EFFICACY AND SAFETY OF LONG ACTING BETA AGONIST/LONG ACTING MUSCARINIC ANTAGONIST/INHALED CORTICOSTEROID ALONG WITH ROSUVASTATIN IN MODERATE TO SEVERE COPD PATIENTS

Dissertation submitted to

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GOVT.STANLEY MEDICAL COLLEGE & HOSPITAL

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI-TAMILNADU

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CERTIFICATE

This is to certify that this dissertation entitled "**Efficacy and safety of long acting beta agonist/long acting muscarinic antagonist/inhaled corticosteroid along with Rosuvastatin in moderate to severe COPD patients**" by the candidate **Dr.G.Vanitha**, for **M.D. (Pharmacology)** is a bonafide record of the research work done by her under guidance of **Dr.R.Sivagami, M.D.**, Associate Professor , Department of Pharmacology, Government Stanley Medical College, during the period of study (2017-2020), in the Department of Pharmacology, Government Stanley Medical College, Chennai-1.

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DECLARATION

I hereby declare that this dissertation entitled in "**Efficacy and safety of long acting beta agonist/long acting muscarinic antagonist/inhaled corticosteroid along with Rosuvastatin in moderate to severe COPD patients**" was written by me in the Department of Pharmacology, Government Stanley Medical College and Hospital, Chennai under the guidance and supervision of **Dr.R.Sivagami, M.D.**,Associate Professor, Department of Pharmacology, Government Stanley Medical College, Chennai-1.

This dissertation is submitted to The Tamilnadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the university regulations for the award of Degree of **M.D., Pharmacology** (Branch VI) Examination to be held in May 2020.

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CERTIFICATE II

This is to certify that this dissertation work titled "**Efficacy and safety of long acting beta agonist/long acting muscarinic antagonist/inhaled corticosteroid along with Rosuvastatin in moderate to severe COPD patients** " of the candidate **Dr.G.Vanitha** with registration number **201716052** for the award of **M.D., Pharmacology** in the branch of **VI**. I personally verified the *urkund.com* website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **3** percentage of plagiarism in the dissertation

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PRINCIPAL INVESTIGATOR : DR. G. VANITHA

DESIGNATION : PG IN MD PHARMACOLOGY,

DEPARTMENT : DEPARTMENT OF PHARMACOLOGY, GOVT. STANLEY MEDICAL COLLEGE.

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 21.12.2017 at the Council Hall, Stanley Medical College, Chennai-1 at 10am.

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator. .

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CONTENTS

ABBREVIATIONS

COPD-Chronic obstructive pulmonary disease

GOLD-Global Initiative for Chronic Obstructive Lung Disease

FEV1-Forced Expiratory Voume in 1second

FVC-Forced Vital Capacity

PEFR-Peak Expiratory Flow Rate

DALY-disability-adjusted life-years

hs-CRP-High sensitive C reactive protein

eNOs-endothelial nitric oxide synthase

MRC-modified Medical Research Council

SGRQ-The St George's Respiratory Questionnaire .

HRCT-High- Resoloution computed tomography

DLCO-Diffusing capacity for carbon monoxide .

NRF2-Nuclear factor erythroid2-related factor

SOD3- Extracellular Superoxide dismutase

MMP-12 matrix metalloproteinase-12

RTP801-The stress induced proteins

HHIP-Hedgehog interacting protein

CVD-Cardiovascular disease

CRP-C reactive protein

BODE-Body mass index,Degree of airflow Obstruction,Dyspnea,Exercise capacity

LAMA-Long actin muscarnic antagonist

LABA-Long acting beta agonist

SABA-Short acting beta agonist

ICS-Inhaled cortico steroid

NIPPV-Noninvasive positive-pressure ventilation .

HoFH -Homozygous Familial Hypercholesterolemia

ACC/AHA-American college of cardiology and American heart association

ASCVD-Athersclerrotic cardio vascular disease

HeFH-Heterozygous familial Hypercholesterolemia

AST- Aspartate aminotransferase

CPK - creatine phosphokinase

Hb-Haemoglobin

CCQ-Clinical COPD Questionnaire

SD-Standard deviation

Max-Maximum

Min-Minimum

INTRODUCTION

INTRODUCTION

Chronic obstructive pulmonary disease is a common preventable and treatable illness. It is characterized by persistent airflow restriction that is usually progressive and linked with chronic inflammatory response in the airway and the lung to toxic particles and gases. Exacerbations and co morbidity contribute to over all severity in individual patient[1]. Chronic obstructive pulmonary disease(COPD) occurs as a result of the combined effects of smoking exposure and genetic susceptibility to the damaging effects of smoking.

The disease is characterised by progressive, minimally reversible airflow limitation that results from varying combinations of lung parenchymal destruction and fixed small airways disease from smooth muscle hypertrophy and airway fibrosis[2-4] . COPD is also a systemic disease with progressive muscle wasting of the skeletal and respiratory system, which further limits exercise capacity[5-7].Systemic manifestations of COPD include coronary artery disease (CAD), osteoporosis and anemia[5-8]. Although goblet cell hyperplasia and excessive mucus production are also clinical manifestations in COPD they do not appear to be associated with poor outcomes in COPD, unlike reduced expiratory volumes and systemic inflammation . COPD, characterized by long-term poorly irreversible airway limitation and persistent respiratory symptoms, is a common and preventable disease [9].

Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines give three criteria which are needed to diagnose the disease

- A post-bronchodilator FEV1:FVC

ratio of less than 70%,

- Appropriate symptoms like dyspnea, sputum production,

chronic cough, or wheezing,

- Significant exposures to toxic environmental stimuli[10]

This disorder has at least three phenotypes: emphysema, chronic bronchitis, and small airway remodelling and obstruction[11] and environmental and inherent factors are involved in the pathogenesis and development of the disease.

Smoking is main cause of the disease, whereas only 10–20% of smokers develop COPD [12] and approximately 25–45% of incidence of COPD is attributed to non smoking risk.[13](The Global Burden of Disease study 2017)[14]

COPD attributed to active smoking, ambient particulate matter pollution, job-related particulate matter/gases/fumes, ambient ozone contamination, household air pollution from solid fuels, second hand smoke, and lead contact was responsible for about 3.46 million of global all-age deaths and 79.78 million of disability-adjusted life-years (DALYs) in 2017. Active smoking and ambient particulate matter pollution were the main causes of deaths and DALYs for COPD .

Although the global age-standardized mortality rates and DALY rates for COPD attributing to each of the above risk factors between 2007 and 2017 was reduced, this epidemical tendency forecasting is not optimistic as the growth and aging of population. It is the fourth important cause of death globally and will become the third leading cause of death by the year 2030. [15]

The GOLD document state that "COPD is a common, preventable and treatable disease that is defined by constant respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities, usually caused by significant exposure to noxious particles or gases[16,17] In 2017 revision GOLD had revised the definition of COPD to include "persistent respiratory symptoms" as an essential feature; however, the reasoning behind this has not been provided and the definition is carried through into the current version[18]

Statins inhibit HMG-CO A (3-hydroxy-3-methyl glutaryl coenzyme A reductase) It is strong inhibitors of cholesterol biosynthesis and have greatly enhanced the management of coronary artery disease. current studies data suggest that Direct antithrombotic and anti-inflammatory property of statins related at least partly related for the decline of cardiovascular events. statins reduce high sensitive C reactive protein (hs-CRP), tumour necrosis factor (TNF) and metalloproteinase 9 production. [21]

Statins are now becoming accepted as powerful anti inflammatory agents that have favorable effects beyond low-density lipoprotein cholesterol reduction(LDL). Up regulation of endothelial function especially endothelial

nitric oxide synthase (eNOS enzyme activity) is thought to be a major mechanism accountable for these anti inflammatory properties.Prufer.et.al[22] give more information that statins decrease inflammation. It also has cardiovascular protective action[23]

Recent data suggest that statins can transform the balance of T helper subset 1 (Th 1) and 2 (Th 2) cells by inhibition of Th1 improvement through augmentation of Th 2 development of CD4+ T cells[24] .H.Yang et al observed a relation between statin use and occurrence of an abnormal Th1 subset of T lymphocytes, CD4 +CD28 null which often expanded in unstable angina [25]. We aimed in this study to assess anti inflammatory effects of statin in COPD patients.

REVIEW OF LITERATURE

Chronic obstructive pulmonary disease (COPD) is defined as a preventable and treatable disorder defined by persistent airflow restriction .It is usually progressive and associated with an enhanced chronic inflammatory response in the airway and the lung to noxious particles or gases[26] .

COPD which is considered an inflammatory disease with pulmonary and systemic components, is predominantly found in patients with a history of cigarette smoking and has an enormous and increasing global health impact [28] COPD is defined as a modifiable and treatable disease [29, 30]. Nevertheless, apart from long-term oxygen treatment in COPD patients with severe hypoxaemia and smoking cessation in patients with mild-to-moderate lung function impairment, to date, no treatment has convincingly been able to influence the accelerated lung function decline or increased mortality characterising this disease [31].

[27] common associated clinical disease associated with COPD is chronic bronchitis which is characterized by chronic cough and sputum production present in about one out of three people with early COPD. When chronic mucus hyper secretion is associated with airflow obstruction, it is often called chronic obstructive bronchitis. Patients with COPD also have small and medium size airway with inflammation, narrowing, tortuosity and fibrosis that contributes to the airflow limitation individuals are often classified as having chronic asthmatic bronchitis and tend to have a some better prognosis for survival than those with typical tobacco-related COPD.

The clinical course of COPD, determined as a continuous excessive loss of ventilator capacity is an important and well-established outcome measure. The long-term benefit of sustained and to a lesser extent, intermittent smoking cessation as regards forced expiratory volume in one second (FEV1) in patients with mild-to-moderate COPD has been convincingly demonstrated.

PATHOPHYSIOLOGY :

COPD has both pulmonary and systemic components . The presence of airflow limitation combined with premature airway closure leads to gas trapping and hyperinflation, adversely affecting pulmonary and chest wall compliance. Pulmonary hyperinflation also results, which flattens the diaphragmatic muscles and leads to an increasingly horizontal alignment of the inter costal muscles, placing the respiratory muscles at a mechanical disadvantage. The work of breathing is therefore markedly increased first on exercise, when the time for expiration is further reduced, but then as the disease advances even at rest.

ENVIRONMENTAL FACTORS:

1. Tobacco smoke: accounts for 95% of cases in the UK
2. Indoor air pollution: cooking with biomass fuels in confined areas in developing countries
3. Occupational exposures, such as coal dust, silica and cadmium

4. Low birth weight: may reduce maximally attained lung fun young adult life

5. Lung growth: childhood infections or maternal smoking may affect growth of the lungs during childhood, resulting in a lower maximally attained lung function in adult life

6.Infections: recurrent infection may accelerate decline in FEV1; and persistence of adenovirus in lung tissue may alter local inflammatory response, predisposing to lung damage; HIV infection is associated with emphysema

7. Low socioeconomic status

8. Cannabis smoking

HOST FACTORS:

(a). Genetic factors: α1-antitrypsin deficiency; other COPD susceptibility genes are likely to be identified

(b). Air way hyper-reactivity

Breathlessness grading related to activities

0 -No breathlessness, except for strenuous exercise

1- Breathlessness when hurrying on the level or walking up a slight hill

2- Walks slower than age group on level ground because of breathlessness or has to stop for breath when walking at own pace

3- Stops for breath after walking about hundred meter or after a few minutes on level ground

4- Too breathless to leave the house, or breathless when dressing or undressing.

CLINICAL FEATURES:

COPD should be suspected in any patient over the age of 40 years who presents with symptoms of chronic bronchitis and/or breathlessness. Depending on the presentation, important differential diagnoses include Chronic asthma, Tuberculosis, Bronchiectasis and Congestive cardiac failure. Cough and associated sputum production are usually the first symptoms, and are often referred to as a 'smoker's cough'. Haemoptysis may complicate exacerbations of COPD but should not be attributed to COPD without thorough investigation.

Breathlessness usually prompts presentation to a health professional. The level should be quantified for future reference, often by documenting what the patient can manage before stopping; scales such as the modified Medical Research Council (MRC) dyspnoea scale may be useful. In advanced disease, enquiry should be made as to the presence of oedema (which may be seen for the first time during an exacerbation and morning headaches (which may suggest hypercapnia).

Physical signs are non-specific, correlate poorly with lung function, and are seldom obvious until the disease is advanced. Breath sounds are typically quiet, crackles may accompany infection but, if persistent, raise the possibility of bronchiectasis. Finger clubbing is not a feature of COPD and should trigger further investigation for lung cancer or fibrosis.

