to the integrity of the lung. The elastase:antielastase hypothesis was proposed in the mid1960s [33,34]. This hypothesis states that elastin-degrading enzymes along with their inhibitors determine the susceptibility of the lung to destruction. This results in air space enlargement. This hypothesis was based on the clinical observation that patients with genetic deficiency in $\alpha1$ antitrypsin ($\alpha1AT$) which is the inhibitor of serine proteinase neutrophil elastase, were at increased risk of emphysema. It was also found that instillation of elastases, which included neutrophil elastase, into animals for experimental purpose results in emphysema [30]. The elastase:antielastase hypothesis remains a prevailing mechanism for the development of emphysema [33,34].
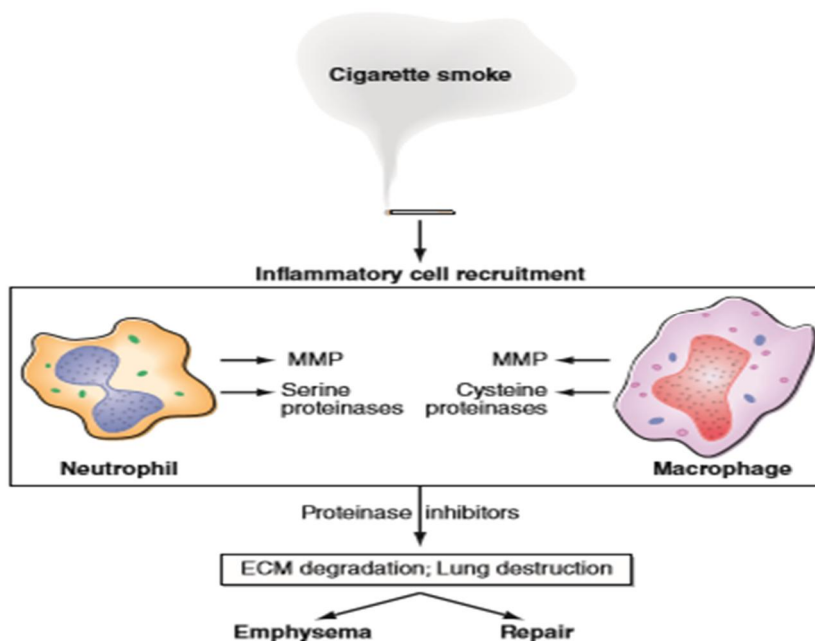

Fig 1. **Pathogenesis of emphysema. Upon long-term exposure to cigarette smoke, inflammatory cells are recruited to the lung; they release proteinases in excess, this leads to air space destruction and enlargement**

INFLAMMATION AND EXTRACELLULAR MATRIX PROTEOLYSIS

Upon exposure to oxidants from cigarette smoke, macrophages and epithelial cells are activated, and proteinases and chemokines are produced. This attracts other inflammatory and immune cells [33]. One mechanism of macrophage activation is oxidant-induced inactivation of histone deacetylase-2 is, which shifts the balance towards acetylated or loose chromatin, thereby leading to exposure of nuclear factor-κB sites. This results in transcription of matrix metalloproteinases, proinflammatory cytokines such as interleukin 8 (IL-8), and tumor necrosis factor α (TNF-α) and leads to neutrophil recruitment. Due to cigarette smoke CD8+ T cells are also recruited. They release interferon-inducible protein-10 (IP-10, CXCL-7). This in turn leads to macrophage production of elastase which is matrix metalloproteinase-12 (MMP-12). Matrix metalloproteinases and serine proteinases, most importantly neutrophil elastase, function together. Their work is to degrade the inhibitor of the other, leading to lung destruction. Proteolytic cleavage products of elastin also function as a macrophage chemokine, increasing the destructive positive feedback loop [33,34]. Autoimmune mechanisms may be involved in promoting the progression of disease. In patients, particularly those with advanced disease, B cells and lymphoid follicles are present. It has been detected that IgG autoantibodies with avidity for pulmonary epithelium have the potential to mediate cytotoxicity. Macrophage phagocytosis and loss of cilia induced by cigarette smoke in the airway epithelium, predispose to bacterial infection and neutrophilia. There remains an exuberant inflammatory response, long after smoking cessation, in end-stage lung disease. This suggests that mechanisms of cigarette smoke–induced inflammation that initiate the disease differ

from mechanisms that sustain inflammation after smoking cessation. Cigarette smoke oxidant-mediated structural cell death occurs via a variety of mechanisms [35]. One of them is rt801 inhibition of mammalian target of rapamycin (mTOR), which leads to cell death as well as inflammation and proteolysis. Uptake of apoptotic cells by macrophages results in production of growth factors and dampens inflammation. This causes promotion of lung repair. This uptake of apoptotic cells by macrophages is impaired by cigarette smoking, thereby limiting lung repair. The ability of the adult lung to repair damaged alveoli appears limited. The process of septation that is responsible for alveologenesis during lung development is very unlikely to be reinitiated [36,37].

PATHOLOGY

Cigarette smoke exposure may affect the large airways, small airways i.e airways which are ≤2 mm in diameter, and alveoli. Changes which occur in large airways are the reason for cough and production of sputum, while changes in small airways and alveoli are found responsible for physiologic alterations. Both emphysema and small airway pathology are present in most persons with COPD. However, they do not appear to be related to each other, and their relative contributions to obstruction seem to vary from one person to another [38,39].

LARGE AIRWAY

Cigarette smoking often results in mucus gland enlargement and goblet cell hyperplasia, leading to cough and mucus production. These symptoms define chronic bronchitis, though these abnormalities are not related to airflow limitation. Goblet cells increase in number and in extent throughout the bronchial tree. Bronchi also undergo squamous metaplasia. This predisposes to carcinogenesis and disrupts mucociliary clearance. Patients may have smooth-muscle hypertrophy and bronchial hyperreactivity, but they are not as prominent as seen in asthma. This is the ultimate cause leading to airflow limitation. Purulent sputum of upper respiratory tract infections has been associated with neutrophil influx [42].

SMALL AIRWAYS

In COPD, the major site of increased resistance is the airways which are ≤2 mm diameter. Characteristic cellular changes in them include goblet cell metaplasia, and surfactant-secreting Clara cells (club cells or bronchiolar exocrine cells) replaced by mucus-secreting cells. Smooth-muscle hypertrophy may also be seen. These abnormalities may lead to luminal narrowing by fibrosis, excess mucus, edema, and cellular infiltration. This leads to reduced surfactant production and may increase surface tension at the air-tissue interface. This predisposes to airway narrowing or collapse. Respiratory bronchiolitis with mononuclear inflammatory cells collecting in distal airway tissues may lead to proteolytic destruction of elastic fibers in the respiratory bronchioles and alveolar ducts. Narrowing and drop-out of small airways precede the onset of emphysematous destruction [14].

LUNG PARENCHYMA

Emphysema is characterized by destruction of air spaces, where gas exchange occurs i.e., the respiratory bronchioles, alveolar ducts, and alveoli. Their walls become perforated and obliterated later with small distinct air spaces coalescing into abnormal and much larger air spaces. Accumulation of macrophages occurs in respiratory bronchioles of essentially all young smokers. Bronchoalveolar lavage fluid which is taken from individuals who smoke contains roughly five times as many macrophages as compared to lavage from nonsmokers. In smokers' lavage fluid, macrophages comprise >95% of the total cell count, and neutrophils, account for 1–2% of the cells. These are nearly absent in nonsmokers' lavage. T lymphocytes, particularly CD8+ cells, are also increased in the alveolar space of smokers. Emphysema is classified into distinct pathologic types, of which the most important ones are centriacinar and panacinar [33]. The type most frequently associated with cigarette smoking is Centriacinar emphysema. Centriacinar type is characterized by enlarged air spaces. It is often focally seen and is usually most prominent in the upper lobes and superior segments of lower lobes. Panacinar emphysema is characterized by abnormal large air spaces which are evenly distributed within and across acinar units. Panacinar type of emphysema is usually observed in patients with α1AT deficiency, which has a predilection for the lower lobes [79].

PATHOPHYSIOLOGY

The most typical finding in COPD is persistent reduction in forced expiratory flow rates. Increases in the residual volume and the residual volume/total lung capacity

ratio, nonuniform distribution of ventilation, and ventilation-perfusion mismatching are also seen [37].

AIRFLOW OBSTRUCTION

Airflow limitation is nothing but obstruction to airflow, is determined by spirometry [6]. In spirometry forced expiratory maneuvers are involved. This is assessed after the subject has inhaled to total lung capacity. Key parameters which are obtained from spirometry include the volume of air exhaled within the first second of the forced expiratory maneuver, called (FEV1) and the total volume of air exhaled during the entire spirometric maneuver which is forced vital capacity [FVC]. Patients with obstruction of airflow which is related to COPD have a chronically reduced ratio of FEV1/FVC. In contrast to asthma, the reduced FEV1 in COPD seldom shows large responses to inhaled bronchodilators, although improvements up to 15% are common. Airflow during forced exhalation is the result of the balance between the promoted flow which is due to elastic recoil of the lungs and the limited flow which is due to resistance of the airways. In lungs affected by COPD, maximal expiratory flow diminishes as the lungs empty because progressively less elastic recoil is provided by lung parenchyma. The cross-sectional area of the airways falls, which raises the resistance to airflow. The abnormality in airflow is only evident at lung volumes at or below the functional residual capacity which is closer to residual volume in the early stages of COPD.

HYPERINFLATION

Lung volumes are routinely assessed in pulmonary function testing. In COPD "air trapping" is seen very often [43,44]. There is increased residual volume and increased ratio of residual volume to total lung capacity. In the late stages of COPD, during tidal breathing hyperinflation of the thorax occurs. This preserves the maximum expiratory airflow, because as lung volume increases, elastic recoil pressure increases, and airways enlarge so that airway resistance decreases. Despite compensating for airway obstruction, hyperinflation can push the diaphragm into a flattened position. This causes a number of adverse effects. Positive abdominal pressure during inspiration is not applied as effectively to the chest wall due to decrease in zone of apposition between the diaphragm and the abdominal wall. This hinders rib cage movement and impairs inspiration. Also, the muscle fibers of the flattened diaphragm are shorter than those of a more normally curved diaphragm, so they are less capable of generating inspiratory pressures than normal. The flattened diaphragm also leads to increased radius of curvature(r). Therefore diaphragm must generate greater tension (t) to develop the transpulmonary pressure (p) which is required to produce tidal breathing. This follows from Laplace's law, $p = 2t/r$. Also, due to distension of the thoracic cage beyond its normal resting volume, during tidal breathing the inspiratory muscles must do work to overcome the resistance of the thoracic cage to further inflation [33,34].

GAS EXCHANGE

The partial pressure of oxygen in arterial blood Pao2 usually remains near normal until the FEV1 is decreased to ~50% of predicted. At rest even much lower FEV1 values can be associated with a normal Pao2. An elevation of arterial level of carbon dioxide (Paco2) is not expected until the FEV1 is <25% of predicted. Pulmonary hypertension severe enough to cause cor pulmonale and right ventricular failure due to COPD typically occurs in individuals who have marked decreases in FEV1 (<25% of predicted) and chronic hypoxemia (Pao2 <55 mmHg) [46]. Nonuniform ventilation and ventilation-perfusion mismatching are characteristic of COPD. Physiologic studies are consistent with the finding that multiple parenchymal compartments have different rates of ventilation due to regional differences in compliance and airway resistance [47,48]. Reduction in Pao2 that occurs in COPD is accounted by ventilation-perfusion mismatch. Therefore, the effectiveness of inspired oxygen in treating hypoxemia due to COPD can be explained.

RISK FACTORS

CIGARETTE SMOKING

By 1964, the Advisory Committee to the Surgeon General of the United States had concluded that cigarette smoking was the major risk factor for COPD and also the reason for mortality [11,14]. Subsequent longitudinal studies have shown accelerated decline in FEV1 in a dose-response relationship to the intensity of cigarette smoking [49]. It is typically expressed as pack-years which is defined as average number of

packs of cigarettes smoked per day multiplied by the total number of years of smoking [1]. Higher prevalence rates of COPD with increasing age is accounted by the dose-response relationship between reduced pulmonary function and cigarette smoking intensity. Higher prevalence of COPD seen among males is due to the higher rate of smoking among males. However, as the gender gap in smoking rates has diminished in the past 50 years the prevalence of COPD among females is increasing. Although pack-years of cigarette smoking is the most significant predictor of FEV1, only 15% of the variability in FEV1 is explained by pack-years [50]. This finding suggests that there are additional environmental and/or genetic factors, which contribute to the impact of smoking on the development of airflow obstruction.

AIRWAY RESPONSIVENESS AND COPD

One of the defining features of asthma is the tendency for increased bronchoconstriction in response to a variety of exogenous stimuli, which includes methacholine and histamine. However, this feature of airway hyperresponsiveness is also shared by many patients with COPD. There is considerable overlap between persons with asthma and those with COPD in airway responsiveness, airflow obstruction, and pulmonary symptoms. Therefore, this has led to the formulation of the Dutch hypothesis [34]. The hypothesis suggests that asthma, chronic bronchitis, and emphysema are variations of the same basic disease, which is modulated by environmental and genetic factors. Asthma is viewed as largely an allergic phenomenon, whereas COPD results from smoking-related inflammation and damage.

Also, the interactions between these postulated genetic factors and environmental risk factors must be taken into account. Longitudinal studies that compared airway responsiveness at the beginning of the study to subsequent decline in pulmonary function have demonstrated that increased airway responsiveness is clearly a significant predictor of subsequent decline in pulmonary function [34].

RESPIRATORY INFECTIONS

The decline in pulmonary function due to the impact of adult respiratory tract infections, are not well defined. Significant reductions in pulmonary functions are not typically seen following an episode of bronchitis or pneumonia [69]. Due to a lack of adequate longitudinal data, the impact of the effects of childhood respiratory illnesses on the subsequent development of COPD has been difficult to assess. Respiratory infections are important causes of exacerbations of COPD. Though this association is present, it is yet to be proven.

OCCUPATIONAL EXPOSURES

Exposure to dust and fumes at work has resulted in increased respiratory symptoms and airflow obstruction. Specific occupational exposures, such as coal mining, gold mining, and cotton textile dust, have also been suggested as risk factors for chronic airflow obstruction. Among coal miners, coal mine dust exposure was a significant risk factor for emphysema in both smokers and non-smokers [71]. Compared to the

effect of cigarette smoking, the magnitude of risk of COPD due to occupational exposures is substantially less important [72].

AMBIENT AIR POLLUTION

Due to increased pollution in the urban settings increased respiratory symptoms have been reported in those living in urban areas [41]. The relationship of air pollution to chronic airflow obstruction disease still remains to be proved. Prolonged exposure to smoke produced by biomass combustion which is a common mode of cooking in some countries, also appears to be a significant risk factor for COPD among women in those countries [45].

PASSIVE, OR SECOND-HAND, SMOKING EXPOSURE

Exposure of children to maternal smoking results in significantly reduced lung growth. In utero, tobacco smoke exposure also contributes to significant reductions in postnatal pulmonary function [52,53]. Although passive smoke exposure has been associated with reductions in pulmonary function, the importance of this risk factor in the development of the severe pulmonary function reductions in COPD remains uncertain.

GENETIC CONSIDERATIONS

 A proven genetic risk factor for COPD is severe α1AT deficiency [6]. Increasing

evidence of other genetic determinants also exist.

α1ANTITRYPSIN DEFICIENCY

 Many variants of the locus of protease inhibitor (PI or SERPINA1) which encodes

α1AT have been described [11]. The common allele that is associated with normal

α1AT levels is M allele. The S allele is associated with slightly reduced α1AT levels,

and the Z allele is associated with markedly reduced α1AT levels. The S allele and Z

allele also occur with frequencies of >1% in most white populations. Inheritation of

null allele, is seen in rare individuals which lead to the absence of any α1AT

production. This occurs through a heterogeneous collection of mutations. Individuals

with two Z alleles or one Z and one null allele are referred to as PiZ. This is the most

common form of severe α1AT deficiency. Approximately only 1% of COPD patients

are found to have severe α1AT deficiency as a contributing cause of COPD. These

patients demonstrate that genetic factors can have a profound influence on the

susceptibility for developing COPD. PiZ individuals often develop early-onset COPD.

Approximately 1 in 3000 individuals in the United States inherits severe α1AT

deficiency, but only a small minority of these individuals has been identified [6]. The

clinical laboratory test used most frequently to screen for α1AT deficiency is

measurement of the immunologic level of α1AT in serum. Cigarette smokers with

severe α1AT deficiency are more likely to develop COPD at early ages. Other factors which appear to increase the risk of COPD in PiZ subjects are asthma and male subjects. Specific treatment in the form of α1AT augmentation therapy is available for severe α1AT deficiency as a weekly IV infusion. Recent studies have suggested that PiMZ subjects are also at slightly increased risk for the development of airflow obstruction [7,12]. It still remains unclear whether all PiMZ subjects are at slightly increased risk for COPD or if only a subset of PiMZ subjects are at an increased risk for COPD due to other genetic or environmental factors. Studies of pulmonary function measurements performed have suggested that genetic factors other than PI type also have influence in variation of pulmonary function. A well-powered association study comprising 8300 patients and 7 separate cohorts found that a minor allele single nucleotide polymorphism (SNP) of MMP12 (rs2276109) associated with decreased MMP12 expression has a positive effect on lung function in children with asthma and in adult smokers [83]. Recent genome-wide association studies have identified several COPD susceptibility loci, including a region near the hedgehog interacting protein (HHIP) gene on chromosome 4, a cluster of genes on chromosome 15 (including components of the nicotinic acetylcholine receptor), and a region within a gene of unknown function (FAM13A) [34]. A regulatory SNP upstream from the HHIP gene has been identified as one potential functional variant; the specific genetic determinants in the other genomic regions are yet to be definitely identified.

NATURAL HISTORY

COPD due to cigarette smoking depends on the intensity of smoking exposure, the timing of smoking exposure, and the baseline lung function of the individual. Most individuals follow a steady increase in pulmonary function during childhood and adolescence which is followed by a gradual decline with aging. The risk of eventual mortality due to COPD is associated with declined levels of FEV1 [55].

The rate of decline in pulmonary function can be modified by changing environmental exposures (i.e., quitting smoking). Smoking cessation at an earlier age provided a more beneficial effect than smoking cessation after marked reductions in pulmonary function have already developed. Genetic factors contribute to the level of pulmonary function achieved during growth and to the rate of decline in response to smoking and potentially to other environmental factors as well.

CLINICAL PRESENTATION

HISTORY

COPD most commonly presents as cough, sputum production, and exertional dyspnea. Many patients have such symptoms for months or years before seeking medical attention [57]. Onset of the disease is attributed to an acute illness or exacerbation by many patients though the development of airflow obstruction is gradual. Symptoms are always present prior to the acute exacerbation. A careful history elicits it. The development of exertional dyspnea, which is described as an increased effort to

breathe, air hunger, or gasping, and a feeling of heaviness, can be insidious. History

should be focused on typical physical activities and how the patient's ability to

perform them has changed. Activities which involve significant arm work, particularly

at the level of shoulder or above it, are particularly difficult for patients with COPD.

Activities that allow the patient to use accessory muscles of respiration and to brace

arms are better tolerated. Examples of such activities include pushing a shopping cart

or walking on a treadmill. The principal feature as COPD advances is worsening of

dyspnea on exertion. This is accompanied by an increasing intrusion on the ability of

the individual to perform vocational or avocational activities. Patients are breathless in

the most advanced stages. Therefore, they can only perform simple activities of daily

living. Worsening airflow obstruction is accompanied by an increased frequency of

exacerbations. Resting hypoxemia is developed in many patients and they require

institution of supplemental oxygen.

PHYSICAL FINDINGS

Patients usually have an entirely normal physical examination in the early stages of

COPD. Signs of active smoking may be seen in current smokers. This includes an

odor of smoke or nicotine staining of fingernails. In patients with more severe disease,

the finding obtained by physical examination is, a prolonged expiratory phase and

expiratory wheezing. Signs of hyperinflation is also seen which include a barrel chest

and enlarged lung volumes with poor diaphragmatic excursion as assessed by

percussion. Use of accessory muscles of respiration is exhibited by patients with

severe airflow obstruction. Patients sit in the characteristic "tripod" position, as the actions of sternocleidomastoid, scalene, and intercostal muscles are facilitated. Patients may develop cyanosis which is visible in the lips and nail beds. Patients with predominant emphysema are termed "pink puffers". These patients are thin and noncyanotic at rest. They have prominent use of accessory muscles. Patients with chronic bronchitis are very likely to be heavy and cyanotic and they are termed "blue bloaters" [33,34]. Current evidence demonstrates that most patients have elements of both bronchitis and emphysema and that the two entities cannot be differentiated by physical examination. Advanced disease may be accompanied by cachexia, with significant weight loss, bitemporal wasting, and diffuse loss of subcutaneous adipose tissue. These signs are associated with both inadequate oral intake due to disease and elevated levels of inflammatory cytokines such as TNF-α. If wasting is seen in COPD, it is considered as a poor prognostic factor. In some patients with advanced disease, Hoover's sign is seen in which there is paradoxical inward movement of the rib cage with inspiration instead of outward as is normal. This implies a flat, but functioning diaphragm. This is the result of alteration of the vector of diaphragmatic contraction on the rib cage due to chronic hyperinflation [48]. An overt complication of COPD is cor pulmonale which shows signs of right heart failure. It is now relatively infrequent due to the advent of supplemental oxygen therapy. Clubbing of the digits is not a sign of COPD. Presence of clubbing should alert the clinician to initiate an investigation for causes of clubbing.

A substantial proportion of COPD patients have extra-pulmonary symptoms and signs. Common manifestations include skeletal muscle weakness, osteoporosis,

cardiac arrhythmias, weakness, ischemic heart disease, stroke, depression, and cancer. The presence of these extra-pulmonary pulmonary manifestations of COPD increases morbidity and mortality. Peripheral skeletal muscle dysfunction is an established systemic feature of COPD [52].

LABORATORY FINDINGS

The hallmark of COPD is airflow obstruction. Pulmonary function testing shows a reduction in FEV1 and FEV1/FVC with airflow obstruction. With worsening disease severity, lung volumes may increase, resulting in an increase in total lung capacity, functional residual capacity, and residual volume. The diffusing capacity may be reduced in patients with emphysema. This reflects the lung parenchymal destruction, which is characteristic of the disease. An important prognostic factor in COPD is the degree of airflow obstruction. This is also the basis for the Global Initiative for Lung Disease (GOLD) severity classification [56].

GOLD classification –

This classification is used to describe the severity of the obstruction or airflow limitation. The worse a person's airflow limitation is, the lower their FEV1. As COPD progresses, FEV1 tends to decline. GOLD staging uses four categories of severity for COPD, based on the value of FEV1:

Stage I	Mild COPD	FEV1/FVC<0.70	FEV1≥ 80% normal
Stage II	Moderate COPD	FEV1/FVC<0.70	FEV1 50-79% normal
Stage III	Severe COPD	FEV1/FVC<0.70	FEV1 30-49% normal
Stage IV	Very Severe COPD	FEV1/FVC<0.70	FEV1 <30% normal, or <50% normal with chronic respiratory failure present

 More recently it has been shown that a multifactorial index incorporating airflow obstruction, exercise performance, dyspnoea, and body mass index is a better predictor of mortality rate than pulmonary function alone [57]. In 2011, the GOLD added an additional classification system which incorporated symptoms and exacerbation history. Resting or Exertional hypoxemia may be demonstrated by arterial blood gases and oximetry. The arterial blood gas is an important component of the evaluation of patients presenting with symptoms of an exacerbation. Arterial blood gases also provide additional information about alveolar ventilation and acid-base status by measuring arterial Pco_2 and pH. In acute state the change in pH with Pco_2 is 0.08 units/10 mmHg and in the chronic state it is 0.03 units/10 mmHg. An elevated hematocrit and signs of right ventricular hypertrophy, suggests the presence of chronic hypoxemia. Classification of the type of COPD is assisted by radiographic studies. Presence of emphysema is suggested by obvious bullae, paucity of parenchymal markings, or hyperlucency. Increased lung volumes and flattening of the diaphragm

suggest hyperinflation. For establishing the presence or absence of emphysema in living subjects, the current definitive test is Computed tomography (CT) scan. From a practical perspective, the CT scan currently does little to influence therapy of COPD except in individuals considering surgical therapy for their disease and as screening for lung cancer. In all subjects with COPD or asthma with chronic airflow obstruction, testing of α1AT deficiency has been suggested by recent guidelines. For subjects with low α1AT levels, the definitive diagnosis of α1AT deficiency requires protease inhibitor (PI) type determination. This is typically performed by isoelectric focusing of serum, which reflects the genotype at the PI locus for the common alleles and many of the rare PI alleles as well. For the common PI alleles (M, S, and Z), molecular genotyping of DNA can be performed.

Fig 2. Chest computed tomography scan of a patient with COPD. There are reduced parenchymal markings in the right lung (left side of figure) as compared to the left lung, representing emphysematous destruction of the lung, and mediastinal shift to the left, indicative of hyperinflation.

TREATMENT

Early Therapies in COPD Treatment

By the mid-20th century, a better understanding of the disease and advancements in medicine started with the use of antibiotics, mucus thinners like potassium iodide and also ephedrine and theophylline [88].

COPD Treatment in the 60s

During the 1960s, the use of short-acting beta-2 agonists named isoproterenol, as an inhaled therapy, was first used as a COPD treatment. These treatments relax the muscles that line the lungs, allowing for increased airflow within minutes. A group of researchers at the University of Colorado Medical Center in Denver did one of the first trials of oxygen therapy in the mid-1960s. Over time, oxygen therapy developed further and is a common treatment for COPD [88].

STABLE PHASE COPD

To influence the natural history of patients with COPD, only three interventions which are smoking cessation, oxygen therapy given for chronically hypoxemic patients, and lung volume reduction surgery which is done in selected patients diagnosed with emphysema, have been demonstrated [59]. Currently there is only suggestive, but not definitive, evidence that the use of inhaled glucocorticoids may alter mortality rate but it may not alter lung function. All other current therapies which are given for COPD are directed at improving symptoms and decreasing the frequency and severity of

exacerbations. An assessment of symptoms, potential risks, costs, and benefits of therapy should be involved in the institution of these therapies. This is followed by assessment of response to therapy. Then a decision should be made whether treatment can be continued or not.

PHARMACOTHERAPY

Bronchodilators

In general, for symptomatic benefit in patients with COPD, bronchodilators are used. For medication delivery to COPD patients, the inhaled route is preferred rather than the use of parenteral medication delivery, because the incidence of side effects is lower.

Anticholinergic Agents

Ipratropium bromide produces acute improvement in FEV1 and improves symptoms. Tiotropium, which is a long-acting anticholinergic, has been shown to reduce exacerbations and improve symptoms. Studies have failed to demonstrate that both ipratropium and tiotropium have influenced the rate of decline in FEV1 [60]. In a large randomized clinical trial, in tiotropium-treated patients there was a trend toward reduced mortality rate which approached, but did not reach, statistical significance [61]. A trial of inhaled anticholinergics is recommended in symptomatic patients with COPD, whose side effects are minor. Recent retrospective analyses in the COPD

population have raised the possibility that anticholinergic use is associated with increased cardiovascular events [69].