Right heart failure may develop in patients with advanced COPD, particularly if there is coexisting sleep apnoea or thrombo embolic disease (‘cor pulmonale’). However, even in the absence of heart failure, COPD patients often have pitting oedema from salt and water retention caused by renal hypoxia and hyper capnia. The term ‘cor pulmonale’ is a misnomer in such patients, as they do not have heart failure. Fatigue, anorexia and weight loss may point to the development of lung cancer or tuberculosis, but are common in patients with severe COPD and the body mass index (BMI) is of prognostic significance.

Depression also common and contribute to morbidity. Two classical phenotypes have been described: ‘pink puffers’ and ‘blue bloaters’. The former are typically thin and breathless, and maintain a normal PaCO2 until the late stage of disease. The latter develop (or tolerate) hypercapnia earlier and may develop oedema and secondary polycythaemia. In practice, these phenotypes often overlap.

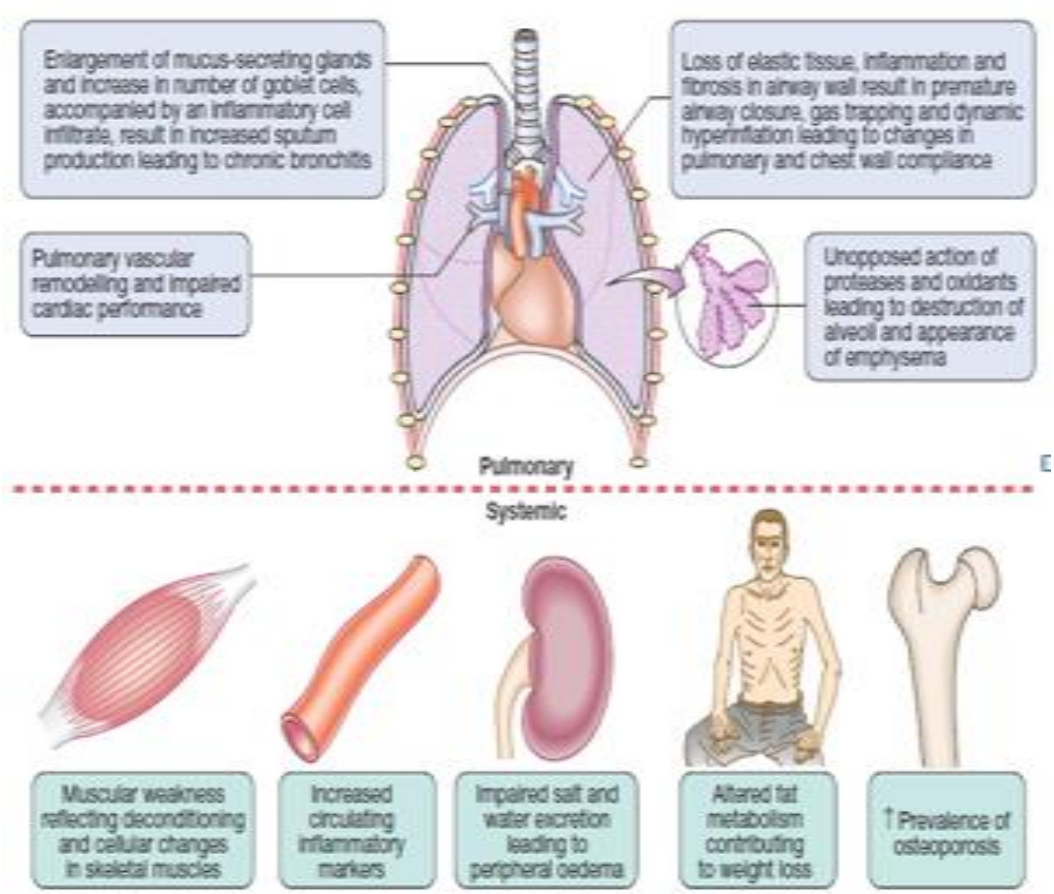

Figure -1.

INVESTIGATIONS:

Although there are no reliable radiographic signs that correlate with the severity of airflow limitation, a chest X-ray is essential to identify alternative diagnoses such as cardiac failure, other complications of smoking such as lung cancer, and the presence of bullae. A blood count is useful to exclude anaemia or document polycythaemia, and in younger patients with predominantly basal emphysema α1-antitrypsin should be assayed. The diagnosis requires objective demonstration of airflow obstruction by spirometry and is established when the post bronchodilator FEV1/FVC is < 70%.

The severity of COPD may be defined in relation to the post-bronchodilator FEV1 . Measurement of lung volumes provide an assessment of hyperinflation. This is generally performed by helium dilution technique However, in patients with severe COPD, and in particular large bullae, body plethysmography is preferred because the use of helium may under-estimate lung volumes.

The presence of emphysema is suggested by a low gas transfer . Exercise tests provide an objective assessment of exercise tolerance and provide a baseline on which to judge the response to bronchodilator therapy or rehabilitation programmes; they may also be valuable when assessing prognosis. Pulse oximetry may prompt referral for a domiciliary oxygen assessment if less than 93%. The assessment of health status by the St George's Respiratory Questionnaire (SGRQ) is commonly used for research.

In practice, the COPD Assessment Test and the COPD Control Questionnaire are easier to administer characterisation and quantification of emphysema and is more sensitive than the chest X-ray at detecting bullae. It is also used to guide lung volume reduction surgery.

Assessment of severity:

The severity of COPD has traditionally been defined in relation to the FEV1% predicted. However, assessing the impact of COPD on individual patients in terms of the symptoms and limitations in activity that they experience and whether they suffer frequent or significant exacerbations may provide a more clinically relevant assessment and help guide

management.HRCT is likely to play an increasing role in the assessment of COPD, as it allows the detection, smokers, and cessation remains the only strategy that impacts favourably on the natural history of COPD.

Complete cessation is accompanied by an improvement in lung function and deceleration in the rate of FEV1 decline . In regions where the indoor burning of biomass fuels is important, the introduction of non-smoking cooking devices or alternative fuels should be encouraged.

Spirometry is an significant diagnosis and classification method based on the severity of airflow restriction in COPD patients. Though, spirometric measures of airflow limitation do not completely reflect the complex pathological and physiological disturbances of mild COPD.

The small airways less than 2 mm in diameter are known as the main sites of airway obstruction in COPD.[32,34] It has been demonstrated that pathologic abnormalities in the small airways include a thickening of the airway wall, inflammatory immune cells infiltration into the wall tissue, and narrowing of the small airway lumen by inflammatory mucous exudates, are the main reasons for airway obstruction in COPD patients with mild airflow restriction.Deesomchok et al[33] noted that the residual volume, functional residual capacity, and total lung capacity were considerably higher than the predicted values in GOLD stage 1, which confirmed the existence of lung hyperinflation.

The presence of an increased residual capacity illustrated improved air trapping because of enhanced airway closure during expiration.[35] earlier

studies showed that a decline in the lung diffusing capacity for carbon monoxide (DLCO) was found in many number of COPD patients with mild airflow restriction compared with controls. [35-38] In addition 20% of the GOLD stage 1 subgroup had DLCO<70% of that predicted, which may recommend that the surface area of gas exchange was abnormal.

[35] In mild COPD patients there is evidence that ventilation–perfusion mismatch and an raised alveolar–arterial oxygen pressure grade develop .[36-39] In the study by Rodriguez-Roisin et al,[39] the alveolar–arterial oxygen tension gradient and ventilation–perfusion disparity were clearly atypical in GOLD stage 1, but t changes throughout GOLD stages 1-4 were moderate, signifying that perfusion heterogeneity had a better role than airflow inadequacy in the early period of COPD development. Considerable abnormalities in the pulmonary micro vascular blood flow also identified in mild COPD patients.

[40] MESA COPD Study indicated that pulmonary micro vascular blood flow reduced in mild COPD in both emphysematous and Non emphysematous lung regions which may demonstrate an pathological increase procedure from small airway disease.

[41] Smokers have earlier been described as GOLD stage 0 “at risk” for COPD,[42] of which 42% had radiological proof of emphysema or airway disease.

[43] Meanwhile, extensive small airway inflammation has been described in smokers at risk for COPD, showing increased airway infiltration of

Polymorphonuclear neutrophils, eosinophils, macrophages,CD4 cells, CD8 cells, and B cells. Moreover, there was no significant difference in the extent of airway inflammation between smokers at risk for COPD and mild COPD.[44]

■INFLAMMATION AND EXTRACELLULAR MATRIX PROTEOLYSIS

Elastin, the main component of elastic fibers, is a highly stable component of the extracellular matrix that is significant to the integrity of the lung. The elastase:antielastase hypothesis state that the equilibrium between elastin degrading enzymes and their inhibitors determines the vulnerability of the lung to damage resulting in air space enlargement.

This theory was based on the clinical surveillance that patients with inherited deficiency in α1 antitrypsin (α1AT) which inhibit the serine proteinase neutrophil elastase ,were at enhanced risk of emphysema and that instillation of elastases, as well as neutrophil elastase, into experimental animals, outcome in emphysema.

A compound network of immune and inflammatory cells and proteinases that lead to emphysema has consequently been recognized. Lung macrophages and epithelial cells get activated when they are exposed to oxidants from smoking and produce proteinases and chemokines which attract other inflammatory and immune cells.

Oxidative stress is a key component of COPD pathobiology; the transcription factor NRF2, a major regulator of oxidant-antioxidant balance, and SOD3, a potent antioxidant, have been implicated in emphysema

pathogenesis by animal models. Mitochondrial dysfunction in COPD may worsen oxidative stress.

One method of macrophage activation occurs through oxidant-induced inactivation of histone deacetylase-2 (HDAC2), shifting the equilibrium toward acetylated / loose chromatin, exposing nuclear factor-kappa B (NF-Kb)sites, and resulting in copy of matrix metalloproteinases and proinflammatory cytokines like interleukin 8 (IL-8) and tumor necrosis factor α (TNF-α).It leads to neutrophil activation. CD8+ T cells are recruited in response to cigarette smoke and liberate interferon-inducible protein-10 which in turn leads to macrophage production of macrophage elastase called matrix metalloproteinase-12 [MMP-12]).

Matrix metalloproteinases and serine proteinases, particularly neutrophil elastase, work collectively by degrading the inhibitor of the other, leading to lung damage. Elastin degradation and disordered repair are thought to be primary mechanisms in the development of emphysema. Some data explained that autoimmune mechanisms may advance the sequence of disease. In advanced COPD patients there is increased number of B cells and lymphoid follicles are present around the airways .

IgG auto antibodies which cause cytotoxicity to pulmonary epithelium have been detected. Loss of cilia in the airway epithelium due to cigarette smoke cause impaired macrophage phagocytosis predispose to bacterial infection with neutrophilia.

In advanced lung disease, after prolonged period of smoking cessation, there remains an exuberant inflammatory reaction, signifying that inflammation induced by cigarette smoking initiates the disease and, in vulnerable individuals establishes a persistent process of cell death .Cigarette smoke oxidant-mediated structural cell death occurs via a variety of mechanisms as well as excessive ceramide production and Rtp801 inhibition of mammalian target of rapamycin (mTOR) leading to cell loss ,inflammation and proteolysis.

Association of mTOR and other senescence markers has led to the thought that emphysema resembles early aging of the lung parenchyma. Heterozygous gene targeting of one of the leading genetic determinants of COPD identified by genome-wide association studies (GWAS), hedgehog interacting protein (HHIP) in a murine model leads to aging related emphysema.

The ability of the adult lung to replace lost smaller airways and microvasculature and to repair damaged alveoli appears limited. Uptake of apoptotic cells by macrophages normally results in production of growth factors and dampens inflammation, promoting lung repair.

Cigarette smoking impair macrophage mediated uptake of apoptotic cells .It also prevents cell repair. Study by Fletcher and Peto recommended that depending on COPD severity the rate of decline in FEV1 accelerated, [45] current studies showed that the yearly FEV1 decrease in patients with Chronic obstructive pulmonary disease in GOLD stage 2 was improved than those in

GOLD stages 3 and4.[46–48] Tantucci and Modina[46] stated that in large COPD patients the mean decline rate of FEV1 in

GOLD stage 2 was between [47] and 79 mL/year, whereas the corresponding person number in GOLD stages 3 and 4 was between 56 and 59 mL/year and lesser than 35mL/year respectively.

Bhatt et al[49] demonstrated that the rate of FEV1 decline was maximum in mild COPD in a population of present and previous smokers. Those with GOLD stage1 had the most rapid rate of FEV1 decline of 53.8 (57.1) mL/year compared to 45.6 (61.1) mL/year, 31.6 (43.6) mL/year, and 5.1 (35.8) mL/year for GOLD stages from 2 to 4 respectively, indicating progressively slower rates of decline with increasing GOLD stages.[49]

Thus, the reduction in pulmonary function, assessed as expiratory airflow decline, seemed to occur mostly in the early course of the illness.

To delay the sequence of the disease early stage intervention can be favorable in chronic obstructive pulmonary disease. In the most of the COPD patients it is usually progressive, as lung function deteriorates over time simultaneously with age-related decline in FEV1.[45] Opposite to earlier reports, the 3-year ECLIPSE study found that the rate of decline in FEV1 was highly variable in COPD patients, and in more than half of the patients, the rate of decline in FEV1 was no higher than that which has been observed in the healthy control group. These outcomes indicated that COPD was not consistently progressive.[48]

Likewise, a further large longitudinal cohort confirmed that an accelerated decline in FEV1 was not an important characteristic of COPD.[50]

Worldwide Three hundred and eighty million people were affected by Chronic obstructive pulmonary disease .The data state that among them twelve percent of adults were over 30 years of age. The occurrence of this disease is rapidly increasing, and it will be the third cause of death worldwide in the year 2020[51,52]. The Co morbid condition associated with COPD is cardiovascular disease (CVD).[53,54]. Pulmonary hypertension (PH) is one of the most essential functional derangements in these patients. It leads to poor prognosis due to chronic hypoxia and loss of vascular bed from emphysematous destruction [55,56]

The significance of CVD and other co morbidities in COPD is such that all the cause of mortality has largely become the most applicable metric for outcomes in patients [57]. Localized chronic inflammation of the airways has long been observed in this disease. There is a emergent understanding of systemic inflammation in subset of COPD patients [58,59]

Particularly high levels of CRP and IL-6 have been related with poor outcomes in COPD [60, 61]. Apart from treatment for dyslipedemia and benefit for CVD as cholesterol lowering drug, it also been studied in a diversity of other disease states, including dementia, contrast-induced nephropathy, and erectile dysfunction and COPD over the past decade [62, 63]. The anti-inflammatory actions that alter the immune system and decrease

inflammatory markers like CRP and IL-6 are gradually being discovered [61,64].

Systematic reviews earlier to 2017 have been recommended that statins are associated with a valuable role in treatment of COPD [65–67], it including reduce all-cause mortality, cause-specific mortality and Pulmonary hypertension. Li et al. investigate which including twenty studies . [66] statins decreased all-cause mortality and COPD exacerbation.. Zhang et al. study including 6 RCTS with both COPD and Pulmonary hypertension patients found statin therapy was associated with improved 6-min walk test (6 MW) and reduced PH. But there was no observed difference in all cause mortality [67].

Statins can reduce inflammation and PH or not remains controversial [67, 68].Current national and international guidelines for the management of patients with chronic obstructive pulmonary disease suggest that maintenance therapy with inhaled long-acting bronchodilators (long-acting β2-adrenergic agonists [LABAs] and long-acting muscarinic antagonists [LAMAs]), inhaled corticosteroids (ICSs) including glucocorticoids, and their combinations (usuallyLABA/ICS in one single inhaler at fixed dose) for the treatment of moderate-to-severe disease.[69-73.] In addition,patients with COPD may experience exacerbations requiring short-term treatment with systemic corticosteroids.[70]

COPD is one of the most important global health problems.[69-70] COPD is characterised by exacerbations, and these exacerbations constitute key

events in COPD progression, prognosis and treatment.[71-73] In recent years there has been a growing body of evidence suggesting systemic inflammation as a key element in the pathogenesis of COPD.[73,74] As a result, there is an increasing focus on whether use of medications that reduce markers of systemic inflammation may also reduce the risk of exacerbations in COPD.[75]

Statins have effects besides a lowering of plasma cholesterol, including antiinflammatory effects which have been investigated in several studies[76,77]. Studies have also shown that statin use has beneficial effects on cardiovascular outcomes, possibly by reduction of C reactive protein (CRP) levels.[78 ,79] In COPD, pharmaceutical database studies have indicated a possible beneficial effect of statin use on exacerbations.[80]

Although this evidence comes from several populations, studies have lacked clinical characteristics and data on markers of systemicinflammation. Furthermore, a recent large randomized trial found no effect of simvastatin on exacerbations in patients with the most severe COPD, but without cardiovascular comorbidity.(81)

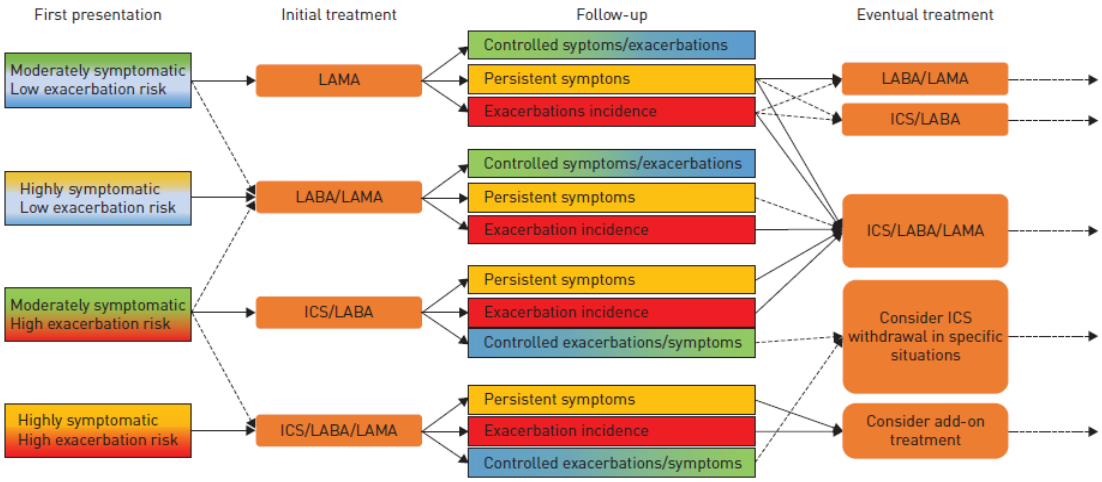

Figure-2

RISK FACTORS

CIGARETTE SMOKING

Cigarette smoking was a important risk factor for mortality from chronic bronchitis and emphysema which was concluded by advisory committee to the Surgeon General of United states. Successive longitudinal studies have shown accelerated decrease in forced expiratory volume in one second in a dose response relationship to the magnitude of cigarette smoking, which is typically expressed as pack-years .Average number of packs of cigarettes smoked per day multiplied by the total number of years of smoking is called pack per years.

This dose-response relationship between reduced pulmonary function and cigarette smoking intensity accounts, at least in part, for the higher prevalence rates of COPD with increasing age. Previously higher rate of smoking among males is the possible explanation for the higher occurrence of illness among them. Now a days the prevalence of COPD between females is increased. So the gender gap in smoking rates has diminished in the past 50 years.

Though the causal relationship between smoking and the progress of COPD has been absolutely proved, there is significant variability in the response to smoking. Pack-years of cigarette smoking is the most highly significant interpreter of FEV1.But only 15% of the variability in FEV1 is explained by pack-years. This result state that additional environmental and

or heritable factors contribute to the effect of smoking on the development of this disease.

Nonetheless, many patients with a history of cigarette smoking with normal spirometry have evidence for worse health related quality of life, reduced exercise capacity, and emphysema and/ or airway disease on chest CT evaluation; thus, they have not escaped the harmful effects of cigarette smoking. While they do not meet the classic definition of COPD based on population normal for FEV1 and FEV1/FVC, studies have shown that these subjects overall have a shift toward lower FEV1 values, which is consistent with obstruction on an individual level . cigar and pipe smoking may also be related with the development of COPD, the facts supporting such relations is less compelling, likely correlated to the lower dose of inhaled tobacco by-products during cigar and pipe smoking. The effect of electronic cigarettes (e-cigarettes) on the development of COPD has not yet decided

AIRWAY RESPONSIVENESS AND COPD

On exposure to exogenous stimuli , such as methacholine and histamine bronchoconstriction occurs which is one of the defining features of asthma. However, many of the COPD patients also share this aspect of airway hyper responsiveness. In older subjects, there is considerable overlap between persons with a history of chronic asthma and smokers with COPD in

terms of airway responsiveness, airflow obstruction, and pulmonary symptoms.

The origin of asthma is viewed as an allergic disease while COPD is thought to primarily result from smoking-related inflammation and damage; however, they likely share common environmental and genetic factors and the chronic form in older subjects can present similarly. This is particularly true for childhood asthmatic subjects who become chronic smokers

A recent study from the Childhood Asthma Management Program identified four lung function trajectories in children with persistent asthma.

Asthmatics with reduced lung function early in life were more likely to meet spirometric criteria for COPD in early adulthood. Patients with features of both asthma and COPD have been described as the asthma-COPD overlap syndrome.

RESPIRATORY INFECTIONS

Respiratory infections during adulthood leading to a decline in pulmonary function is controversial, but considerable long-term reductions in pulmonary function are not typically seen following an individual episode of acute bronchitis or pneumonia. However, respiratory infections are important causes of COPD exacerbations, and recent results from the COPD Gene and ECLIPSE studies suggest that COPD exacerbations are associated with increased loss of lung function longitudinally, particularly among those individuals with better baseline lung function levels.

Due to a lack of adequate data the impact of the effects of childhood respiratory illnesses on the consequent development of COPD has been difficult to assess , but recent studies have suggested that childhood pneumonia may lead to increased risk for COPD later in life.

OCCUPATIONAL EXPOSURES

Occupational exposure to dust and fumes lead to increased respiratory symptoms and airflow obstruction and other risk factors including coal mining, gold mining, cotton textile dust have been implicated as risk factors for chronic airflow obstruction.

Due to occupational exposure nonsmokers can develop some reductions in FEV1.Because dust exposure is a risk factor for COPD, independent of cigarette smoking, is not definite for most of these exposure. Among coal miners, coal mine dust exposure was a considerable risk factor for emphysema in both smokers and nonsmokers

AMBENT AIR POLLUTION

Some investigators data have reported there is increased respiratory symptoms in those living in urban compared to rural areas, which explain that augmented pollution in the urban settings. After Prolonged exposure to smoke created by biomass combustion(method of cooking in some countries)also a important risk factor for COPD between women in those countries. Conversely, in most populations, ambient air contamination is less important risk factor for COPD than cigarette smoking.

PASSIVE, OR SECOND-HAND, SMOKING EXPOSURE

In children there is reduced lung growth occur due to maternal smoking habit. During antenatal period, tobacco smoke exposure contributes to significant reductions in postnatal pulmonary function. Decline in pulmonary function occurs due to passive smoking .The importance of this risk factor in the development of the severe lung function reductions often noted in COPD remains doubtful.

GENETIC CONSIDERATIONS

Although cigarette smoking is the major environmental risk factor for the development of COPD, the development of airflow obstruction in smokers is highly variable. Severe α1AT deficiency is a proven genetic risk factor for COPD; there is increasing evidence that other genetic determinants also exist.

` **Antitrypsin Deficiency -**Many variants of the protease inhibitor locus that encodes α1AT have been described. The alleles M,S and Z are associated with normal,slightly and markedly reduced α1AT levels respectively.

Atypical individuals inherit null alleles lead to the lack of any α1Antitrypsin production through a a range of compilation of mutations. persons with two Z alleles or one Z and one null allele are referred to as PiZ, which is the common form of severe α1Anti trypsinT insufficiency.

PiZ individuals frequently develop early-onset Chronic obstructive pulmonary disease , but the ascertainment bias in the published series of PiZ individuals—means that the tiny proportion of PiZ individuals who will

develop COPD and the age-of-onset for the development of Chronic obstructive pulmonary disease in PiZ subjects not known.

The clinical laboratory test used most frequently to screen for α1AT deficiency is measurement of the immunologic level of α1AT in serum.

A significant percentage of the variability in pulmonary lung function amongst PiZ individuals is defined by smoking. Cigarette smokers with severe α1AT deficiency are more likely to develop COPD at early ages. The development of COPD in PiZ subjects, even among current or ex-smokers, is now not absolute. Asthma and male gender also appear to increase the danger of COPD in PiZ subjects. Other genetic and/or environmental elements possibly make a contribution to this variability.

Specific treatment in the structure of α1AT augmentation therapy is available for extreme α1AT deficiency as a weekly IV infusion. The danger of lung ailment in heterozygous PiMZ individuals, who have intermediate serum stages of α1AT (60% of PiMM levels) has been controversial. Several recent giant studies have tested that PiMZ topics who smoke are in all likelihood at multiplied chance for the development of COPD.