Beta Agonists

These drugs have provided symptomatic benefit in COPD. The main side effects are tremor and tachycardia. Inhaled long-acting β agonists, such as salmeterol or formoterol, have benefits which can be compared to ipratropium bromide. Their use is more convenient than short-acting agents. An incremental benefit has been demonstrated by the addition of a β agonist to inhaled anticholinergic therapy [63]. A recent study in asthma suggests that those patients, particularly African Americans, using a long-acting β agonist without concomitant inhaled corticosteroids have an increased risk of deaths resulting from respiratory causes [48]. The applicability of these data to patients with COPD is unclear and requires further investigation.

Inhaled Glucocorticoids

A number of well-designed randomized trials have not demonstrated an apparent benefit from the regular use of inhaled glucocorticoids on the rate of decline of lung function. Patients who were studied included those who were found to have mild to severe airflow obstruction and also included current and ex-smokers [49]. Use of inhaled glucocorticoids has been associated with increased rates of oropharyngeal candidiasis and an increased rate of loss of bone density [64]. Available data suggest that inhaled glucocorticoids have reduced frequency of exacerbations by ~25%. The impact of inhaled corticosteroids on mortality rates in COPD is controversial. A meta-analysis and several retrospective studies have suggested a benefit in mortality [47]. In

patients with frequent exacerbations, which is defined as two or more per year, a trial of inhaled glucocorticoids should be considered. It should also be given to patients who demonstrate a significant amount of acute reversibility in response to inhaled bronchodilators.

Oral Glucocorticoids

The chronic use of oral glucocorticoids for COPD is not recommended because it is associated with significant side effects such as osteoporosis, weight gain, cataracts, glucose intolerance, and increased risk of infection. A recent study demonstrated that patients tapered off chronic low dose prednisone (~10 mg/d) did not experience any adverse effect on the frequency of exacerbations, health-related quality of life, or lung function [61,62].

Theophylline

Theophylline, a methylxanthine, produces modest improvements in expiratory flow rates and vital capacity and a slight improvement in arterial oxygen and carbon dioxide levels in patients with moderate to severe COPD. Its bronchodilator property is due to increase in cAMP levels which favour bronchial relaxation. Nausea is a common side effect of Theophylline. Tachycardia and tremor have also been reported. Cardiovascular and central nervous system toxicities have also been reported. Therefore, monitoring of blood theophylline levels is required [18,36]. The selective phosphodiesterase 4 (PDE4) inhibitor roflumilast has been demonstrated to reduce exacerbation frequency in COPD patients with chronic bronchitis and a prior history of exacerbations [50,51].

Antibiotics

There are strong data evidences implicating bacterial infection as a precipitant of a substantial portion of exacerbations. Early trials of prophylactic or suppressive antibiotics, given either seasonally or year round, failed to show a positive impact on exacerbation occurrence [65]. More recently, a randomized clinical trial of azithromycin, chosen for both its anti-inflammatory and antimicrobial properties, administered daily to subjects with a history of exacerbation in the past 6 months has demonstrated a reduced frequency of exacerbation and a longer time to first exacerbation [84].

Oxygen

Supplemental O2 is the only pharmacologic therapy demonstrated to decrease mortality rates in patients with COPD. Significant impact on mortality rate has been demonstrated for patients with resting hypoxemia. Resting hypoxia means - resting O2 saturation ≤88% or <90% along with signs of right heart failure or pulmonary hypertension. Patients who meet these criteria should be on continual oxygen supplementation because the mortality benefit is proportional to the number of hours per day oxygen has been used. Various delivery systems are available which include portable systems that patients may carry to allow mobility outside the home. Patients with exertional hypoxemia or nocturnal hypoxemia are commonly prescribed with supplemental oxygen. The benefits of such therapy are not well substantiated, although the rationale for supplemental O2 is physiologically sound [23,73].

Other Agents

 N-acetyl cysteine has been used in patients with COPD as it possesses both mucolytic and antioxidant properties. A prospective trial did not find any benefit with respect to decline in lung function or prevention of exacerbations [17]. Specific treatment in the form of IV α1AT augmentation therapy is available for individuals with severe α1AT deficiency. As α1AT is a blood derived product, despite sterilization procedures, Hepatitis B vaccination is recommended prior to starting augmented therapy. Although biochemical efficacy of α1AT augmentation therapy has been shown, a randomized controlled trial of α1AT augmentation therapy has failed to establish the efficacy of augmentation therapy in reducing decline of pulmonary function [18]. Eligibility for α1AT augmentation therapy requires a serum α1AT level <11 μM which is approximately 50 mg/dL. This is mostly recommended for PiZ type of AT deficiency. Other rare types associated with severe deficiency (e.g., null-null) are also eligible for therapy. Because only a fraction of individuals with severe α1AT deficiency will develop COPD, α1AT augmentation therapy is not recommended for severely α1AT-deficient persons with normal pulmonary function and a normal chest CT scan [34].

Inducible nitric oxide synthase inhibitors – NO is increased in COPD as a result of increased production of iNOS in airways. Several selective nitric oxide synthase inhibitors are now under development.

Cytokine modifiers – Cytokines play an important role in perpetuating and amplifying inflammation in COPD. Anti cytokines may be beneficial as therapy.

Chemokine receptor antagonists – Chemokines are involved in COPD and play an important role in recruitment of anti inflammatory cells. CXCR2 antagonists prevent neutrophil and monocyte chemotaxis, and have been effective in animal models of COPD.

Soluble epoxide hydrolase inhibitors - They ease inflammation in animals that are exposed to tobacco smoke.

Selective glucocorticoid receptor modulators - These help the steroids used now to treat COPD work better, and cause fewer unpleasant side effects.

New to the history of COPD treatment is stem cell therapy. In stem cell therapy, the cells are extracted from the patient through blood or bone marrow, separated in our onsite lab and then reintroduced to the patient intravenously. Because stem cell therapy works to promote healing from within, many patients report experiencing an improved quality of life after treatment.

Identification of novel therapeutic targets

It is important to identify the genetic factors that determine why only 10–20% of smokers develop COPD [86,87]. Identification of genes that predispose to the development of COPD in smokers may identify novel therapeutic targets. Powerful techniques such as high density DNA arrays (gene chips) are able to identify multiple polymorphisms; differential display may identify the expression of novel genes and the proteomics of novel proteins expressed.

Pharmacotherapy for Smoking Cessation

Middle aged smokers who were able to successfully stop smoking experienced a significant improvement in the rate of decline in pulmonary function. The pulmonary function returned to annual changes which was similar to that of non smoking patients. Thus, all patients with COPD should be educated about the benefits of quitting and strongly urged to quit smoking. It has been demonstrated by an emerging body of evidence that when pharmacotherapy is combined with traditional supportive approaches, the chances of successful smoking cessation is considerably enhanced. To the problem there are three principal pharmacologic approaches. They are1) bupropion given orally as tablet; 2) nicotine replacement therapy which is available as gum, transdermal patch, lozenge, inhaler, and nasal spray; and 3)varenicline, a nicotinic acid receptor agonist/antagonist. Current recommendations are that all adult, nonpregnant smokers who considering quitting should be offered pharmacotherapy, in the absence of any contraindication to treatment [34,35].

General Medical Care

Patients with COPD should receive the influenza vaccine annually. Polyvalent pneumococcal vaccine is also recommended, although definitive proof of efficacy in the population is not known. Similar recommendations and limitations of evidence also exist for vaccination for Bordetella pertussis [66].

NONPHARMACOLOGIC THERAPIES

Pulmonary Rehabilitation

Pulmonary rehabilitation refers to a treatment program that incorporates cardiovascular conditioning and education. In COPD, pulmonary rehabilitation has been demonstrated to improve health-related quality of life, dyspnea, and exercise capacity. It has also been shown to reduce rates of hospitalization over a 6- to 12-month period [42,43].

Lung Volume Reduction Surgery (LVRS)

In the 1950s, Surgery was first introduced to reduce the volume of lung in patients with emphysema with minimal success. It was then reintroduced in the 1990s. Patients who are excluded from surgery are those with a significant pleural disease, extreme deconditioning, congestive heart failure, pulmonary artery systolic pressure >45 mmHg, or other severe comorbid conditions. Patients with an FEV1 <20% of predicted and either diffusely distributed emphysema on CT scan or those patients with diffusing capacity of lung for carbon monoxide (DlCO) <20% of predicted have an increased mortality rate after the procedure [67,68]. Thus these patients are not candidates for LVRS. LVRS offers both a symptomatic benefit and mortality benefit in certain patients with emphysema, has been demonstrated by The National Emphysema Treatment trial [85]. The anatomic distribution of emphysema and post-rehabilitation exercise capacity are important characteristics for prognosis of disease. Those patients who are most likely to benefit from LVRS are those with upper lobe–predominant emphysema and a low post-rehabilitation exercise capacity [73].

Lung Transplantation

 COPD is currently the second leading indication for lung transplantation. Current recommendations for lung transplantation are that candidates should have severe disability despite maximal medical therapy and should be free of comorbid conditions such as liver, renal, or cardiac disease. The presence of pulmonary hypertension and the anatomic distribution of emphysema are not contraindications to lung transplantation, which is in contrast to LVRS [47].

EXACERBATIONS OF COPD

 A prominent feature of the natural history of COPD is exacerbations. Exacerbations are characterised by episodes of increased cough and dyspnea and change in the amount and character of sputum. Other signs of illness, which may accompany the exacerbations, are fever, sore throat and myalgias [14]. The frequency of exacerbations increases as airflow obstruction increases. In patients with moderate to severe airflow obstruction (GOLD stage III or IV), one to three episodes per year are seen on an average. A strong predictor of future exacerbations is a history of prior exacerbations. Increased risk of COPD exacerbations has been associated with an elevated ratio of the diameter of the pulmonary artery to aorta on chest CT recently [74]. The approach to a patient experiencing an exacerbation includes an assessment of both, acute and chronic components of the severity of the patient's illness; an attempt to identify the reason for precipitation of the exacerbation; and the institution of therapy.

Precipitating Causes and Strategies to Reduce Frequency of Exacerbations

The final common pathway of airway inflammation is the result of a variety of stimuli. Increased symptoms are the characteristics of COPD exacerbations. Studies have reported that acquiring a new strain of bacteria is associated with increased near-term risk of exacerbation [86]. Also bacterial infection/superinfection is involved in over 50% of exacerbations. Approximately one-third of COPD exacerbations are due to viral respiratory infections [62,63]. No specific precipitant can be identified in a significant minority of instances which contribute to 20–35% [44]. The role of pharmacotherapy in reducing frequency of exacerbation is less well studied. It has been suggested that chronic use of oral glucocorticoids are not recommended for this purpose from previous studies [38,39]. In most analyses it has been suggested that inhaled glucocorticoids has reduced the frequency of exacerbations by 25–30%. Consideration of use of inhaled glucocorticoids in patients with frequent exacerbations should be done. Similar magnitudes of reduction have been reported after administration of anticholinergic and long-acting β-agonist therapy [40]. In vaccine, the influenza vaccine has been shown to reduce exacerbation rates in patients with COPD [42]. As outlined above, on daily administration of azithromycin to subjects with COPD and to those who have an exacerbation history reduction of frequency of exacerbation is seen.

Patient Assessment

The severity of the exacerbation and the severity of preexisting COPD should be established. If either of these two components is severe, it is more likely that the

patient will require hospital admission. In the history quantification of the degree of dyspnea should be included by asking about breathlessness during activities of daily living and assessing typical activities for the patient. The patient should be elicited about fever; change in character of sputum; any ill contacts. The history should also include associated symptoms such as nausea, vomiting, diarrhea, myalgias, and chills. Important information can be acquired by inquiring about the frequency and severity of prior exacerbations. The degree of distress of the patient can be assessed by incorporation of physical examination. Specific attention should be focused on tachycardia, tachypnea, use of accessory muscles, signs of perioral or peripheral cyanosis, the ability to speak in complete sentences, and the patient's mental status. The presence or absence of focal findings, degree of air movement, presence or absence of wheezing can be established by chest examination. An asymmetry observed in the chest examination suggests large airway obstruction or pneumothorax. These conditions can mimic an exacerbation [78]. The presence or absence of paradoxical motion of the abdominal wall also can simulate as an exacerbation. Chest x-ray should be done in patients with severe underlying COPD, who are in moderate or severe distress, or those with focal findings. The most frequent findings in this clinical situation are pneumonia and congestive heart failure. An arterial blood-gas measurement should be done in patients with a history of hypercarbia advanced COPD, or those in significant distress. Hypercarbia, defined as a PCO2 $>$45 mmHg, is an important implications for treatment. Measurement of pulmonary function has not been demonstrated to be helpful in the diagnosis or management of exacerbations of COPD which is in contrast to its utility in the management of exacerbations of asthma

[79]. Definitive guidelines regarding inpatient treatment of exacerbations has not been defined. Admission to the hospital should be done in patients with respiratory acidosis and hypercarbia, significant hypoxemia, or severe underlying disease or those whose living situation is not conducive to careful observation and the delivery of prescribed treatment [33,34].

ACUTE EXACERBATIONS

Bronchodilators

Typically, patients are treated with an inhaled β agonist, often with the addition of an anticholinergic agent. These may be administered separately or together, and the frequency of administration depends on the severity of the exacerbation. Patients are often treated initially with nebulized therapy, as such treatment is often easier to administer in older patients or to those in respiratory distress. It has been shown, however, that conversion to metered-dose inhalers is effective when accompanied by education and training of patients and staff. This approach has significant economic benefits and also allows an easier transition to outpatient care. Consideration to addition of methylxanthines such as theophylline to this regimen can be done, although convincing proof of its therapeutic efficacy is lacking. If added, serum levels should be monitored in an attempt to minimize toxicity [36,37].

Antibiotics

Patients with COPD are frequently colonized with potential respiratory pathogens. It is often difficult to identify a specific species of bacteria to be responsible for a particular clinical event. Bacteria which are frequently implicated in COPD exacerbations include Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis. In addition, Mycoplasma pneumoniae or Chlamydia pneumoniae are found in 5–10% of exacerbations. The choice of antibiotic should be based on local patterns of antibiotic susceptibility of the above pathogens as well as the patient's clinical condition. Most practitioners treat patients with moderate or severe exacerbations with antibiotics, even in the absence of data implicating a specific pathogen [80].

Glucocorticoids

The use of glucocorticoids in exacerbations of COPD has been demonstrated to reduce the length of stay, hasten recovery, and reduce the chance of subsequent exacerbation or relapse for a period of up to 6 months. One study demonstrated that 2 weeks of glucocorticoid therapy produced benefit indistinguishable from 8 weeks of therapy [82]. The GOLD guidelines recommend 30–40 mg of oral prednisolone or its equivalent for a period of 10–14 days. Hyperglycemia, particularly in patients with preexisting diagnosis of diabetes, is the most frequently reported acute complication of glucocorticoid treatment [68].

Oxygen

Supplemental O2 should be supplied to keep arterial saturations ≥90%. Previous studies have demonstrated that administration of supplemental O2 in patients with acute and chronic hypercarbia, does not reduce minute ventilation [73]. Though, in some patients, a modest increase in arterial PCO2 has been reported. This is due to altering ventilation-perfusion relationships within the lung [20]. This should not deter practitioners from providing the oxygen needed to correct hypoxemia.

Mechanical Ventilatory Support

The initiation of non invasive positive pressure ventilation (NIPPV) in patients with respiratory failure, defined as PaCO2 >45 mmHg, results in a significant reduction in mortality rate, need for intubation, complications of therapy, and hospital length of stay. Contraindications to NIPPV include cardiovascular instability, impaired mental status or inability to cooperate, copious secretions or the inability to clear secretions, craniofacial abnormalities or trauma precluding effective fitting of mask, extreme obesity, or significant burns [33]. Invasive i.e conventional mechanical ventilation via an endotracheal tube is indicated for patients with severe respiratory distress despite initial therapy, life-threatening hypoxemia, severe hypercarbia and/or acidosis, markedly impaired mental status, respiratory arrest, hemodynamic instability, or other complications. The goal of mechanical ventilation is to correct the aforementioned conditions. The factors to be considered during mechanical ventilatory support are the need to provide sufficient expiratory time in patients with severe airflow obstruction and the presence of auto-PEEP (positive end-expiratory pressure). The mortality rate

of patients requiring mechanical ventilatory support contributes to 17–30% for that particular hospitalization [34]. For patients age >65 admitted to the intensive care unit for treatment, the mortality rate doubles over the next year to 60%, regardless of whether mechanical ventilation was required [68].

PHARMACOLOGICAL PROFILE OF ROFLUMILAST

Roflumilast, Phosphodiesterase 4 (PDE4) inhibitor, prevents breakdown of cAMP. Cyclic AMP regulates many cellular functions, including relaxation of smooth muscle and reduction in immune and inflammatory activity of specific cells.

Inhibition of PDE4 results in inhibiting release of cytokines and chemokines, which in turn results in decrease in immune cell migration and activation. Roflumilast reduce inflammation in smaller airways leading to reduction in hyperinflation and a change in internal airflow distribution (IAD) [62].

The change in IAD enhances the deposition of Long acting B2 agonists / Inhalational corticosteroid therapy, which are commonly used for COPD, leading to clinical improvements. Roflumilast has also been shown to reduce allergen-induced inflammation and also stabilizes lipopolysaccharide-induced systemic inflammation [63].

Roflumilast is available in a once-daily oral dosage form (500 µg tablets) with a bioavailability of approximately 80%. Maximum plasma concentrations of roflumilast are achieved in ~1 hour (range: 0.5–2 hours) after a single dose, and maximum

concentrations of the active *N*-oxide metabolite are achieved in ~8 hours (range: 4–13 hours). Roflumilast is a highly protein bound drug (≥97%) and its active metabolite also has the same property. Metabolism occurs by Phase I which includes enzymes cytochrome P450 (CYP) and by Phase II conjugation. Half-life is approximately 17 hours. Roflumilast is three times more potent than its metabolite, but the metabolite has approximately ten times greater exposure (plasma area under the curve) than the active drug [32]. Patients with hepatic dysfunction may have impaired elimination, although dose adjustments are not necessary. No dosage adjustments are required for renal impairment. However, roflumilast should not be coadministered with strong inhibitors of CYP3A4 or dual inhibitors of CYP3A4 and CYP1A2 (eg, erythromycin, ketoconazole, fluvoxamine, enoxacin, cimetidine, or rifampicin). The macrolide azithromycin, which is commonly used in patients with COPD, is only a weak inhibitor of CYP3A4 and is expected to interact with roflumilast to a much lesser degree than erythromycin [64,65].

Fig 3 : Roflumilast oral tablet

ROLE OF SPIROMETRY IN COPD

Pulmonary function tests (PFTs) are most commonly measured using Spirometry instrument. Spirometry measures lung function, specifically the amount (volume) and/or speed (flow) of air that can be inhaled and exhaled. It is also helpful in assessing breathing patterns that leads to identification of conditions such as asthma, COPD, cystic fibrosis, and pulmonary fibrosis [57,58].

Indications

Spirometry is indicated for the following reasons:

- to diagnose or manage asthma

- to distinguish respiratory from cardiac disease as the cause of breathlessness

- to measure bronchial responsiveness in patients suspected of having asthma

- to diagnose and differentiate between obstructive lung disease and restrictive lung disease

- to follow the natural history of disease in respiratory conditions

- to assess of impairment from occupational asthma

- to identify those at risk from pulmonary barotrauma while scuba diving

- to conduct pre-operative risk assessment before anaesthesia or cardiothoracic surgery

- to measure response to treatment of conditions which is detected by spirometry

- to diagnose vocal cord dysfunction [57,58].

PROCEDURE

The basic forced volume vital capacity (FVC) test varies slightly depending on the equipment used.

Generally, the patient is 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. When assessing possible upper airway obstruction, it is sometimes directly followed by a rapid inhalation.

Soft nose clips may be used to prevent air escaping through the nose when the test is being performed. To prevent the spread of microorganisms, filter mouthpieces may be used [59,60].

Bronchial challenge test is used to determine bronchial hyperresponsiveness to inhalation of cold/dry air, rigorous exercise, or with agents such as methacholine or histamine. Spirometry can also be a part of it.

 A bronchodilator is administered before performing another round of tests for comparison, to assess the reversibility of a particular condition. This is referred to as a *reversibility test*, or a *post bronchodilator test* (Post BD). This test is used to differentiate asthma from COPD [68].

Forced vital capacity (FVC)

Forced vital capacity (FVC) is the volume of air that is forcibly blown out after full inspiration. It is measured in litres. FVC is the most basic manoeuvre in spirometry tests.

Forced expiratory volume in 1 second (FEV1)

FEV1 is the volume of air that is forcibly blown out in one second, after full inspiration. Values between 80% and 120% of the average value are considered normal [66].

FEV1/FVC ratio (FEV1%)

FEV1/FVC (FEV1%) is the ratio of FEV1 to FVC. In healthy adults the normal value is approximately 70–85%. This declines with age. In obstructive diseases such as asthma, COPD, chronic bronchitis, emphysema, FEV1 is diminished because of increased airway resistance to expiratory flow. FVC may be decreased but not in the same proportion as FEV1. This is due to the premature closure of airway in expiration. FEV1 is more affected because of the increased airway resistance. A reduced value (<80%, often ~45%) is seen in these conditions. In restrictive diseases, such as pulmonary fibrosis, both FEV1 and FVC are reduced proportionally. The value may be normal or even increased as a result of decreased lung compliance.

FEV1% predicted is another derived value of FEV1%. This is defined as FEV1% of the patient divided by the average FEV1% in the population [62].

Peak expiratory flow

Peak expiratory flow (PEF) is the maximal flow (or speed) achieved during the maximally forced expiration initiated at full inspiration, measured in litres per minute or per second [59].

AIM & OBJECTIVE

AIMS AND OBJECTIVES

Aim

To study the efficacy of Roflumilast as add on therapy in Chronic Obstructive Pulmonary Disease and its ability in reducing the exacerbations in Chronic Obstructive Pulmonary Disease.

Objective

1. To determine whether Roflumilast improves lung function whose parameters are assessed using spirometry and decreases exacerbation frequency over a period of 6 months in patients with Chronic Obstructive Pulmonary Disease.

2. To determine whether Roflumilast increases quality of life using Quality of life Questionairre.

MATERIALS AND

METHODS

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.

The study procedure required screening for patients with Chronic Obstructive Pulmonary Disease, who satisfy the inclusion criteria, their subsequent recruitment, randomization and grouping. This was followed by a 6 month treatment regimen and analysis of post therapy investigations which assessed the efficacy of the treatment given.

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:

$$n = \frac{2(Za+Z1-\beta)^{2\sigma^2}}{\Delta^2}$$

where *n* is the required sample size

Z_α, *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; using the above tables, we get the following values: $Z_{\alpha,}$ 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% (i.e., 0.15).

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 was done at Govt. Thiruvoteeswarar Tuberculosis and Chest Hospital, Otteri, Chennai which is a unit of Govt. Kilpauk Medical College. The study procedure required screening for patients with Chronic Obstructive Pulmonary Disease, from those who attended outpatient department of the hospital. COPD was diagnosed in the patients based on the GOLD criteria. Patients (old and newly diagnosed) who satisfied the inclusion criteria and those who were willing to take part in study were recruited. 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

A patient was considered suitable for the study if he/ she satisfied the following 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

Patients with the following criteria were excluded from the study:

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

Recruitment

Patients fulfilling the inclusion criteria and those who were chosen for the study were briefed about the study. Written informed consent was obtained from those willing to participate in the study. A detailed history and clinical examination was performed on the participants.

Randomization

A simple randomization method was adopted. Patients diagnosed with COPD and those who were willing to participate were randomised into 2 groups, i.e, Roflumilast drug therapy group and the standard treatment group.

Patients were administered drugs based on the group they belonged to for 6 months. The two groups, the drugs administered, dose and regimen are given below.

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.

Grouping

The study design envisaged a randomisation of the study population into 2 groups.

Group 1 consisted of patients who received standard treatment for COPD comprising of Inhalational steroids and Beta2 agonists.

Group 2 patients in addition to standard treatment, also received Roflumilast 500 microgram once daily.

The study period was 6 months for each patient.

Drugs used in the study

1. Salmeterol 250ug was given orally and steroid Fluticasone 50ug was given by inhalational route twice daily 12 hours apart.

2. Tablet Roflumilast 500ug, Phosphodiesterase 4 inhibitor was taken once daily in the morning after food.

   All supplements were administered for a period of 6 months.

Assessment of Participants

A clinical assessment of General examination, vital signs and systemic examination was performed on every patient recruited after obtaining a detailed history. The findings were duly noted in the case report forms (CRF).

Procedure

After recruitment of patients and before initiation of therapy, lung function test is 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.

Lung function tests such as FEV1 (Forced expiratory volume in 1 second), PEFR (Peak expiratory flow rate) and FVC (Forced vital capacity) were determined. Patients with value of FEV1/FVC <0.7, were recruited in the study.

Group 1 patients received salmeterol 250ug and inhalational steroid 50 ug twice daily 12 hours apart for 6 months.

Group 2 patients received oral Roflumilast 500ug along with salmeterol and inhalational steroid once daily for 6 months.

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 and proportion of participants experiencing exacerbations was noted and compared between the two groups.

Lung function tests readings were done every month, i.e. in the beginning after recruitment, then at the end of 1, 2, 3, 4, 5, and 6 months and changes in improvement or decrement were noted.

Fig 4 – Spirometry machine

Fig 5 – Report of a patient given by Spirometry

Department of Physiology
Govt Kilpauk Medical College
Chennai - 10

Patient Information

Name	Prakash	Test Type	FVL (ex/in)
ID	007/phy/2016	Test Date	7/11/2016 10:12:50 AM
Age	34	Interpretation	GOLD(2008)/Hardie
Height	160 cm	Predicted	Knudson 83 * 0.87
Weight	48 kg	Value Selection	Best Trial
Gender	Male		
Ethnicity	Asian		
Asthma	No		
Smoker	No		

Parameter	Pred	LLN	Best Trial 1	%Pred
FVC [L]	3.23	2.62	3.12	97
FEV1 [L]	2.72	2.15	2.11*	77
FEV1/FVC	0.831	0.722	0.676*	81
FEF25-75% [L/s]	3.51	1.94	1.73*	49
PEF [L/s]	7.86	-	2.92	37
FET [s]	-	-	13.2	-
FIVC [L]	3.23	2.62	-	-
PIF [L/s]	-	-	-	-

System Interpretation   Pre   No interpretation, not enough acceptable maneuvers
Caution: Poor session quality. Interpret with care.
* Indicates below LLN or significant post change.
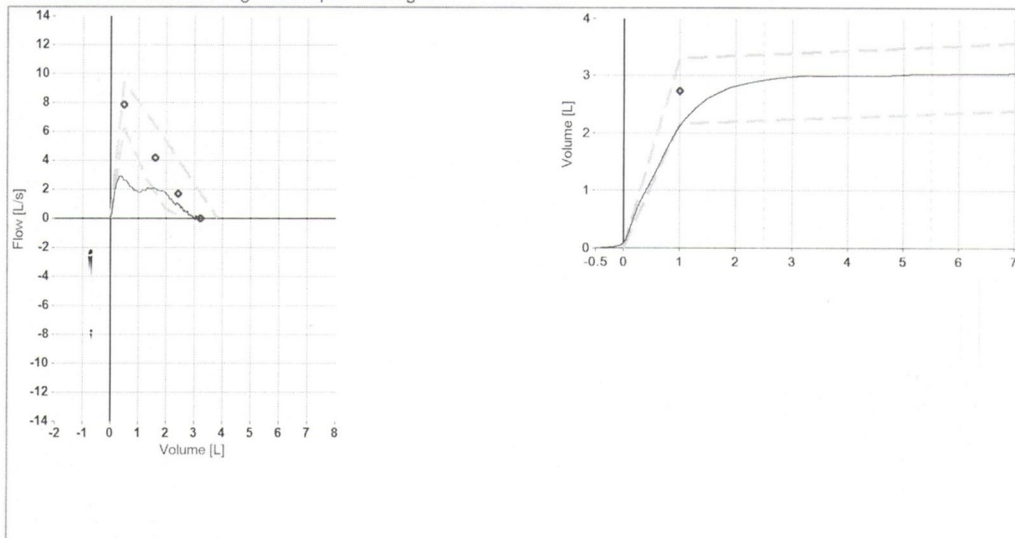
Custom report
JKFVC-INTERPRETATION

67

Patients were also questioned about their improvement in quality of life with the help

of a questionnaire at the end of every month and were also enquired about any

subjective side effects experienced due to intake of drug. They were also examined for

any external manifestations which may have been obtained due to the ingestion of

drug such as rashes, symptoms of hypersensitivity reactions.