Other Genetic Risk Factors

Familial aggregation of airflow obstruction vulnerability loci which includes a area close to the HHIP gene on chromosome 4, a group of genes on chromosome 15 and a region within a gene of unknown function (FAMI3A).Like other complex diseases, the risk associated with individual

GWAS loci is modest, but these genetic determinants may identify important biological pathways related to COPD. Gene-targeted murine models for HHIP,FAMI3A, and IREB2 exposed to chronic smoke had changed emphysema susceptibility, signifying that those genes are likely to be involved in COPD pathogenesis. A regulatory single nucleotide polymorphisms (SNP) upstream from the HHIP gene has been recognized as one potential functional variant; the specific genetic determinants in the different COPD GWAS genomic areas have yet to be definitively identified.

NATURAL HISTORY

The effects of cigarette smoking on pulmonary function appear to depend on the intensity of smoking exposure, the timing of smoking exposure during growth, and the baseline lung function of the individual;other environmental factors may have similar effects. Most individuals follow a steady trajectory of increasing pulmonary function with growth during childhood and adolescence, followed by a plateau in early adulthood, and then gradual decline with aging.

Individuals appear to track in their quantile of pulmonary function based on environmental and genetic factors that put them on different tracks. The mortality in COPD is closely linked with reduction in FEV1.

Disability or fatality from COPD can result from a normal rate of decline after a decreased growth phase (curve C). Although accelerated rates of lung function decline have classically been associated with COPD, recent analyses of several population-based cohorts demonstrated that many subjects meeting the spirometric criteria for COPD had reduced growth but normal rates of lung function decline. The degree of decline in pulmonary function can be modified by using changing environmental exposures (i.e., quitting smoking), with smoking cessation at an in the young age is more beneficial compared to those who stops smoking after developing disease .

The absolute annual loss in FEV1 tends to be highest in mild COPD and lowest in very severe COPD. Multiple genetic factors influence the level of pulmonary function achieved during growth; genetic determinants likely also influence the rate of decline in response to smoking and potentially to other environmental factors as well.

CLINICAL PRESENTATION

HISTORY

Most common symptoms in COPD are cough, sputum production, and exertional dyspnea. The development of airflow obstruction is a gradual process, several patients identified the onset of their disease during acute illness or exacerbation.

A careful history normally reveals the occurrence of symptoms prior to acute exacerbation. Exertional dyspnea often developed during augmented

effort to breathe, air hunger can be insidious. It is best obtained by a detail careful history focused on typical physical activities .

Actions involving considerable arm work mostly at or above shoulder level, are particularly difficult for many patients with COPD. on the contrary, patients well tolerated when they use accessory muscles of respiration such as walking on a treadmill.

In advanced cases, the primary feature is deterioration of dyspnea on effort with increasing disturbance on the capacity to perform occupational or activities. In Later stages, patients are breathless doing simple actions of daily living, worsening airflow obstruction and increased occurrence of exacerbations . They also develop resting hypoxemia and need institution of supplemental oxygen.

PHYSICAL FINDINGS

Physical examinations are completely normal in initial stage of disease .But signs of active smoking like an odor of smoke or nicotine discoloration of fingernails are noted. In severe disease, the physical examination of the lungs is remarkable for a prolonged expiratory phase , expiratory wheezing. signs of hyperinflation(barrel chest)and inflated lung volumes with poor diaphragmatic excursion as assessed by percussion.

Other features of severe disease:

- They also show signs of use of accessory muscles of respiration sitting in the feature “Tripod” position .
- cyanosis, noticeable in the lips and nail beds.

Emphysema patients described as “Pink puffers,”. They are thin and non cyanotic at rest and have prominent use of accessory muscles. chronic bronchitis are more likely to be cyanotic termed as“Bluebloaters”. Recent data stat that the majority patients have elements of both chronic bronchitis and emphysema. So the physical examination does not reliably distinguish the two entities.

Advanced disease features

- Cachexia, with significant weight loss
- Bi temporal wasting
- Diffuse loss of subcutaneous adipose tissue.

This syndrome has been related with both inadequate oral intake and elevated levels of inflammatory cytokines (TNF-α). Such wasting is an independent poor predictive factor in COPD. Some patients with advanced disease have Hoover’s sign: paradoxical inward movement of the rib cage with inspiration result of alteration of the vector of diaphragmatic contraction on the rib cage as a result of chronic hyperinflation in advanced disease.

In COPD clubbing of the digits is not a sign and its presence should aware the clinician to initiate an investigation for causes of clubbing. In this population, the development of lung cancer is the most likely reason for newly developed clubbing.

LABORATORY FINDINGS

The feature of COPD is airflow obstruction . Pulmonary function testing shows airflow obstruction with a decrease in FEV1 and FEV1/FVC . In emphysema, the diffusing capacity may be reduced, reflecting the lung parenchymal destruction feature of the disease.

The level of airflow obstruction is a significant prognostic factor in COPD and it is the basis for the GOLD spirometric severity classification. Although the degree of airflow obstruction generally correlates with the presence and severity of respiratory symptoms, exacerbations, emphysema, and hypoxemia, the correlations are far from perfect. Thus, clinical features should be carefully assessed in each individual patient with COPD to determine the most appropriate therapies.

It has been shown that a multi factorial index[Body mass index(B),Degree of airflow obstruction(O),Dyspnea(D),Exercise capacity(E) BODE] incorporating airflow obstruction, exercise performance, dyspnea, and body mass index is a better predictor of mortality rate than pulmonary function alone. The latest, GOLD clssification added additional elements to their classification system incorporating respiratory symptoms and exacerbation history these metrics are used to guide COPD treatment.

Arterial blood gases and oximetry may show resting or exertional hypoxemia. It also provide further information about alveolar ventilation and acid-base status by measuring arterial Pco2 and pH. The change in acute and chronic state pH with Pco2 is 0.08 units/10 mmHg and 0.03 units/10 mmHg

respectively. he arterial pH hence allows the classification of ventilatory failure, defined as Pco2 >45 mmHg, into acute or chronic conditions with acute respiratory failure being associated with acidemia. The arterial blood gas is an important element of the assessment of patients presenting with symptoms of an exacerbation.

Radiographic studies may support in the classification of the category of COPD. On chest x-ray of emphysema patients we find out Obvious bullae, paucity of parenchymal markings, or hyperlucency. Increased lung volumes and flattening of the diaphragm suggest hyperinflation but do not afford information about chronicity of the changes.

Chest computed tomography (CT) scan is the current definitive test to rule out emphysema, the pattern of emphysema and the presence of significant disease involving medium and large airways.

It also enables the discovery of coexisting interstitial lung disease and bronchiectasis, which are common complications in COPD.

Smokers with COPD are at high risk for development of lung cancer, which can be identified on a chest CT scan. In advanced COPD, CT scans can help determine the possible value of surgical therapy .

Current guidelines have recommended testing for α1AT deficiency in all patients with COPD or asthma with chronic airflow obstruction. The serum α1AT level is a reasonable initial test and subjects with low α1AT levels, the definitive diagnosis requires PI type determination. This is generally performed by isoelectric focusing of serum or plasma, which reflects

the genotype at the PI locus for the common alleles and also many of the rare PI alleles as well. Molecular genotyping of DNA can be performed for the common PI alleles (M, S, and Z).

Chronic Obstructive Pulmonary Disease

STABLE PHASE COPD

The two main goals of therapy are to provide symptomatic relief (reduce respiratory symptoms, improve exercise tolerance, improve health status) and reduce future risk (prevent disease progression, prevent and treat exacerbations, and reduce mortality).

The institution of therapies should be based on symptom assessment, benefits of therapy, potential risks, and costs. Response to therapy should be assessed, and decisions should be made whether or not to continue or alter treatment chronically hypoxemic patients, and lung volume reduction surgery (LVRS) in selected patients with emphysema have been confirmed to improve survival of patients with COPD. There is indicative, but not definitive, data that the use of inhaled corticosteroids (ICS) and muscarinic antagonists may reduce the mortality rate.

PHARMACOTHERAPY:

Smoking cessation

In middle-aged smokers who were able to effectively stop smoking experienced a significant improvement in the rate of decline in pulmonary function and returning to annual changes similar to that of nonsmoking patients. In addition, smoking cessation improves survival. Thus, all patients

with COPD should be strongly urged to stop smoking and educated about the benefits of quitting.

An emerging body of evidence demonstrates that combining pharmacotherapy with traditional supportive approaches considerably enhances the chances of successful smoking cessation.

The three principal pharmacologic approaches to the problem:

(1) Nicotine replacement therapy available as gum, transdermal patch, lozenge, inhaler

(2) Nasal spray; bupropion

(3) Varenicline, a nicotinic acid receptor agonist/antagonist.

Recent recommendations from the United States Surgeon General are that all adult, non pregnant smokers considering quitting will offered pharmacotherapy, in the absence of any contraindication to treatment. Smoking cessation counselling is also recommended and free counselling is available through state Smoking Quit Lines.

Bronchodialators:

Bronchodialators are the primary treatment for almost all patients with COPD and are used for symptomatic benefit and to reduce exacerbations. The inhaled route is delivery because side effects are less than with systemic medication delivery. In symptomatic patients, preferred for medication both regularly scheduled use of long-acting agents and needed short-acting medications are indicated.

ANTICHOLINERGIC- MUSCARINIC ANTAGONISTS

Short-acting ipratropium bromide improves symptoms with acute improvement in FEV1. Long-acting muscarinic antagonists (LAMA, including aclidinium, glycopyrrolate, tiotropium, and umeclidinium) improve symptoms and reduce exacerbations. In a large randomized clinical trial state that there was a trend toward reduced mortality rate in tiotropium treated patients that approached statistical significance.

Side effects are minor; dry mouth is the most frequent side effect.Beta agonist Short-acting beta agonists ease symptoms with acute improvements in lung function. Long-acting agents (LABA) provide symptomatic benefit and reduce exacerbations, though to a lesser extent than a LAMA.

Currently available long-acting inhaled β agonists are arformoterol, formoterol, indacaterol, olodaterol, salmeterol, and vilanterol. The main side effects are tremor and tachycardia.

COMBINATIONS OF BETA AGONIST-MUSCARINIC ANTOGONIST:

The combination inhaled β agonist and muscarinic antagonist therapy has greater effect than either agent alone and reduces exacerbations. Inhaled corticosteroid, the main role of ICS is to reduce exacerbations.

Their use has been linked with increased rates of oropharyngeal candidiasis and pneumonia and in some other studies an increased rate of loss of bone density. A trial of ICS should be considered in patients with frequent exacerbations, defined as two or more per year and also in patients with

features of asthma. In stable patients ICS withdrawal may be considered. Though ICS withdrawal does not lead to an increase in exacerbations, there may be a small decline in lung function.

ORAL GLUCOCORTICOIDS:

The chronic use of oral glucocorticoids for treatment of COPD is not suggested because of an unfavorable benefit/risk ratio.

Side effects oral glucocorticoids on prolonged use in COPD patients:

(1) Osteoporosis

(2) Weight gain

(3) Cataracts

(4) Glucose intolerance and

(5) Increased risk of infection.

THEOPHYLLINE:

Theophylline produces modest improvements in airflow and vital capacity, but it is not first-line therapy due to side effects and drug interactions. Among side effects Nausea is the most common followed by tachycardia and tremor. To decrease the toxicity Therapeutic Drug Monitoring (TDM) of blood theophylline levels is required.

The selective phosphodiesterase 4 (PDE4) inhibitor roflumilast has been proved that it minimize the exacerbation frequency in patients with severe COPD, persistent bronchitis, and with a previous history of exacerbations.It also have modest effects on symptoms and airflow obstruction .

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ANTIBIOTICS:

There are strong data implicating bacterial infection as one of aggravating , considerable portion of exacerbations. A randomized clinical trial of azithromycin, chosen for both its anti-inflammatory and antibacterial properties. The drug administered daily to subjects with a history of exacerbation in the past 6 months .It demonstrated a reduced exacerbation frequency and longer time to first exacerbation in the macrolide-treated cohort (hazard ratio, 0.73).

OXYGEN:

Supplemental O2 is the only pharmacologic treatment demonstrated to unequivocally reduce mortality rates in patients with COPD. For patients with resting hypoxemia (resting O2 saturation ≤88% in any patient or ≤89% with signs of pulmonary hypertension or right heart failure), the use of O2 has been demonstrated to have a considerable impact on mortality.

Patients meeting these criteria should be on continuous oxygen supplementation because the mortality benefit is proportional to the number of hours per day oxygen is used. A variety of delivery systems are available, including portable systems that patients may carry to allow mobility outside the home.

ALPHA-1 AUGMENTATION THERAPY:

For severe α1AT there is Specific treatment in the form of intravenous alpha one augmentation therapy is available for individuals with this

deficiency. Due to sterilization procedures for these blood derived products and the absence of reported cases of viral infection from therapy, several physicians recommend hepatitis B vaccination prior to starting augmentation therapy. Although biochemical efficacy of α1AT augmentation therapy has been shown, the benefits of α1AT augmentation therapy are controversial.

A recent randomized study recommended a reduction in emphysema progression patients receiving α1AT augmentation therapy. Eligibility for α1AT augmentation therapy requires a serum α1AT level <11 Mm(~50 mg/dL). characteristically, PiZ individuals will qualify, although other rare types associated with severe deficiency are also eligible. Because only a tiny proportion 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 .

NONPHARMACOLOGIC THERAPIES

COPD Patients must receive the influenza vaccine annually. Pneumococcal and Bordetella pertussis vaccines are recommended.

PULMONARY REHABILITATION:

This refers to a comprehensive treatment program that incorporates exercise, education, and psychosocial and nutritional counselling. In COPD, pulmonary rehabilitation has following beneficial effects which include improve health-related pleasant of life, dyspnea, and workout capacity as well to reduce fees of hospitalization over a 6- to 12-month duration

LUNG VOLUME REDUCTION SURGERGY

In correctly selected patients with emphysema, surgery to remove the most emphysematous portions of lung improves exercise, lung function, and survival. Patients with upper lobe predominant emphysema and a low post-rehabilitation exercise capacity are likely to have advantage from LVRS.

Candidates not suitable for LVRS:

(1) Patients with an FEV1 <20% of predicted and either diffusely distributed emphysema on CT scan

(2) Diffusing capacity of lung for carbon monoxide (DLCO) <20% of predicted have increased mortality after the procedure.

Methods of achieving lung volume reduction by using bronchoscopic techniques are under investigation.

LUNG TRANSPLANTATION:

At present COPD is the second leading indication for lung transplantation.

Indications for lung transplantation :

(1) very severe airflow limitation

(2) severe disability despite maximal medical therapy and

(3) free of significant comorbid conditions such as liver, renal, or cardiac disease.

EXACERBATIONS OF COPD:

It defined by episodic acute worsening of respiratory symptoms including increased dyspnea, cough, wheezing, and or change in the amount and character of sputum. During episode they may or may not be accompanied by other signs of illness such as fever, myalgias, and sore throat.

The strongest single predictor of exacerbations is a history of a previous exacerbation. conversely, some individuals with very severe airflow obstruction do not have it frequently .

Factors influence exacerbations:

(1) Elevated ratio of the diameter of the pulmonary artery to aorta on chest CT .

(2) Gastro esophageal reflux.

Financial analyses have shown that more than 70% of COPD-related health care expenditures are due to emergency department visits and hospital care for COPD exacerbations; this translates to over $10 billion annually in the United States.

PRECIPITATING CAUSES AND STRAEGIES TO REDUCE FREQUENCY OF EXACEBRATIONS:

A diversity of stimuli may lead to the final common pathway of airway inflammation and increased respiratory symptoms that are characteristic of COPD exacerbations. Many data suggest that acquiring a new strain of bacteria is associated with increased near-term of exacerbation and that

bacterial infection/superinfection is involved in more than 50% of exacerbations.

Viral respiratory infections are present in approximately one-third of COPD exacerbations. In a considerable minority of instances (20–35%), no specific precipitant can be identified.

In History the following information should included:

(1) Quantification of the degree and change in dyspnea by asking about breathlessness during activities of daily living and typical activities for the patient.

(2) The patient should be asked about fever; change in character of sputum and associated symptoms such as wheezing, nausea, vomiting, diarrhoea, myalgias, and chills.

(3) Inquiring about the frequency and severity of prior exacerbations can provide important information; the single greatest risk factor for hospitalization with an exacerbation is a history of previous hospitalization.

(4) 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.

Chest examination should evaluate following findings:

(1)Presence or absence of focal findings

(2)Degree of air movement

(3) Presence or absence of wheezing

(4) Asymmetry in the chest examination and

(5) The presence or absence of paradoxical motion of the abdominal wall.

TREATMENT OF ACUTE EXACERBATIONS

Bronchodialators:

Typically, patients are treated with inhaled β agonists and muscarinic antagonists.

In this condition we can use two type of device:

(1) Nebulized therapy, as such treatment is often easier to administer in those in respiratory distress.

(2) The change 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.

The addition of methylxanthines (theophylline) to this treatment can be considered, although convincing proof of its efficacy is lacking. During treatmen serum levels should be monitored(Therapeutic Drug Monitoring - TDM)in an effort to minimize toxicity.

Antibiotics :

COPD patients are susceptible to colonize with potential respiratory pathogen. It is often complex to identify conclusively a specific species of bacteria responsible for a particular clinical event.

Following Bacteria were frequently involved in COPD exacerbations

(1) streptococcus pneumoniae,

(2) Haemophilus influenza

(3) Moraxella catarrhalis.

(4) Mycoplasma pneumonia or chlamydia pneumonia are found in 5–10% of exacerbations.

The antibiotic choice is done based on local patterns of drug Sensitivity of the above pathogens as well as their clinical condition. In severe conditions they are treated with antibiotics, in the absence of statistics implicating a specific pathogens.

The use benefits of systemic glucocorticoids in hospitalization:

(a)reduces the length of stay

(b) Accelerate recovery and

(c) Lower the rate of subsequent exacerbation or relapse.

One study demonstrated that two weeks of glucocorticoid therapy produced advantage indistinguishable from eight weeks of therapy.

Current recommendations suggest 30–40 mg of oral prednisolone or its equivalent typically for a period of 5–10 days in outpatients. Hyperglycemia in known diabetic patients is is the most frequently reported acute complication of glucocorticoid treatment.

OXYGEN:

Supplemental O2 ,the saturation of oxygen should be more than or equal to ≥90%.Studies data stated that In patients with acute or chronic

hypercarbia the administration of supplemental O2 does not decrease minute ventilation. It does, in some patients, result in modest increases in arterial Pco2, chiefly by changing in ventilation-perfusion relationships within the lung.

MECHANICAL VENTILATORY SUPPORT:

In patients with respiratory failure(defined as Paco2 >45 mmHg) the initiation of noninvasive positive-pressure ventilation (NIPPV) results in a significant reduction in death rate, need for intubation, complications of therapy and hospital length of stay.

Contraindications to NIPPV :

- cardiovascular instability,
- impaired mental status,
- 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.

In patients with severe respiratory distress conventional mechanical ventilation via an endotracheal tube is indicated.

The goal of mechanical ventilation:

- In spite of initial therapy, life-threatening hypoxemia,
- Severe hypercarbia and/or acidosis

- Markedly impaired mental status,
- Respiratory arrest,
- Hemodynamic instability, or other complications

Factors to consider during mechanical ventilatory support include the need to give sufficient expiratory time in patients with severe airflow obstruction and the presence of auto-PEEP (positive end-expiratory pressure), which can result in patients having to generate significant respiratory effort to trigger a breath during a demand mode of ventilation. The mortality rate of patients requiring mechanical ventilatory support is 17–30% for that particular hospitalization.

For patients aged more than 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 essential. Following a hospitalization for COPD, about 20% of patients are re-hospitalized in the subsequent 30 days and 45% are hospitalized in the next year. Mortality following hospital discharge is about 20% in the following year. (82)

CURRENT TREATMENT IN COPD[83]

The mainstay of treatment in COPD is short- and long-acting b-agonist therapy to relax smooth muscle and dilate airways [84]. This approach is very successful in relieving the brochoconstriction in asthma where hyperreactive airways and smooth muscle constriction are important. The bronchodilating response to this treatment is considerably less in COPD due to small airway

fibrosis and emphysema secondary to matrix remodelling (imbalance of elastin/collagen content).

Inhaled corticosteroids are also used to inhibit airway inflammation of COPD although it is strongly neutrophil driven rather than the T-helper (TH) type-2 inflammatory response of asthma, where activated lymphocytes are thought to play a central role [84]. Given these significant differences in pathogenic pathways underlying COPD and asthma, it is perhaps not surprising that current treatments in COPD modestly improve symptoms but do no restore patients back to normal lung function.

Given that corticosteroids do little for neutrophilic inflammation [84, 89], it is also not surprising that COPD is characterised by a progressive decline in lung function, exercise tolerance and premature death despite these treatments. Although some studies suggest marginal benefits on mortality from inhaled corticosteroids or combined b-agonist/corticosteroid therapy, the data are not terribly convincing [90–92]. Based on these limitations [93, 94], interest has turned to treatments with greater impact on neutrophil or macrophage derived inflammation[94–97].

COPD AND SYSTEMIC INFLAMMATION

There are a growing number of studies showing that CRP is a marker of systemic inflammation and a possible effector molecule in vascular disease[85,87]. Several cross-sectional and prospective studies have shown the close inverse relationship between high-sensitivity CRP and lung function [99–101]. CRP is synthesized and released by the liver into the systemic circulation

in response to IL-6 released by inflammatory stimuli. This link between IL-6, CRP and COPD is supported by population studies showing an inverse relationship between serum IL-6 levels and FEV1 [86, 102, 103], and murine models of emphysema resulting from IL-6 over expression [104].

Interestingly, alpha1-antitrypsin is also an acute-phase protein released by the liver at the time of inflammation. It should be noted that serum IL6 and IL-8 levels are elevated in smokers with COPD in excess of those with normal lung function [105, 89, 106]. It would appear conceivable that, in those disposed to COPD, smoking initiates an increase in the cytokines IL-6 and IL-8 which might underlie the systemic (‘‘spill over’’ effect [85, 88]) and pulmonary inflammation, respectively.

This could explain the observation that patients with COPD have a greater than two-fold risk of coronary heart disease [87]. Genetic variation may confer important effects on the expression of these effector molecules (e.g. CRP, IL-6 and IL-8) that mediate the downstream effects on COPD [107] and lung cancer .[136,108,109].

The heavy oxidant load derived from smoking has effects both locally in lung parenchyma and systemically on muscle function. Given these diverse pathways and anatomically distant events, what evidence exists to suggest that statin therapy (or 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) might affect any of these pathological events.

STATIN EFFECTS ON CLINICAL OUTCOMES IN COPD:

AN OVERVIEW

Statins are known to inhibit endogenous cholesterol synthesis in hepatocytes by blocking the synthesis of cholesterol in the mevalonate pathway. This explains the ability of statins to lower serum cholesterol. However, facts from both human and animal studies has shown that statins have strong immune-modulating effects in both the systemic [110] and pulmonary circulation [111,112], which may have useful anti-inflammatory actions in COPD [98, 112- 135].

STATIN DRUG THERAPY:

Mechanism of Action

Statins exert their major effect—reduction of LDL levels—through a mevalonic acid–like moiety that competitively inhibits HMG-CoA reductase. By reducing the conversion of HMG-CoA to mevalonate, statins inhibit an early and rate-limiting step in cholesterol biosynthesis.[137]

Statins affect blood cholesterol levels by inhibiting hepatic cholesterol synthesis, which results in increased expression of the LDL receptor gene. Some studies suggested that statins also can reduce LDL levels by enhancing the removal of LDL precursors (VLDL and IDL) and by decreasing hepatic VLDL production. The reduction in hepatic VLDL production induced by statins is thought to be mediated by reduced synthesis of cholesterol, a required component of VLDLs.