The COPD questionnaire to assess Quality of Life

	Almost every day	Several days a week	A few days a month	Only with lung or respiratory infections	Not at all
1. Over the last 4 weeks, I have coughed					
2. Over the last 4 weeks, I have brought up phlegm (sputum)					
3. Over the last 4 weeks, I have had shortness of breath					
4. Over the last 4 weeks, I have had episodes of wheezing					

How would you describe your lung/respiratory condition?

_____ The most important problem I have
_____ Causes me a lot of problems
_____ Causes me a few problems
_____ Causes me no problem

When do you feel breathlessness?   YES   NO

	YES	NO
Sitting or lying still		
Washing yourself or dressing		
Walking in the house		
Walking outside on level ground		
Walking up a flight of stairs		
Walking uphill		
Playing sports or active games (tennis, cricket etc)		

For the first two questions, scores were given from 0 to 4 based on severity from mild to severe, respectively.

For the third questionnaire, 'yes' was given 1 score and 'no' was given 0 score.

This questionnaire was asked to the patient after recruitment, and then every month during follow up. The values at the end of 6 months were compared to the values at the beginning. The score given was as follows:

0 -10: mildly disabled

11-20: moderately disabled

21-30: severely disabled

Based on above score, the quality of life index of patients of both groups was compared.

STATISTICAL ANALYSIS

Continuous variables were to be described as means along with their standard deviations while discrete variables were expressed as frequencies and percentages. Within each group, mean change in lung function tests i.e. FVC and FEV1 from baseline to post therapy was assessed using repeated measures ANOVA. A two way ANOVA was employed to assess the significance of changes in parameters between the two groups.

IBM SPSS version 22 was used for statistical analysis [76].

A descriptive analysis was undertaken for the analysis of Adverse Drug Reactions that occurred during the study period.

RESULTS

All patients attending outpatient department were screened for COPD according to GOLD criteria. On an alternate basis of randomization, patients were recruited into the standard and treatment group. 100 of them who fit the inclusion criteria were included in the study consisting of 50 in each group.

Demographics

Most of the participants recruited belonged to the male gender, as smoking was the most common risk factor associated. Among the recruited patients, 24 participants were female and the rest 76 were male. As per the inclusion criteria, only participants aged above 30 years were recruited.

The mean age was 56.17±9.665 in Control group and mean age was 58.12 ± 9.260 in Roflumilast group. The mean difference across the group is (-1.95). It is statistically not significant (P Value 0.360).

Table 1: Comparison of mean Age across study groups (N=100)

Group	Age Mean±STD	Mean difference	95% CI		P value
			Lower	Upper	
Control	56.17 ± 9.665	-1.95	-6.16363	2.26363	0.360
Roflumilast	58.12 ± 9.260				

All patients in Roflumilast group reported improvement in symptoms such as cough, breathlessness and increase in sputum production. The patients in Roflumilast group

reported that their breathing was easier than before and there was improvement in quality of life compared to control group. This was assessed by Quality of life questionnaire at the end of 6 months. There was only mild disability in Roflumilast group compared to moderate and severe disability in control group.

Table 2: Comparison of mean Quality of life questionnaire score across study groups (N=100)

Group	Quality of life questionnaire score Mean±STD	Mean difference	95% CI		P value
			Lower	Upper	
CONTROL	21.47 ± 2.275	11.15	10.23054	12.06946	0.001
ROFLUMILAST	10.32 ± 1.831				

The mean Quality of life questionnaire score was 21.47 ± 2.275 in subjects belonging to Control and mean Quality of life questionnaire score10.32±1.83 in subjects belonging to Roflumilast. The mean difference across the group is 11.15. It is statistically significant (P Value 0.001).

Acute exacerbations

Acute exacerbations of COPD were assessed by

i) number of exacerbations occurred, and

ii) median time to exacerbation.

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

COMPARISON OF MEAN CHANGE IN PARAMETERS FROM BASELINE TO END OF 6 MONTHS

A) Forced Expiratory Volume (FEV1)

Table 3: Comparison of mean change in FEV1 at 1 month across study groups (N=100)

Group	Change in FEV1 at 1 month Mean±SD	Mean difference	95% CI Lower	95% CI Upper	P value
CONTROL	0.076 ± 0.194	-0.05	-0.13079	0.03579	0.260
ROFLUMILAST	0.123 ± 0.179				

The mean change in FEV1 at 1 month was 0.076±0.194 in subjects belonging to Control and mean change in FEV1 at 1 month was 0.123±0.179 in subjects

belonging to Roflumilast. The mean difference across the group is (-0.05). It is statistically not significant (P Value 0.260).

Table 4: Comparison of mean Change in FEV1 at 2 months across study groups (N=100)

Group	Change in FEV1 at 2 months Mean±SD	Mean difference	95% CI		P value
			Lower	Upper	
CONTROL	0.05 ± 0.148	-0.13	-0.21537	-0.03963	0.005
ROFLUMILAST	0.177 ± 0.236				

The mean change in FEV1 at 2 months was 0.05±0.148 in subjects belonging to control and mean change in FEV1 at 2 months was 0.177±0.236 in subjects belonging to Roflumilast group. The mean difference across the group is (-0.13). It is statistically significant (P Value 0.005).

Table 5: Comparison of mean Change in FEV1 at 3 months across study groups (N=100)

Group	Change in FEV1 at 3 months Mean±SD	Mean difference	95% CI		P value
			Lower	Upper	
CONTROL	0.053 ± 0.196	-0.19	-0.29303	-0.09347	0.001
ROFLUMILAST	0.246 ± 0.248				

The mean change in FEV1 at 3 months was 0.053±0.196 in subjects belonging to Control and mean change in FEV1 at 3 months was 0.246±0.248 in subjects belonging

to Roflumilast group. The mean difference across the group is (-0.19). It is statistically significant (P Value 0.001).

Table 6: Comparison of mean change in FEV1 at 4 months across study groups (N=100)

Group	Change in FEV1 at 4 months Mean±SD	Mean difference	95% CI		P value
			Lower	Upper	
CONTROL	0.078 ± 0.197	-0.21	-0.30114	-0.10986	0.001
ROFLUMILAST	0.283 ± 0.230				

The mean change in FEV1 at 4 months was 0.078±0.197 in subjects with Control and mean change in FEV1 at 4 months was 0.283±0.230 in subjects belonging to Roflumilast group. The mean difference across the group is (-0.21). It is statistically significant (P Value 0.001).

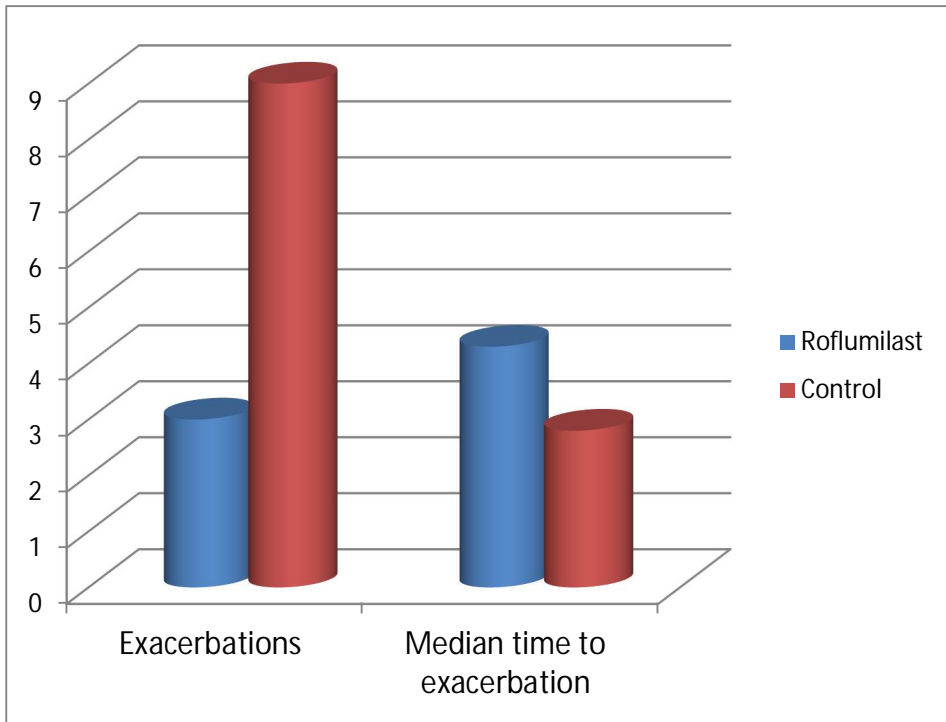**Table 7: Comparison of mean Change in FEV1 at 5 months across study groups (N=100)**

Group	Change in FEV1 at 5 months Mean±SD	Mean difference	95% CI		P value
			Lower	Upper	
CONTROL	0.103 ± 0.214	-0.20	-0.30179	-0.10421	0.001
ROFLUMILAST	0.306 ± 0.228				

The mean change in FEV1 at 5 months was 0.103±0.214 in subjects belonging to Control and mean change in FEV1 at 5 months was 0.306±0.228 in subjects

belonging to Roflumilast. The mean difference across the group is (-0.20). It is statistically   significant (P Value 0.001).

Table 8: 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 7: Comparison of mean change in FEV1 across study groups (N=80)
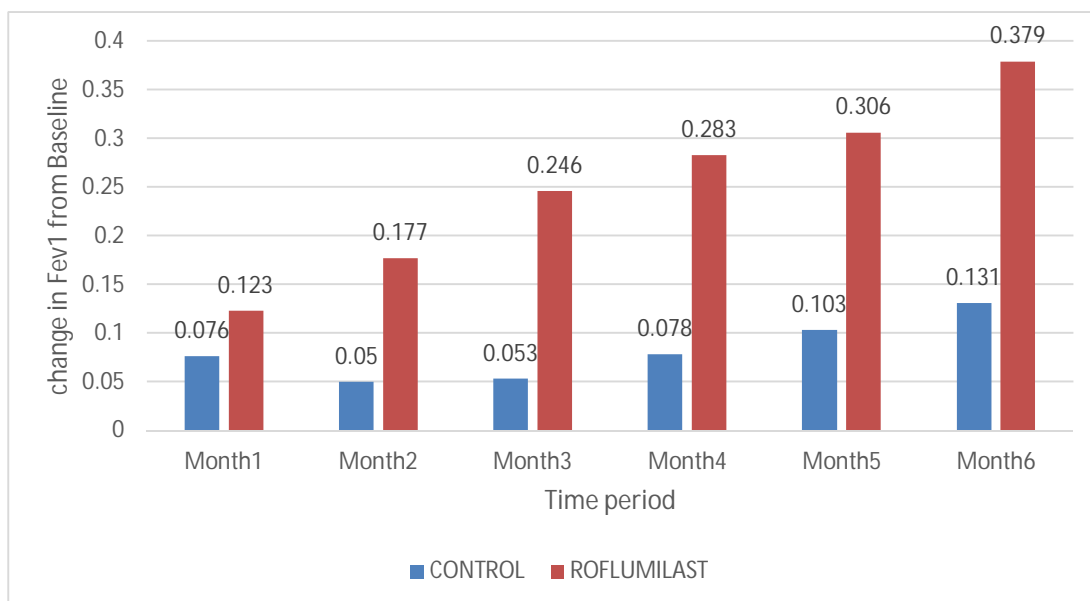
B) Forced vital Capacity (FVC)

Table: 9 Comparison of mean   Change in FVC at 1 month across study groups (N=100)

Group	Change in FVC at 1 month Mean±STD	Mean difference	95% CI		P value
			Lower	Upper	
CONTROL	-0.02 ± 0.285	-0.08	-0.18886	0.03586	0.179
ROFLUMILAST	0.054 ± 0.213				

The mean change in FVC at 1 month was -0.02±0.285 in subjects belonging to

Control and mean change in FVC at 1 month was 0.054±0.213 in subjects belonging

to   Roflumilast. The mean difference across the group is (-0.08). It is   statistically

not significant   (P Value 0.179).