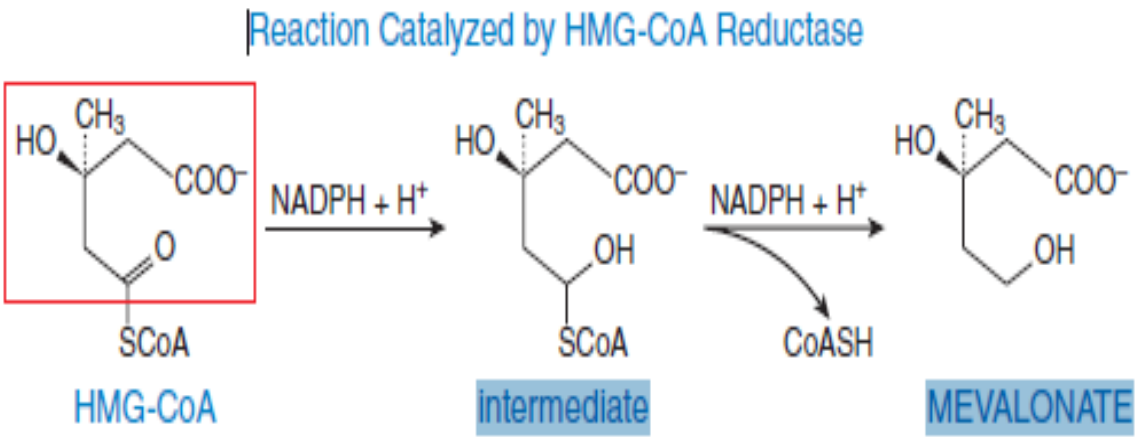


Figure-3

ABSORPTION /DISTRIBUTION/METABOLISM/EXCRETION:

After oral administration, intestinal absorption of the statins is variable (30%–85%). All the statins, except simvastatin and lovastatin, are administered in the β-hydroxy acid form, which is the form that inhibits HMG-CoA reductase. Simvastatin and lovastatin are administered as inactive lactones that must be transformed in the liver to their respective β-hydroxy acids, simvastatin acid, and lovastatin acid. There is extensive first-pass hepatic uptake of all statins, mediated primarily by the organic anion transporter OATP1B1 .

HEPATIC CHOLESTEROL SYNTHESIS :

It is maximal between midnight and 2AM So thus statin with half life of 4 hrs less all but atrovastatin and rosuvastatin should be taken in the evening. Atorvastatin and rosuvastatin both have longer half-lives and may be taken at other times of day to optimize adherence. Due to extensive first-pass

hepatic uptake, systemic bioavailability of the statins and their hepatic metabolites varies between 5% and 30% of administered doses.

The metabolites of all statins, except fluvastatin and pravastatin, have some HMG-CoA reductase inhibitory activity. Under steady-state conditions, small amounts of the parent drug and its metabolites produced in the liver can be found in the systemic circulation. In the plasma, more than 95% of statins and their metabolites are protein bound, with the exception of pravastatin and its metabolites, which are only 50% bound. Peak plasma concentrations of statins are achieved in 1–4 h. The *t*1/2 of the parent compounds are 1–4 h, except in the case of atorvastatin and rosuvastatin, which have half-lives of about 20 h, and simvastatin with a *t*1/2 of about 12 h.

The longer *t*1/2 of atorvastatin and rosuvastatin may contribute to their greater cholesterol-lowering efficacy. The liver bio transforms all statins, and more than 70% of statin metabolites are excreted by the liver, with subsequent elimination in the faeces.

Therapeutic Effects

Triglyceride levels greater than 250 mg/dL are reduced substantially by statins, and the amount reduction achieved is similar to the percentage reduction in LDL-C.Most studies of patients treated with statins have systematically excluded patients with low HDL-C levels. In studies of patients with elevated LDL-C levels and gender-appropriate HDL-C levels (40–50 mg/dL for men; 50–60 mg/dL for women), an increase in HDL-C of 5%–10% was observed, irrespective of the dose or statin employed. However, in

patients with reduced HDL-C levels (<35 mg/dL), statins may differ in their effects on HDL-C levels. More studies are needed to ascertain,

STATIN EFFECT ON LDL-C LEVEL:

Dose-response relationships for all statins demonstrate that the efficacy of LDL-C lowering is log linear; LDL-C is reduced by about 6% (from baseline) with each doubling of the dose. Maximal effects on plasma cholesterol levels are achieved within 7–10 days.

The statins are effective in almost all patients with high LDL-C levels. The exception is patients with HoFH who have very attenuated responses to the usual doses of statins because both alleles of the LDL receptor gene code for dysfunctional LDL receptors.

Adverse Effects and Drug Interactions

HEPATOTOXICITY:

Serious hepatotoxicity is rare and unpredictable, with a rate of about one case per million person-years of use. ACC/AHA guidelines recommend measuring ALT at baseline prior to initiation of statins. However since 2012, the FDA has no longer recommended routine monitoring of ALT or other liver enzymes following the initiation of statin therapy because routine periodic monitoring does not appear to be effective in detecting or preventing serious liver injury. Liver enzymes should be evaluated in patients with clinical symptoms suggestive of liver injury following initiation or changes in statin treatment (FDA, 2012).

MYOPATHY

The major adverse effect associated with statin use is myopathy. Myopathy refers to a broad spectrum of muscle complaints, ranging from mild muscle soreness or weakness to life-threatening rhabdomyolysis. The risk of muscle adverse effects increases in proportion to statin dose and plasma concentrations. Consequently, factors inhibiting statin catabolism are associated with increased myopathy risk, including advanced age (especially > 80 years of age), hepatic or renal dysfunction, peri operative periods, small body size, and untreated hypothyroidism.

Measurements of creatinine kinase are not routinely necessary unless the patient also is taking a drug that enhances the risk of myopathy. Concomitant use of drugs that diminish statin catabolism or interfere with hepatic uptake of drugs that diminish statin catabolism or interfere with hepatic uptake is associated with increased risk of myopathy and rhabdomyolysis.

The most common statin interactions occur with fibrates, especially gemfibrozil (38%), and with cyclosporine (4%),digoxin(5%),warfarin (4%), macrolide antibiotics (3%), and azole antifungals (1%).

Other drugs that increase the risk of statin-induced myopathy include niacin (rare), HIV protease inhibitors amiodarone and nefazodone. . Gemfibrozil, the drug most commonly associated with statin-induced myopathy, both inhibits uptake of the active hydroxy acid forms of statinsinto hepatocytes by OATP1

OATP1B1 and interferes with the transformation of most statins by glucuronidases. Coadministration of gemfibrozil nearly doubles the plasma concentration of the statin hydroxy acids. When statins are administered with niacin, the myopathy probably is caused by an enhanced inhibition of skeletal muscle cholesterol synthesis (a pharmacodynamic interaction). In 2016, the FDA withdrew approval for statin drug combinations containing fibrates or niacin (FDA, 2016).

Drugs that interfere with statin oxidation are those metabolized primarily by CYP3A4 and include certain macrolide antibiotics; azole antifungals ; cyclosporine; nefazodone a phenylpiperazine antidepressant; HIV protease inhibitors; and amiodarone. These pharmacokinetic interactions are associated with increased plasma concentrations of statins and their active metabolites. Atorvastatin, lovastatin, and simvastatin are primarily metabolized by CYPs 3A4 and 3A5.

Fluvastatin is mostly (50%–80%) metabolized by CYP2C9 to inactive metabolites, but CYP3A4 and CYP2C8 also contribute to its metabolism. Pravastatin, however, is not metabolized to any appreciable extent by the CYP system and is excreted unchanged in the urine . Because pravastatin, fluvastatin, and rosuvastatin are not extensively metabolized by CYP3A4, these statins may be less likely to cause myopathy when used with one of the predisposing drugs. However, the benefits of combined therapy with any statin should be carefully weighedagainst the risk of myopathy.

Other consideration:

The choice of statins should be patient specific and based on factors such as cost, drug interactions, possible adverse effects, and desired intensity. Statin doses are characterized as low, moderate, or high intensity , based on the degree of LDL-C lowering expected (range 30%–60%).

Rosuvastatin and pravastatin may be better tolerated than other statins and should be considered in patients with a history of myalgias with other statins. Lovastatin absorption is increased when taken with food, and patients should be encouraged to take with their evening meal.

According to a 2012 FDA warning, simvastatin should not be used in combination with cyclosporine, HIV protease inhibitors, erythromycin, or gemfibrozil. In patients taking amlodipine or amiodarone, the daily dose of simvastatin should not exceed 20 mg. No more than 10 mg of simvastatin should be used in combination with diltiazem or verapamil. Concerns have been raised about possible cognitive impairment with statins, although review of the published data do not suggest that statins harm cognition.

In contrast, other studies suggested statins may have a role in the prevention of dementias. Statins, especially at higher doses, likely confer a small increased risk of developing diabetes. However, the beneficial effects of statins on ASCVD events and mortality outweigh any increased risk conferred by promoting the development of diabetes.

Atorvastatin is often the statin of choice for patients with severe renal dysfunction as it does not require dose adjustment. Some statins have been

approved for use in children with heFH. Atorvastatin, lovastatin, and simvastatin are indicated for children 11 years and older. Pravastatin is approved for children 8 years and older. Statins are contraindicated during pregnancy and should be discontinued prior to conception,. Data regarding statin use while breastfeeding are limited, and use should be discouraged[137].

β2 Adrenergic Agonists

The inhaled LABAs, salmeterol and formoterol, have a much longer duration of effect, providing bronchodilation and bronchoprotection for more than 12 h (Cazzola et al., 2013b).[138] Formoterol has a bulky substitution in the aliphatic chain and has moderate lipophilicity, which appears to keep the drug in the membrane close to the receptor, so it behaves as a slow-release drug. Salmeterol has a long aliphatic chain, and its long duration may be due to binding within the receptor binding cleft ("exosite") that anchors the drug in the binding cleft. Once-daily β2 agonists, such as indacaterol, vilanterol, and olodaterol, with a duration of action more than 24 h have now been developed.

.LONG –ACTING INHALED BETA2 AGONIS.

The LABAs salmeterol, formoterol,and arformoterol have proved to be a significant advance in asthma and COPD therapy. These drugs have a bronchodilator action of more than 12hrs and also protect against bronchoconstriction for a similar period.

Once-daily LABAs, such as indacaterol, vilanterol, and olodaterol, with a duration of over 24 h have now been developed and are more

effective in patients with COPD than twice-daily LABAs and more frequent SABAs.

In COPD, LABAs are effective bronchodilators that may be used alone or in combination with anti cholinergics or ICSs. LABAs improve symptoms and exercise tolerance by reducing both air trapping and exacerbations.

Combination Inhalers.

Combination inhalers that contain a LABA and a corticosteroid (e.g., fluticasone/salmeterol, budesonide/formoterol) are now widely used in the treatment of asthma and COPD. . The combination inhaler is more convenient for patients, simplifies therapy, and improves adherence with the ICS. Also, delivering the two drugs in the same inhaler ensures they are delivered simultaneously to the same cells in the airways, allowing the beneficial molecular interactions between LABAs and corticosteroids to occur.

Combination inhalers are also more effective in patients with COPD than a LABA and an ICS alone, but the mechanisms accounting for this beneficial interaction are less well understood than in patients with asthma.

SIDE EFFECTS

Muscle tremor due to stimulation of β2 receptors in skeletal muscle is the most common side effect. It may be more troublesome with elderly patients and so is a more frequent problem in patients with COPD.

- Tachycardia and palpitations are due to reflex cardiac stimulation secondary to peripheral vasodilatation, from direct stimulation of atrialβ2

receptors (human heart has a relatively high proportion of β2 receptors;, and possibly also from stimulation of myocardial β1 receptors as the doses of β2 agonist are increased.

- Hypokalemia is a potentially serious side effect.

  This is due to β2 receptor stimulation of potassium entry into skeletal muscle, which may be secondary to a rise in insulin secretion. Hypokalemia might be serious in the presence of hypoxia, as in acute asthma, when there may be a predisposition

to cardiac arrhythmias

. In practice, however, significant arrhythmias after nebulized β2 agonists are rarely observed in acute asthma or patients with COPD.

- Ventilation-perfusion V/Q mismatch due to pulmonary vasodilatation in blood vessels previously constricted by hypoxia results in the shuntingof blood to poorly ventilated areas and a fall in arterial oxygen tension.

Although in practice the effect of β2 agonists on Pao2 is usually very small (<5 mm Hg fall), occasionally in severe COPD it can be large, although it may be prevented by giving additional inspired oxygen.

- Metabolic effects (increase in free fatty acid, insulin, glucose, pyruvate, and lactate) are usually seen only after large systemic doses.[138]

AIM:

To compare the Efficacy and safety of long acting beta agonist/long acting muscarnic antagonist/inhaled corticosteroid along with Rosuvastatin in moderate to severe COPD patients .

OBJECTIVES:

(1) To compare the efficacy and safety of long acting beta agonist/long acting muscarnic antagonist/inhaled corticosteroid along with Rosuvastatin in moderate to severe COPD patients .

(2)To understand the safety profile of Rosuvastatin

METHODOLOGY

MATERIALS AND METHODS

The study was carried out after obtaining the Institutional Ethics committee clearance.

METHODOLOGY

60 patients who were attending Respiratory medicine outpatient department Govt .Stanley Medical College satisfying inclusion &exclusion criteria were included in the study, the study subject was randomly allocated into 2 groups of 30 patients each. Group 1 patients (control) were treated with LABA/LAMA/ICS once daily. Group 2 patients (case) were treated with LABA/LAMA/ICS with rosuvastatin10mg once daily. Patients was followed for 12 weeks .

MATERIALS AND METHODS

- STUDY DESIGN: Randomized prospective open labelled comparative study.
- MATERIALS AND METHODS:
- Patients diagnosed with COPD as per Global initiative for Chronic Ostructive Lung Disease(GOLD) guidelines and spirometry values.

INCLUSION CRITERIA

- i)All adult patients (between 40-70 yrs of age)diagnosed with moderate to severe COPD as per spirometry and dyspnoeic scale (mMRC,CAT scale) criteria
- (ii) willing for investigations
- (iii) Agreed to give informed written consent
- (iv) willing for follow up visits

EXCLUSION CRITERIA

- (i)Major respiratory illness other than COPD
- (ii)Pulmonary disease or impairment in lung functions
- (iii)Patients with co-morbid conditions like ischemic heart disease congestive cardiac failure ,renal &hepatic dysfunction ,neurological ,endocrinal &haematological abnormalities.
- (iv)Pregnant and lactating women
- (v)History of known allergy/intolerance/hypersensitivity to study drug
- (vi)Patients on regular treatment with drug that interact with rousuvastatin
- (vii)Patients who do not give consent for study

- (viii) obstructive airway disease other than COPD
- (xi)COPD patients with pulmonary hypertension and cor pulmonale
- (x)COPD patients coexistence with other parenchymal or interstitial disease

After getting the written informed consent ,patients were enrolled in the study. Patients Demography details , respiratory symptoms, personal history were recorded. Baseline pulmonary function test laboratory investigations such as AST, CPK and Hb % level were recorded.

METHODOLOGY

- 60 patients who were attending Respiratory medicine outpatient department Govt .Stanley Medical College satisfying inclusion &exclusion criteria have been included in the study. The study subjects were randomly allocated into 2 groups of 30 patients each.
- Control group patients were treated with LABA/LAMA/ICS once daily. Case group patients were treated with LABA/LAMA/ICS with rosuvastatin10mg once daily. Patients were followed for 12 weeks .
- (i)Data collected were analysed for efficacy by Pulmonary Functions Test (Spirometry) parameters like FEV1, FVC and PEFR were recorded.
- (ii)Clinical COPD questionnaires for symptoms reduction

- (iii)Use of rescue medicines like LABA/LAMA/ICS and rosuvastatin in previous 12 weeks

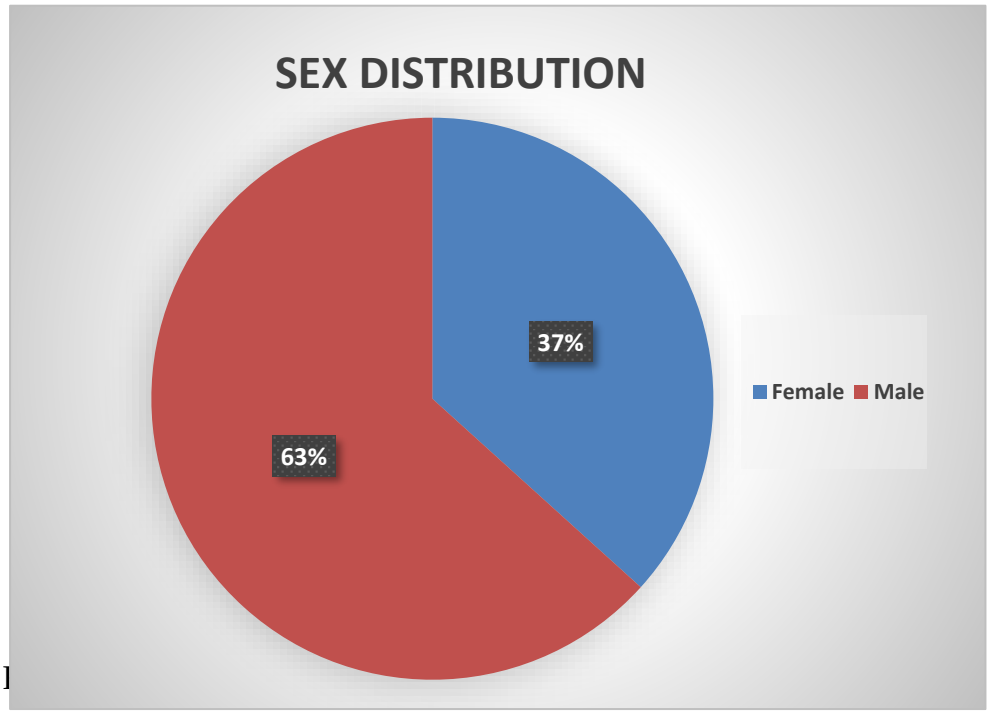
- (iv)Safety by adverse drug reactions reported voluntarily by the patients ,observed or enquired were recorded.:

- Investigation like Aspartate aminotransferase(AST) and creatine phosphokinase(CPK) assessments at baseline and 12 weeks were recorded.

STATISTICAL ANALYSIS:

The statistical analysis done by using the SPSS version 23 and Excel software .The difference between FVC, FEV1,PEFR, AST CPK was found by the t- test.

RESULTS



As per the inclusion and inclusion criteria, 60 patients were randomized into rosuvastatin and control group.Demographic and baseline characteristic .The

Baseline and clinical characteristics of patients are shown into Tables 1 and

TABLE-1

	Case		Control	
	Mean	Standard Deviation	Mean	Standard Deviation
AGE	52	6	52	6
HEIGHT	161	9	158	7
WEIGHT	59	15	57	9

TABLE-2

		Case	Control
SEX	Female	9	13
	Male	21	17
SMOKING	YES	18	15

In our study 22 were females(37%) and 38were males(63%).the mean age was 52(+/-6) years both control and case . Mean height in case

161cm(+/-9) and in control158cm(+/-7)Mean weight in control 59kg(+/-15) and in case57kg(+/-7)

PULMONARY FUNCTIONS:

spirometry values Forced vital capacity (FVC),Forced expiratory volume with in 1s (FVC) and Peak expiratory flow(PEFR) rate recorded at the time of enrolment and at end of the study

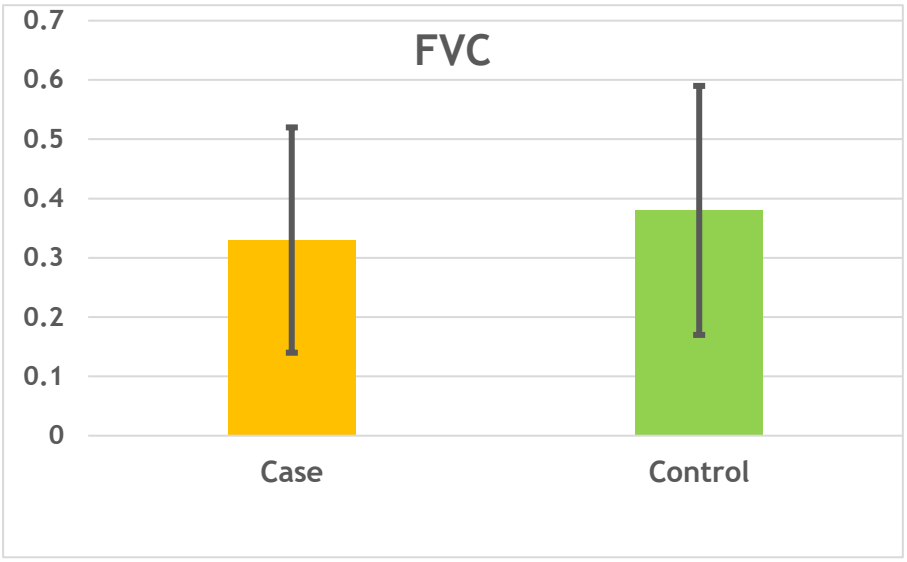
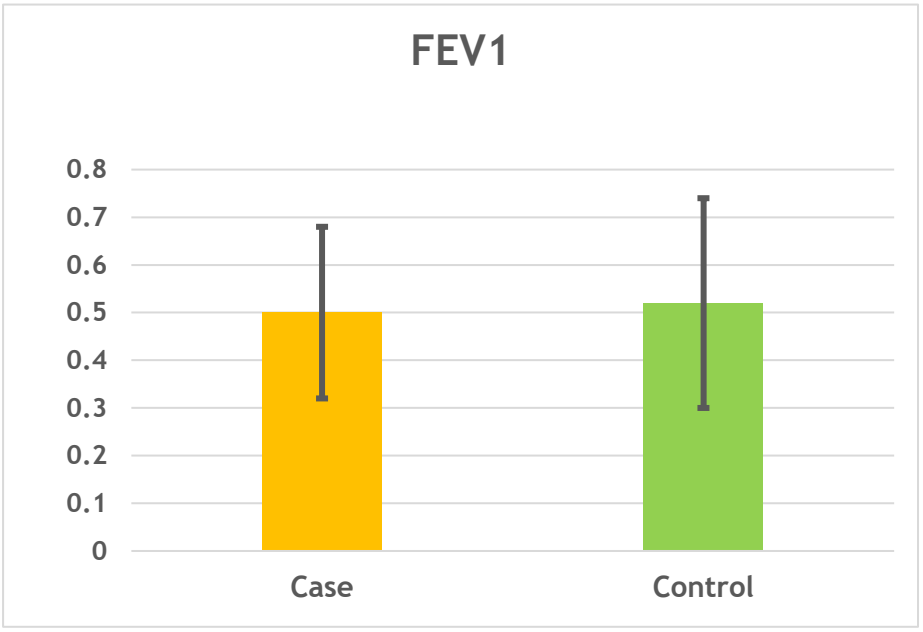


Figure-5



Figuer-6

TABLE.3

	Group							
	Case				Control			
	Mean	SD	Min	Max	Mean	SD	Min	Max
FVC-Baseline	1.83	0.4	0.85	2.54	1.68	0.54	0.79	2.43
FVC–After 12 Weeks	2.16	0.39	1.2	2.7	2.06	0.47	1.3	2.81

FVC-Liters/second

Forced vital capacity (FVC) Mean baseline values of case 1.83L (+/-0.4) ,control 1.68L (+/-0.54) .At the end of study Mean value of case 2.16L(+/-.39),control 2.06L(+/-0.47) There was no significant change in both groups.

TABLE.4

	Group							
	Case				Control			
	Mean	S D	Min	Max	Mean	SD	Min	Max
FEV – Baseline	1.13	.32	.64	1.71	1.13	.44	.47	2.40
FEV – After 12 Weeks	1.63	.31	1.11	2.34	1.65	.33	1.11	2.60

FEV1-Liters/second

Forced expiratory volume (FEV1) Mean baseline values of case1.13 L (+/-.32) ,control 1.13 L (+/-.44) At the end of study Mean value of case 1.63L(+/-.31),control 1.65 L(+/-.33). There was no significant change in both groups.