Table 10: Comparison of mean   Change in FVC at 2 months across study groups (N=100)

Group	Change in FVC at 2 months Mean±STD	Mean difference	95% CI		P value
			Lower	Upper	
CONTROL	-0.02 ± 0.304	-0.11	-0.25955	0.03355	0.129
ROFLUMILAST	0.089 ± 0.351				

The mean change in   FVC at 2 months was -0.02±0.394   in subjects belonging to

Control and mean change in FVC at 2 months was 0.089±0.351 in subjects belonging

to Roflumilast group. The mean difference across the group is (-0.11). It is

statistically   not significant (P Value 0.129).

Table11: Comparison of mean Change in FVC at 3 months across study groups (N=100)

Group	Change in FVC at 3 months Mean±STD	Mean difference	95% CI		P value
			Lower	Upper	
CONTROL	-0.00 ± 0.354	-0.17	-0.31404	-0.03246	0.017
ROFLUMILAST	0.173 ± 0.273				

The mean change in FVC at 3 months was -0.00±0.354 in subjects belonging to control and mean change in FVC at 3 months was 0.173±0.273 in subjects belonging to Roflumilast group. The mean difference across the group is (-0.17). It is statistically significant (P Value 0.017).

Table 12: Comparison of mean Change in FVC at 4 months across study groups (N=100)

Group	Change in FVC at 4 months Mean±STD	Mean difference	95% CI		P value
			Lower	Upper	
CONTROL	-0.02 ± 0.343	-0.23	-0.37270	-0.08930	0.002
ROFLUMILAST	0.207 ± 0.291				

The mean change in FVC at 4 months was -0.02±0.343 in subjects belonging to Control and mean change in FVC at 4 months was 0.207±0.291 in subjects belonging to Roflumilast group. The mean difference across the group is (-0.23). It is statistically significant (P Value 0.002).

Table 13: Comparison of mean   Change in FVC at 5 months across study groups (N=100)

Group	Change in FVC at 5 months Mean±STD	Mean difference	95% CI		P value
			Lower	Upper	
CONTROL	-0.02 ± 0.338	-0.22	-0.35289	-0.08161	0.002
ROFLUMILAST	0.192 ± 0.266				

The mean change in FVC at 5 months was -0.02±0.338   in subjects belonging to

Control and mean change in FVC at 5 months was 0.192±0.266 in subjects belonging

to Roflumilast group. The mean difference across the group is (-0.22). It is

statistically significant (P Value 0.002).

Table 14: 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 8: Comparison of mean change in FVC across study groups (N=100)

C) % FEV1 (FV1/FVC)

Table 15: Comparison of mean Change in FEV1/FVC at 1 month across study groups (N=100)

Group	Change in FEV1/FVC at 1 month Mean±STD	Mean difference	95% CI		P value
			Lower	Upper	
CONTROL	0.061 ± 0.130	0.01	-0.04023	0.05973	0.699
ROFLUMILAST	0.052 ± 0.090				

The mean change in FEV1/FVC at 1 month was 0.061±0.130 in subjects belonging to Control and mean change in FEV1/FVC at 1 month was 0.052±0.090 in subjects belonging to Roflumilast group. The mean difference across the group is (0.01). It is statistically not significant (P Value 0.699).

Table 16: Comparison of mean Change in FEV1/FVC at 2 months across study groups (N=100)

Group	Change in FEV1/FVC at 2 months Mean±STD	Mean difference	95% CI		P value
			Lower	Upper	
CONTROL	0.046 ± 0.128	-0.03	-0.08881	0.02081	0.221
ROFLUMILAST	0.080 ± 0.116				

The mean change in FEV1/FVC at 2 months was 0.046±0.128in subjects belonging to control group and mean change in FEV1/FVC at 2 months was 0.080±0.116 in subjects belonging to Roflumilast group. The mean difference across the group is (-0.03). It is statistically not significant (P Value 0.221).

Table 17: Comparison of mean Change in FEV1/FVC at 3 months across study groups (N=100)

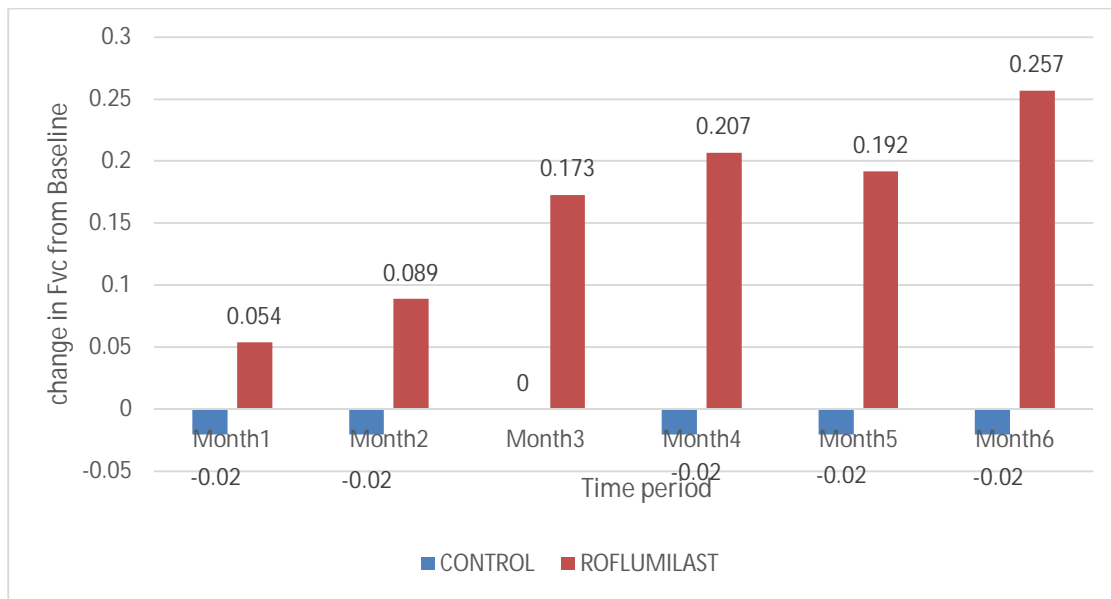| Group	Change in FEV1/FVC at 3 months Mean±STD	Mean difference	95% CI		P value
			Lower	Upper	
CONTROL	0.044 ± 0.109	-0.04	-0.09639	0.01039	0.113
ROFLUMILAST	0.087 ± 0.129				

The mean change in FEV1/FVC at 3 months was 0.044±0.109 in subjects belonging to Control and mean Change in FEV1/FVC at 3 months was 0.087±0.129 in subjects belonging to Roflumilast group. The mean difference across the group is (-0.04). It is statistically   not   significant   (P Value 0.113).

Table 18: Comparison of mean Change in FEV1/FVC at 4 months across study groups (N=100)

Group	Change in FEV1/FVC at 4 months Mean±STD	Mean difference	95% CI		P value
			Lower	Upper	
CONTROL	0.068 ± 0.128	-0.04	-0.09788	0.01438	0.143
ROFLUMILAST	0.11 ± 0.123				

The mean change in FEV1/FVC at 4 months was 0.068±0.128 in subjects belonging to Control and mean change in FEV1/FVC at 4 months was 0.11±0.123 in subjects belonging to Roflumilast group. The mean difference across the group is (-0.04). It is statistically not significant (P Value 0.143).

Table 19: Comparison of mean Change in FEV1/FVC at 5 months across study groups (N=100)

Group	Change in FEV1/FVC at 5 months Mean±STD	Mean difference	95% CI		P value
			Lower	Upper	
CONTROL	0.097 ± 0.125	-0.02	-0.07351	0.03251	0.444
ROFLUMILAST	0.118 ± 0.111				

The mean change in FEV1/FVC at 5 months was 0.097±0.125 in subjects belonging to Control and mean change in FEV1/FVC at 5 months was 0.118±0.111 in subjects belonging to Roflumilast group. The mean difference across the group is (-0.02). It is statistically not significant (P Value 0.444).

Table 20: 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 9: Comparison of mean Change in FEV1/FVC across study groups (N=100)
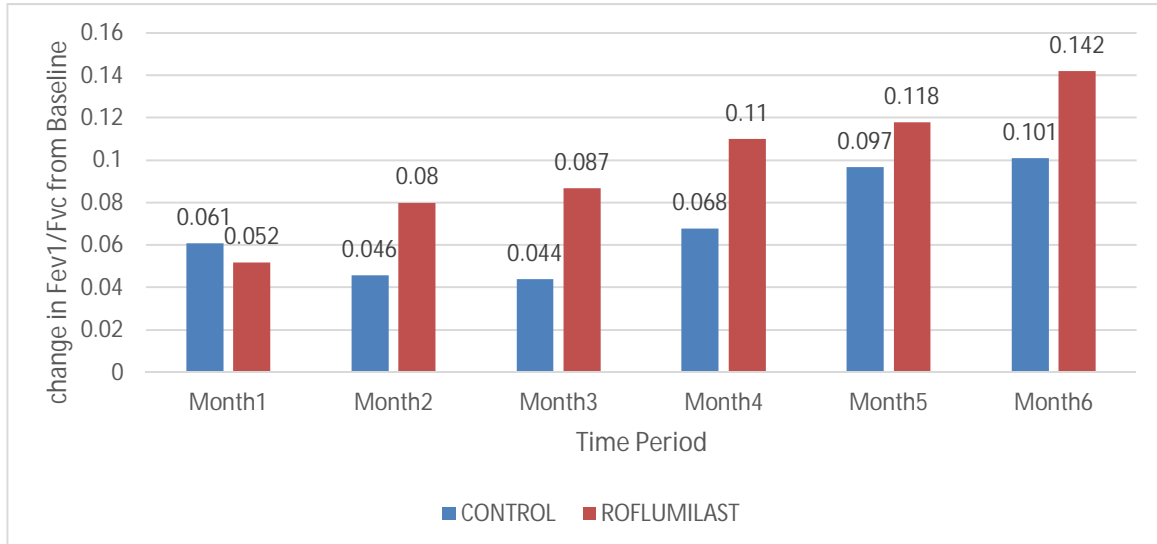
ADVERSE DRUG REACTIONS

Out of 50 patients recruited in the Roflumilast group, 27 patients reported adverse effects due to their medications. Most of the adverse effects were reported spontaneously. Most of the patients complained of headache a few hours after ingestion of the drug. The second most common complaint was tremors. A few reported 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. Depression, suicidal thoughts which were a rare side effect reported in previous studies due to Roflumilast did not occur in any participant in this study [81].

In the group which received standard treatment, less adverse effects were recorded. Most common was tremor which was seen in 8 patients.

Fig10. Adverse effects in Roflumilast group

ADVERSE EFFECTS

Legend: headache, tremors, nausea, insomnia, giddiness, diarrhea, acute exacerbations

headache 28%, tremors 18%, nausea 11%, insomnia 7%, giddiness 14%, diarrhea 11%, acute exacerbations 11%
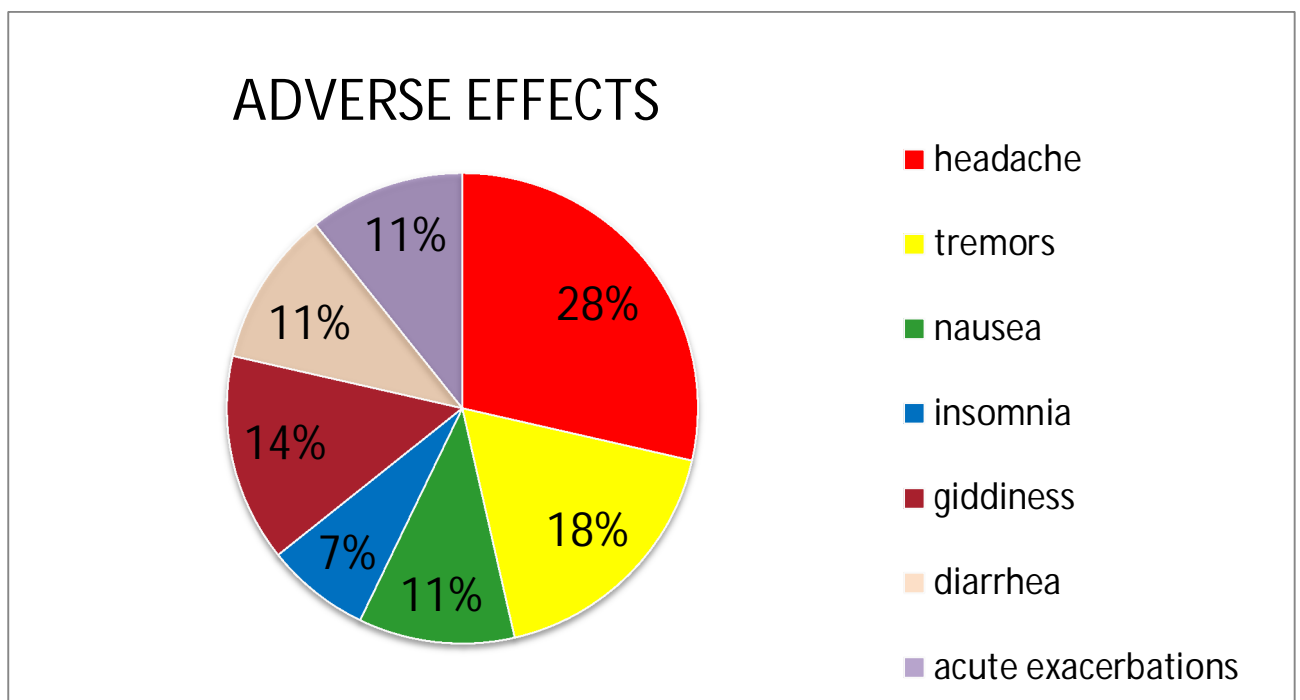
ADHERENCE TO TREATMENT REGIMEN

After recruitment into study, after intake of treatment of regimen, there were dropouts of patients due to loss of contact, due to shifting to other place, changing hospital and due to adverse effects of the drug. Those patients were excluded from the study and new patients were recruited into the study till a sample size of 50 was attained in each group. Each participant was followed up for 6 months after recruitment in the study.

Table 21: No. of dropouts

	No. of dropouts
Loss of contact	3
Shifting to other place	2
Change of hospital	3
Adverse effects	3

DISCUSSION

DISCUSSION

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 [74].

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 [75]. One such study is FARIECE study done in Mexico conducted by J.C.Fernández et al [82].

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 [63]. The mean change in Fvc at 6 months was -0.02±0.345 in subjects belonging to control group from baseline compared to   0.257±0.253 in subjects belonging to Roflumilast group. The mean difference across the group is 0.29%. 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 change in lung function, is unlikely to have modified the patients' degree of breathlessness, but could have contributed to the reduction in exacerbations [77]. The mean change in Fev1/Fvc at 6 months was   0.101±0.120 in subjects belonging to control and the mean change seen in subjects belonging to Roflumilast group was 0.142±0.108. But this finding was not statistically significant. This may be attributed to the low sample size. In previous studies by Vestbo et al [74], Stephen et al [75], the improvement in %FEV1 was found to be statistically significant.

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 which improved their quality of life. Patients recruited in group receiving Roflumilast, at the end of 6 months were only

mildly disabled and there was improvement in their quality of life when compared to their baseline values before intake of drug Roflumilast. In the control group, the patients were moderately to severely disabled and there was no improvement in quality of life.

Roflumilast was efficacious in reducing exacerbations of COPD. Only 3 patients in Roflumilast group experienced exacerbations and were admitted in hospital. The duration of stay was also comparatively less and they recovered faster than patients in the control group. In the control group, 9 patients experienced exacerbations and their duration of stay in hospital was longer. This proved that Roflumilast reduced exacerbations of COPD, thus reducing hospital admissions and duration of stay in hospital. The study has shown positive clinical and economic implications and justifies the decision to target at-risk patients with chronic obstructive pulmonary disease. Also, the mean time to exacerbation was 2.8 months in control group compared to 4.3 months in patients receiving Roflumilast. This showed that Roflumilast reduced the time to 1st exacerbation and also postponed the episodes of exacerbation. The result obtained is in correlation to previous studies done by Field et al, Vestbo et al [75,76]. Roflumilast saw significant reduction in the incidence of exacerbations in patients who had frequent COPD exacerbations (≥2) in the year prior to treatment with roflumilast.

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 [78]. 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 other than exacerbation of disease. No deaths were reported. The anticipated adverse effects such as suicidal tendency and depression which were reported in previous studies by Stephen et al in Europe [77] were not observed.

Thus by a derivation of this study, Roflumilast is an effective drug in reducing exacerbations of COPD, and in improving quality of life in patients diagnosed with COPD and can be used as add on therapy to standard treatment.

CONCLUSION

CONCLUSION

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.

BIBLIOGRAPHY

BIBLIOGRAPHY

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. O'Driscoll, BR; Howard, LS; Davison, AG; British Thoracic, Society (October 2012). "BTS guideline for emergency oxygen use in adult patients". doi:10.1136/thx.2008.102947

27. Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V, et al. (December 2012). "Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet*. 380 (9859). doi:10.1016/S0140-6736(12)61729-2

28. Davies Adeloye, Stephen Chua, Chinwei LeeGlobal and regional estimates of COPD prevalence: Systematic review and meta– analysis. IJPM May 2012.

29.Celli, B. R. (2004). The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. https://doi.org/10.1056/NEJMoa021322

30.Int J Chron Obstruct Pulmon Dis. 2012; 4: 137–148

31.Shavelle, R. M., et al. (2009). Years of life lost and life expectancy in chronic obstructive pulmonary disease: Findings the NHANES III follow-up study. https://doi.org/10.2147/COPD.S5237

32.Boswell-Smith, V; Spina, D (2007). "PDE4 inhibitors as potential therapeutic agents in the treatment of COPD-focus on roflumilast". International Journal of Chronic Obstructive Pulmonary Disease. 2 (2): 121–9. ISSN 1178-2005. PMC 2695611 . PMID 18044684

33. Davidson's Principles and Practice of Medicine 23rd Edition pg 1205 - 1209
34. Harrison Principles of Internal Medicine 19th Edition pg 1700-1708

35. Calverley PM, Koulouris NG (2005). "Flow limitation and dynamic hyperinflation: key concepts in modern respiratory physiology". Eur Respir J. 25 (1): 186–199. *PMID 15640341*. doi:10.1183/09031936.04.00113204.

36. Currie, Graeme P. (2010). *ABC* of COPD (2nd ed.). Wiley-Blackwell, BMJ *Books. p. 32.* ISBN 978-1-4443-2948-3.

37. O'Donnell DE *(2006). "*Hyperinflation, Dyspnea, and Exercise Intolerance in Chronic Obstructive Pulmonary Disease". The Proceedings of the American Thoracic Society. 3 *(2): 180–4.* PMID 16565429. doi:10.1513/pats.200508-093DO.

38. *Cooper, CB (October 2006). "*The connection between COPD symptoms and hyperinflation and its impact on exercise and function.*".* The American Journal of Medicine. doi*:*10.1016/j.amjmed.2006.08.004

39. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, Ezzati M, Shibuya K, Salomon JA, et al. (December 2012). "Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010". doi:10.1016/S0140-6736(12)61689-4.

40.Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V, et al. (December 2012). "Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010". Lancet. 380 (9859): 2163–96. PMID 23245607. doi:10.1016/S0140-6736(12)61729-2.

41.Medicine, prepared by the Department of Medicine, Washington University (2nd ed.). Wolters Kluwer Health/Lippincott Williams & Wilkins. ISBN 978-0-7817-9155-7

42.Puhan, Milo A.; Gimeno-Santos, Elena; Cates, Christopher J.; Troosters, Thierry (2016-12-08). "Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease". doi:10.1002/14651858.CD005305.pub4.

43. Zainuldin, Rahizan; Mackey, Martin G.; Alison, Jennifer A. (2011-11-09). "Optimal intensity and type of leg exercise training for people with chronic obstructive pulmonary disease". doi:10.1002/14651858.CD008008.pub2.

44. McCarthy B ,Casey D; DevaneD; Murphy K; Murphy E; Lacasse,Y (23 February 2015). "Pulmonary rehabilitation for COPD" Cochrane Database Syst Rev 2. doi:10.1002/14651858.CD003793.pub3.

45. McNamara, Renae J.; McKeough, Zoe J.; McKenzie, David K.; Alison, Jennifer A. (2013-12-18). "Water-based exercise training for chronic obstructive pulmonary disease". The Cochrane Database of Systematic Reviews (12). doi:10.1002/14651858.CD008290.pub2.

46**.** Menadue, Collette; Piper, Amanda J; van 't Hul, Alex J; Wong, Keith K. (2014-05-14). "Non-invasive ventilation during exercise training for people with chronic obstructive pulmonary disease". The Cochrane Database of Systematic Reviews (5): CD007714. doi:10.1002/14651858.CD007714.pub2

47.Vestbo, Jørgen (2013) Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Global Initiative for COPD pp. 19–30

48. Cave, AC.; Hurst, MM. (May 2011). "The use of long acting β-agonists, alone or in combination with inhaled corticosteroids, in chronic obstructive pulmonary disease (COPD): a risk-benefit analysis". Pharmacol Ther. 130 (2) doi:10.1016/j.pharmthera.2010.12.008.

49.Spencer, S; Karner, C; Cates, CJ; Evans, DJ (Dec 7, 2011). Spencer, Sally, ed. "Inhaled corticosteroids versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease". Cochrane Database Syst Rev (12). doi:10.1002/14651858.CD007033.pub3.

50. Wang, J; Nie, B; Xiong, W; Xu, Y (April 2012). "Effect of long-acting beta-agonists on the frequency of COPD exacerbations: a meta-analysis". Journal of clinical pharmacy and therapeutics. doi:10.1111/j.1365-2710.2011.01285.x.

51. Geake, James B.; Dabscheck, Eli J.; Wood-Baker, Richard; Cates, Christopher J. (2015-01-10). "Indacaterol, a once-daily beta2-agonist, versus twice-daily beta□-agonists or placebo for chronic obstructive pulmonary disease". The Cochrane Database of Systematic Reviews. doi:10.1002/14651858.CD010139.pub2

52.Gartlehner G, Hansen RA, Carson SS, Lohr KN (2006). "Efficacy and Safety of Inhaled Corticosteroids in Patients With COPD: A Systematic Review and Meta-Analysis of Health Outcomes". doi:10.1370/afm.517.

53.Chinet, T; Dumoulin, J; Honore, I; Braun, JM; Couderc, LJ; Febvre, M; Mangiapan, G; Maurer, C; Serrier, P; Soyez, F; Terrioux, P; Jebrak, G (29 January 2016). "The place of inhaled corticosteroids in COPD" Revue des maladies respiratoires. PMID 26831345. doi:10.1016/j.rmr.2015.11.009.

54.Dong, YH; Lin, HH; Shau, WY; Wu, YC; Chang, CH; Lai, MS (January 2013). "Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: systematic review and mixed treatment comparison meta-analysis of randomised controlled trials." doi:10.1136/thoraxjnl-2012-201926.

55. Nannini, LJ; Poole, P; Milan, SJ; Kesterton, A (30 August 2013). "Combined corticosteroid and long-acting beta(2)-agonist versus inhaled corticosteroids alone for COPD.". Cochrane Database Syst Rev. 8: CD006826. PMID 23990350. doi:10.1002/14651858.CD006826.pub2

56. Vestbo, Jørgen (2013). "Diagnosis and Assessment"(PDF). Global Strategy for the Diagnosis, Management, and Prevention of COPD pp. 9–17

57.Qaseem Amir; Wilt TJ; Weinberger SE; Hanania NA; Criner G; Van Der Molen T; Marciniuk DD; Denberg T; Schünemann H; Wedzicha W; MacDonald, R; Shekelle P. Annals of Internal Medicine. 155 (3): 179–91. PMID 21810710. doi:10.7326/0003-4819-155-3-201108020-00008.

58. Siu, Albert L.; Bibbins-Domingo, Kirsten; Grossman, David C.; Davidson, Karina W.; Epling, John W.; García, Francisco A. R.; Gillman, Matthew; Kemper, Alex R.; Krist, Alex H.; Kurth, Ann E.; Landefeld, C. Seth; Mangione, Carol M.; Harper, Diane M.; Phillips, William R.; Phipps, Maureen G.; Pignone, Michael P. (5 April 2016). "Screening for COPD". JAMA. **315** (13): 1372. doi:10.1001/jama.2016.2638.

59. Young, Vincent B. (2010). Blueprints medicine (5th ed.). Wolters Kluwer Health/Lippincott Williams & Wilkins. p. 69. ISBN 978-0-7817-8870-0.

60. "COPD Assessment Test (CAT)". American Thoracic Society. Retrieved November 29,2013.

61. Simon, Michael R.; Chinchilli, Vernon M.; Phillips, Brenda R.; Sorkness, Christine A.; Lemanske Jr., Robert F.; Szefler, Stanley J.; Taussig, Lynn; Bacharier, Leonard B.; Morgan, Wayne (1 September 2010). "Forced expiratory flow between 25% and 75% of vital capacity and FEV1/forced vital capacity ratio in relation to clinical and physiological parameters in asthmatic children with normal FEV1 values". Journal of Allergy and Clinical Immunology. **126** (3): 527–534.e8. doi:10.1016/j.jaci.2010.05.016

62. Boswell-Smith, V; Spina, D (2007). "PDE4 inhibitors as potential therapeutic agents in the treatment of COPD-focus on roflumilast". International Journal of Chronic Obstructive Pulmonary Disease.

63.Herbert, C; Hettiaratchi, A; Webb, DC; Thomas, PS; Foster, PS; Kumar, RK (May 2008). "Suppression of cytokine expression by roflumilast and dexamethasone in a model of chronic asthma". Clinical & Experimental Allergy. 38 (5): 847–56. ISSN 1365-2222. PMID 18307529. doi:10.1111/j.1365-2222.2008.02950.x.

64.Hohlfeld, JM; Schoenfeld, K; Lavae-Mokhtari, M; Schaumann, F; Mueller, M; Bredenbroeker, D; Krug, N; Hermann, R (August 2008). "Roflumilast attenuates pulmonary inflammation upon segmental endotoxin challenge in healthy subjects:

a randomized placebo-controlled trial". Pulmonary Pharmacology & Therapeutics. doi:10.1016/j.pupt.2008.02.002.

65. Field, SK (May 2008). "Roflumilast: an oral, once-daily selective PDE-4 inhibitor for the management of COPD and asthma". Expert Opinion on Investigational Drugs doi:10.1517/13543784.17.5.811

66. Goodman and Gilman's The Pharmacological Basis of Therapeutics, 13th Edition

67. Basic and Clinical Pharmacology Bertram G. Katzung, 13th edition

68. Rang and Dale's Pharmacology 8th edition

69. Cheyne, Leanne; Irvin-Sellers, Melanie J.; White, John (2015-09-22). "Tiotropium versus ipratropium bromide for chronic obstructive pulmonary disease". The Cochrane Database of Systematic Reviews (9): doi:10.1002/14651858.CD009552.pub3

70. Rennard, Stephen (2013). Clinical management of chronic obstructive pulmonary disease (2nd ed.). Informa Healthcare. P23

71. Anita Sharma ; with a contribution by David Pitchforth ; forewords by Gail Richards; Barclay, Joyce (2010). COPD in primary care. Radcliffe Pub. p.9

72. Goldman, Lee (2012). Goldman's Cecil medicine (24th ed.). Elsevier/Saunders. p. 537

73. van Agteren, JE; Carson, KV; Tiong, LU; Smith, BJ (14 October 2016). "Lung volume reduction surgery for diffuse emphysema.". The Cochrane database of systematic reviews. doi:10.1002/14651858.CD001001.pub3

74. Vestbo J, Hurd SS, Agusti AG, et al. Global strategy for the diagnosis, management, and prevention of COPD: GOLD executive summary Crit Care Med 2013

75. Beghe B, Rabe KF, Fabbri LM. Phosphodiesterase-4 inhibitor therapy for lung diseases. Am J Respir Crit Care Med 2013; 188: 271–78.

76. Machines IB. IBM SPSS Statistics for Windows, Version 22.0. IBM Corp Armonk, NY; 2013.

77. 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

78. 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.

79. Kemp SV, Polkey MI, Shah PL. The epidemiology, etiology, clinical features, and natural history of emphysema. Thorac Surg Clin. 2009;19 (2): 149-58. doi:10.1016/j.thorsurg.2009.03.003

80. Roflumilast: a review of its use in the treatment of COPD Int J Chron Obstruct Pulmon Dis. 2016; 11: 81–90

81. Roflumilast : risk of suicidal behaviour
From:Medicines and Healthcare products Regulatory Agency 29 January 2013

82. 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.

83. Association of MMP -12 polymorphisms with severe COPD BMC Medicak genetics : Imran Haq 2010.

84.Antibiotic prevention of acute exacerbations of COPD, New England Journal of Medicine Jul 26, 2012 Richard P Wenzel

85. National Emphysema Treatment trial, New England Journal of Medicine 2003

86. Laënnec RTH. In: A treatise on the diseases of the chest (English translation from the French) Forbes J, editor. London: T and G Underwood; 1821.

87. Hutchinson J. On the capacity of the lungs, and on the respiratory functions, with a view of establishing a precise and easy method of detecting disease by the spirometer. Medico-Chirurgical Transactions (London) 1846;29:137–61.

88. History of COPD Treatment, Lung Institute, 23 Aug 2014.

ANNEXURES

INSTITUTIONAL ETHICS COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,
CHENNAI-10
Protocol ID. No. 1/2016 Dt: 11.02.2016
CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "A Prospective comparative study of effect of Roflumilast and its efficiency in reduction of exacerbations in COPD patients" - For Project Work submitted by Dr.D.Tamizh Vani, PG MD., (Pharmacology), Govt. Kilpauk Medical College, Chennai.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

DEAN,
Govt.Kilpauk Medical College,
Chennai – 10.

PC 2<ME I Section<Ethical Committee 1

Patient proforma

Name: Outpatient No.

Age: Sex:

Presenting complaints:

History of presenting illness:

Past history:

Family history:

Personal history:

General Examination:

Vital signs:

Systemic examination:

Investigations :

Complete blood count

Random Blood sugar level

 Serum Urea level

Serum Creatinie level

Chest X Ray

Lung function tests

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
FEV1						
FVC						
PEFR						

நோயாளி தகவல் தாள்

இந்த மாத்திரை பொதுவாக நாள்பட்ட நுரையீரல் அடைப்பு (COPD) வியாதிக்கான பராமரித்தல் சிகிச்சைக்காக மற்றும் நாட்பட்ட முச்சுக் குழாய் அழற்சி வியாதிக்காக உபயோகிக்கப்படுகிறது.

வயதானவர்களுக்கு ஏற்படும் இருமல், சளி, மூச்சிறைப்பு போன்ற காரணங்களுக்காக கொடுக்கப்படும்.

இந்த மாத்திரை தினமும் ஒன்று வீதம் தன்னீருடன் விழுங்க வேண்டும், மேலும் இந்த மாத்திரையை தினமும் குறிப்பிட்ட ஓரே நேரத்தில் பல வாரங்களுக்கு குறைந்தபட்சம் ஆறு மாதகாலத்திற்கு எடுத்துக் கொண்டால், நல்ல பலன் கிடைக்கும் இதை சாப்பிடு வதற்கு முன்போ அல்லது பின்போ உட்கொள்ளலாம்

Patient Information sheet in English

This tablet is prescribed for Chronic Obstructive Pulmonary Disease which comprises of increase in cough, breathlessness, and sputum production for a long period of time. This tablet should be taken at the most for 6 months to obtain benefit from the disease. The tablet 0f 500 micro gram should be taken orally, once daily. It can be taken before food or after food.

Patient consent form in Tamil

நோயாளி ஒப்புதல் படிவம்

ஆராய்ச்சியின் விவரம்:

ஆராய்ச்சி மையம்:

நோயாளியின் பெயர்:   நோயாளியின் வயது:

பதிவு எண்:

நோயாளி கீழ்கண்டவற்றுள் கட்டங்களை (✓) செய்யவும்

1. மேற்குறிப்பிட்டுள்ள ஆராய்ச்சியின் நோக்கத்தையும் பயனையும் முழுவதுமாக புரிந்துகொண்டேன். மேலும் எனது அனைத்து சந்தேகங்களையும் கேட்டு அதற்கான விளக்கங்களையும் தெளிவுபடுத்திக் கொண்டேன். ☐

2. மேலும் இந்த ஆராய்ச்சிக்கு எனது சொந்த விருப்பத்தின் பேரில் பங்கேற்கிறேன் என்றும், மேலும் எந்த நேரத்திலும் எவ்வித முன்னறிவிப்புமின்றி இந்த ஆராய்ச்சியிலிருந்து விலக முழுமையான உரிமை உள்ளதையும், இதற்கு எவ்வித சட்ட பிணைப்பும் இல்லை என்பதையும் அறிவேன். ☐

3. ஆராய்ச்சியாளரோ, ஆராய்ச்சி உதவியாளரோ, ஆராய்ச்சி உபயத்தாரோ, ஆராய்ச்சி பேராசிரியரோ, ஒழுங்குநெறி செயற்குழு உறுப்பினர்களோ எப்போது வேண்டுமானாலும் எனது அனுமதியின்றி எனது உள்நோயாளி பதிவுகளை இந்த ஆராய்ச்சிக்காகவோ அல்லது எதிர்கால பிற ஆராய்ச்சிகளுக்காகவோ பயன்படுத்திக்கொள்ளலாம் என்றும், மேலும் இந்த நிபந்தனை நான் இவ்வாராய்ச்சியிலிருந்து விலகினாலும் தகும் என்றும் ஒப்புக்கொள்கிறேன். ஆயினும் எனது அடையாளம் சம்பந்தப்பட்ட எந்த பதிவுகளும் (சட்டபூர்வமான தேவைகள் தவிர) வெளியிடப்படமாட்டாது என்ற உறுதிமொழியின் பெயரில் இந்த ஆராய்ச்சியிலிருந்து கிடைக்கப்பெறும் முடிவுகளை வெளியிட மறுப்பு தெறிவிக்கமாட்டேன் என்று உறுதியளிக்கின்றேன். ☐

4. இந்த ஆராய்ச்சிக்கு நான் முழுமனதுடன் சம்மதிக்கின்றேன் என்றும் மேலும் ஆராய்ச்சிக் குழுவினர் எனக்கு அளிக்கும் அறிவுரைகளை தவறாது பின்பற்றுவேன் என்றும் இந்த ஆராய்ச்சி காலம் முழுவதும் எனது உடல் நிலையில் ஏதேனும் மாற்றமோ அல்லது எதிர்பாராத பாதகமான விளைவோ எற்படுமாயின் உடனடியாக ஆராய்ச்சி குழுவினரை அணுகுவேன் என்றும் உறுதியளிக்கின்றேன். ☐

5. இந்த ஆராய்ச்சிக்குத் தேவைப்படும் அனைத்து மருத்துவப் பரிசோதனைகளுக்கும் ஒத்துழைப்பு தருவேன் என்று உறுதியளிக்கின்றேன். ☐

6. இந்த ஆராய்ச்சிக்கு யாருடைய வற்புருத்தலுமின்றி எனது சொந்த விருப்பத்தின் பேரிலும் சுயஅறிவுடனும் முழுமனதுடனும் சம்மதிக்கின்றேன் என்று இதன் மூலம் ஒப்புக்கொள்கிறேன். ☐

நோயாளியின் கையொப்பம் / பெருவிரல் கைரேகை   ஆராய்ச்சியாளரின் கையொப்பம்

இடம்:   தேதி:

Patient consent form in English

Name of the Participant:

Name of the Principal Investigator:

Name of the Institution:

Documentation of the informed consent:

I _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in :

1. I have read and understood this consent form and the information provided to me.

2. I have had the consent document explained to me.

3. I have been explained about the nature of the study.

4. I have been explained about my rights and responsibilities by the investigator.

5. I have been informed the investigator of all the treatments I am taking or have taken in the past _____ months including any native (alternative) treatment.

6. I have been advised about the risks associated with my participation in this study.

7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms.

8. I have not participated in any research study within the past_____month(s).

9. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital.

10. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent.

12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.

13. I have understood that my identity will be kept confidential if my data are publicly presented.

14. I have had my questions answered to my satisfaction.

15. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

Name and signature / thumb impression of the participant (or legal representative if participant incompetent)

Name _____ Signature_____

Date_____

 Name and Signature of the investigator or his representative obtaining consent:

Name _____ Signature_____

Date_____

Plagiarism certificate

URKUND

Document: Introduction.docx (D30296074)
Submitted: 2017-08-30 20:54 (+05:0-30)
Submitted by: D.Thamizh Vani (thamizhvani007@gmail.com)
Receiver: thamizhvani007.mgrmu@analysis.urkund.com
Message: Show full message

14% of this approx. 36 pages long document consists of text present in 1 sources.

Rank	Path/Filename
	Introduction.docx
Alternative sources	
	http://www.file.ptools.ir/harrison/Harrison_2377.pdf
	http://slideplayer.com/slide/6168225/
	http://med.mui.ac.ir/clinical/orJanc/COPD.ppt
	http://www.ssu.ac.ir/cms/fileadmin/user_upload/Moavenatha/MBehdashti/TebKar/Power_points/COPD.pptx
	Titel2.docx
	GOLD COPD Pocket-Guide-20162.pdf
	https://www.slideshare.net/BismvJoseph/copdbiz

1 Warnings   Reset   Export   Share

Introduction

Chronic obstructive pulmonary disease (COPD) is a type of obstructive lung disease which is characterised by poor air flow for a long term. It lasts for years and can be present lifelong. The disease makes it hard for the person to breathe. 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 [27,28]. Prevalence of COPD in India accounts to about 30 million people [2]. It occurs in people above 40 years old i.e. 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. COPD is the cause of about 2.9 million deaths every year and this number is progressing every year [2]. It forms the third leading cause of death in the world. Low and middle income countries contribute to the burden of deaths due to COPD. In India, mortality due to COPD occurs in 102.3/100,000. In the world COPD contributes to 6740,000 DALYs out of 27,756,000 [2]. The disease thus 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]. Likelihood of developing COPD increases with the overall exposure of smoke. Bidi smokers were at higher risk of developing COPD than those who smoked cigarettes [4]. Other types of smoke like marijuana, cigar, water pipe smoke are also risk factors. Cooking fuel, kerosene, biomass fuel, firewood also contributed to the development of disease. Poorly ventilated cooking fires leads to indoor air pollution and is the common cause of disease in developing countries. Second hand smoke is the cause of COPD in about 20% of cases [5]. Second hand smoke is also called environmental tobacco smoke. It is a combination of two forms of smoke that is formed due to burning of tobacco – 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. 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. People who live in large cities have a higher rate of developing COPD as compared to people living in rural areas. Genetic factor plays a small role in development of COPD. Alpha 1-antitrypsin deficiency is the only clearly inherited risk factor [6]. This contributes to about 1 – 5% of cases. Acute exacerbation of COPD is defined as increased shortness of breath, cough, and production

of

sputum in a patient diagnosed with COPD. There is sudden worsening of symptoms. It is triggered by infection, environmental pollutants, and cold temperature. Those with severe disease have more frequent exacerbations. Lung function deteriorates at a faster rate [7,8,9,10]. Diagnosis of COPD is done using Spirometer in persons presenting with the clinical symptoms. Spirometry determines the severity of airflow limitation [12,13,14]. The current treatment modalities available for COPD are inhaled bronchodilators which is the primary medication. The two major types are beta2 agonists and anticholinergics. Both long acting and short acting forms are available [15]. In mild disease, short acting form is recommended whereas long acting form is used in severe disease and in maintenance therapy [16]. They reduce shortness of breath and exercise limitation and result in an improved quality of life. If these drugs are ineffective, then corticosteroids are added [17]. Methylxanthines are used as a second line agent if not controlled by other measures [18]. 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 [19]. Reducing risk factors like stopping smoking is a must. Pulmonary rehabilitation which

Urkund Analysis Result

Sources included in the report:

Titel2.docx (D20250824)
1-s2.0-S0954611111000540-main.pdf (D11569893)
Paper 3 Roflumilast Increases Bacterial Load and Dissemination in a Model of Pseudomononas
Aeruginosa Airway Infection.pdf (D25107559)
http://www.rxlist.com/daliresp-drug.htm
http://accessmedicine.mhmedical.com/content.aspx?
sectionid=79745089&bookid=1130&jumpsectionID=79745089
http://www.ssu.ac.ir/cms/fileadmin/user_upload/Moavenatha/MBehdashti/TebKar/Power_points/
COPD.pptx
https://cld.pt/dl/download/0eb230b8-5ca8-422e-9a33-3c54d6d5822f/FMUC/6%C2%BA%20Ano/
Harrison/03%20-%20Altera%C3%A7%C3%B5es%2018E%20vs%2019E/Pneumologia/dpoc.pdf
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3212861/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3085868/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2915539/
https://doi.org/10.2147/COPD.S5237
https://doi.org/10.1016/j.hgmx.2015.09.001
b31a77d9-44e8-41df-a99e-7685aa1551f6