PEAK EXPLORATORY FLOW RATE(PEFR):

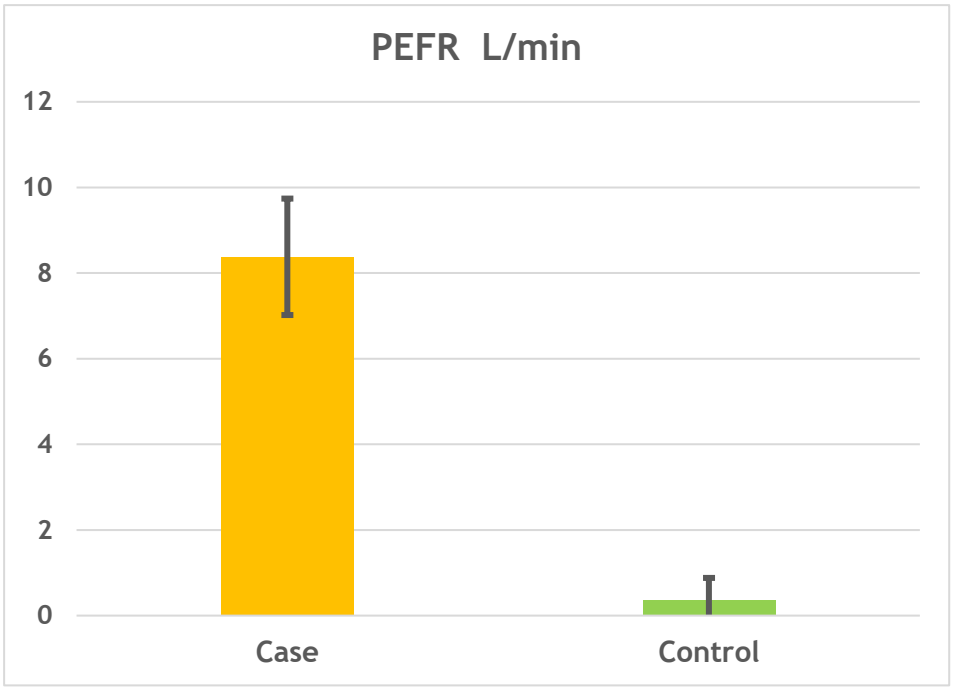


Figure-7,PEFR L/min

On comparing PEFR of both groups ,there was a difference of 8L/min in median change from baseline in rosuvastatin group as compared to control at 12weeks which was statistically significant (P=0.001)

TABLE-5

	Group							
	Case				Control			
	Mean	SD	Min	Max	Mean	SD	Min	Max
PEFR – Baseline	178.3	56.3	105.6	294	188.6	77.1	94.2	360
PEFR – After 12 Weeks	186.7	56.4	113	302	188.9	77	95	360

PEAK EXPIRATORY FLOW RATE (PEFR) initial baseline values in case178.3 L/min,control 188,6L/m At the end of 12week Mean value of PEFR in case 186.7L/min and in control 188.9L/min

TABLE-6

	Group	Mean Difference	Standard Deviation	P Value
FVC	Case	0.33	0.19	0.37
	Control	0.38	0.21	
FEV1	Case	0.50	0.18	0.75
	Control	0.52	0.22	
PEFR	Case	8.38	1.36	<0.001
	Control	0.35	0.53	

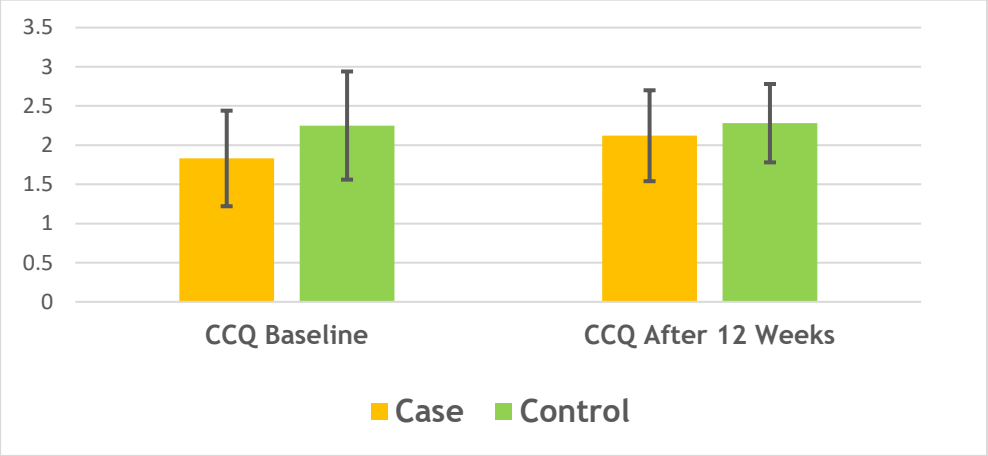


Figure-8

On comparing both group mean change in CCQ symptom score was not significant during study period (12 weeks)

Table-7

	Group							
	Case				Control			
	Mean	SD	Min	Max	Mean	S D	Min	Max
AST – Baseline	23.2	8.5	11	34.7	24.5	8.3	12.2	39
AST – After 12 Weeks	27	8.5	14.2	39.1	28.5	8	16	40.1

AST-Units/litter

Aspartate transaminase mean base line value in case 23.2 and control 24.5 after 12 weeks in case 27 and in control 28.5

TABLE-8

	Group							
	Case				Control			
	Mean	SD	Min	Max	Mean	SD	Min	Max
CPK – Baseline	39.1	8.5	26.4	55	40.1	9.1	27	55
CPK – After 12 Weeks	43.7	8.6	30.4	60.2	44.7	9.7	29.9	60

CPK-units/litter

Creatinine phosphokinae mean base line value in case39.1 and control 40.1after 12 weeks in case 43.7 and in control 44.7.

TABLE-9

	Group							
	Case				Control			
	Mean	S D	Min	Max	Mean	SD	Min	Max
HB Baseline	12.7	1.8	8.8	15.5	12.0	2.3	8.8	15.5
HB – After 12 Weeks	12.9	1.9	9.2	15	12.3	2.4	8.5	15.5

Haemoglobin-gms/dl

Haemoglobin mean base line value in case12.71 and control 12.9 After 12 weeks in case 12.02 and in control 12.3 ‘

The laboratory values AST, CPK and Hb% at the end of study there were no significant change.

This study suggest that the study drug improve only peak expiratory flow rate (PEFR)8L/min. During study period rosuvastatin was well tolerated safe, significant therapeutic effect in patients with moderate to severe COPD.

DISCUSSION:

Present study was carried out with the aim to evaluate the efficacy of Rosuvastatin along with long acting beta agonist, long acting muscarinic antagonist and inhaled corticosteroid in moderate to severe COPD patients.

Chronic obstructive pulmonary disease is non communicable disease combined with pulmonary and systemic inflammation[139-140] .It is one of the element in pathogenisis of chronic obstructive pulmonary disease. statin have anti-inflammatory action which influence inflammatory process of airway disease. smoking is one of leading cause for COPD in Indian population

Oxidative stress in the vascular wall lead to low grade inflammation due to decreased level of endothelium derived nitric oxide .this is the initial step in the atherosclerotic plaque formation[(141)]

Statin have beneficial pleotropic effect on immune system which is in dependant of the effect on lipids[142].Experimental study explained that statin have beneficial effects on airway inflammation .In Altose study state that current treatment with long acting beta agonist therapy in chronic obstructive relax smooth muscle and dilate airway[(143)] which is very useful in asthma patients who have hyper responsive airway and smooth muscle constriction. This bronchodilating effect is considerably less in COPD due to fibrosis of small airway and emphysema secondary to imbalance between elastin and collagen content.

Airway inflammation in COPD mainly due to neutrophil driven rather than T-helper type -2 cell(Th-2).inhaled corticosteroid inhibit neutrophil mediated airway inflammation in lesser extent.[143,144]

Wright et al study explained that the pulmonary vasodilator Endothelin(ET) have role in pathogensis and treatment of COPD patients[145].Endothelin and nitric oxide maintain the patency of blood vessel. Damaged blood vessel endothelin is synthesised and also released in large amounts but there is no increase in synthesis and release of nitric oxide It will lead to imbalance of endothelin and nitric oxide cause pulmonary artery remodelling,

Studies have shown that fluvastatin therapy increase the post transcriptional activity of the endothelial nitric oxide synthase gene ,inhibit the synthesis and secretion of Endothelin (ET), promote the NO synthesis and secretion and improve pulmonary function[146,147]

Biomarkers of disease progression in early COPD are uncertain. The lungs secreted club cell and is consider to have an anti-inflammatory characteristic. The data from the ECLIPSE Study state that baseline levels of serum CC-16 were combined with accelerated FEV1 decline in COPD patients over 3 years.[148] A similar result was also reported by the Lung Health Study.[149] Therefore, serum CC-16 may be apply as a biomarker of disease progression. In addition to CC-16, the plasma pro-surfactant protein B (pro-SFTPB) and the soluble iso form of the receptor for advanced glycation end products (sRAGE) are also reported as possible biomarkers for

disease evolution.[150,151].vanfletern l et al state that compared to LAMA/LABA or LAMA/LABA triple therapy decreased the risk of exacerbations and better pulmonary function and health condition.it also denote that triple therapy showed a improved survival. it explained that triple therapy is most effective treatment in moderate to severe symptomatic patients with chronic obstructive pulmonary disease with risk of exacerbations, with mild if any risk of adverse effects along with pneumonia.studies are examining the role of triple therapy in less severe symptomatic patients with COPD and asthma-COPD overlap slight[152].chronic inflammatory sequale stimulate vascular endothelial cells and smooth muscle cell to synthesis Endothelin ,promote the formation of pulmonary hypertension.

Atrovastatin can reduce the secretion of IL-6 and TNF- alpha,decrease the release of CRP,reduce the inflammatory effect , regulate the equilibrium between Nitric oxide and ET-1 and reduce the pulmonary artery pressure and improve pulmonary function by inhibiting the transcription of nuclear factor (NF)- KB.[153]

60 patients were evaluated in our study. They were randomly allocated into two groups. Each group have 30patients.They were named as case(study) and control .

Case group treated with Long acting beta agonist(LABA),Long acting muscarinic antagonist(LAMA),Inhaled corticosteroids and Rosuvastatin 10mg, and control group treated with Long acting beta agonist(LABA)/Long acting muscarinic antagonist(LAMA)/Inhaled corticosteroids for 12 weeks out of 60 patients 22 were female(37%) and38 were male(63%).End of the study all patients were assessed by pulmonary function test, clinical COPD Questionnaire symptoms score and laboratory investigations

There was no change in pulmonary function test such as FVC and FEV1,CCQ questionnaire symptom score Laboratery investigations [AST,CPK,HB%] in both the groups. In case group there was significant improvement in PEFR 8L/min from the baseline which is statistically significant(0.001).

Study done by Chogtu .et al on Rosuvastsin in COPD and Pulmonary hypertension also shows PEFR difference of 10L/min from baseline with Rosuvastatin group as compared to placebo at 12 weeks which was statistically significance(P-0.04)[154]

CONCLUSION:

From this study we are concluding that Rosuvastatin 10mg with LABA/LABA/ICS for 12week regimen in moderate to severe COPD patients. There was no change in FEV and FEV1.In study group there is significant improvement in PEFR 8L/min which is statistically significant. In our study rosuvastatin was well tolerated, safe has significant therapeutic effect in patients with moderate to severe COPD

SUMMARY:

In our study patients randomly allocated into two groups named as study group(case) control group. Each group consists of 30 in number .case group treated with LAMA/LABA/ICS with rosuvastatin 10mg for 12 weeks. control treated with LABA/LAMA/ICS for weeks.

According to GOLD guideline treatment of COPD depending on symptoms and exacerbations various drugs include bronchodialators and corticosteroids. But these drugs does not alter the basic pathology. The basic pathology of COPD due to inflammatory process on the basis of available study reports our study has been designed as Efficacy of long acting beta agonist /long acting muscarinic antagonist Inhaled corticosteroid along with rosuvastatin in moderate to severe COPD patients .

This study was conducted in tertiary care teaching hospital in Chennai after approval from Institutional Ethics committee .After obtaining informed consent 60 patients were enrolled in this study .patients were followed up for 12weeks all patients were assessed by pulmonary function test.

Patients symptoms reduction assed by pulmonary function test. Patients were followed up for 12 weeks .At the end of 12 weeks 60 patients completed their treatment . There was no significant change in FVC, FEV1 in both group .

In study group shows significant improvement in PEFR 8L/ min which was statistically significant (P=0.001).In our study Rosuvastatin was well tolerated and safe has significant therapeutic effect in patients with moderate to severe chronic obstructive pulmonary disease.

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ANNEXURES

Annexures

STUDY PROFORMA

PATIENT INFORMATION:

NAME:

OP Number:

Height:

AGE:

Weight:

GENDER:

OCCUPATION:

SMOKING STATUS:

ADDRESS:

PHONE NUMBER

HISTORY OF PRESENTING ILLNESS:

H/O COUGH AND SPUTUM

SPUTUM-QUANTITY

COLOUR

HALISTOSIS

H/O BREATHLESSNESS

H/O WHEEZE

H/O FEVER

H/O OLIGURIA

H/O PEDAL EDEMA

PAST HISTORY:

H/O DM/HT

H/O BRONCHIAL ASTHMA

H/O PREVIOUS ATT

H/O INTERSTIAL LUNG DISEASE

H/O EXACERBATIONS OF COPD& HOSPITAL ADMISSION

H/O DRUG ALLERGY:

PERSONAL HISTORY:

H/O ALCOHOL INTAKE

DRUG HISTORY:

DRUGS FOR COPD:ORAL/INHALED MEDICATIONS

GENERAL EXAMINATION:

PULSE RATE

RESPIRATORY RATE

BLOOD PRESSURE

PEDAL EDEMA

CARDIOVASCULAR SYSTEM

RESPIRATORY SYSTEM

PER ABDOMEN

CENTRAL NERVOUS SYSTEM

LABORATORY INVESTICATIONS

1. COMPLETE HAEMOGRAM

   HB-

   RBC/WBC-

2. LIVER FUNCTION TEST

   AST

3. CPK

SPIROMETERY

CLINICAL COPD QUESTIONNAIRES

சுய ஒப்புதல் படிவம்

ஆய்வின் தலைப்பு : நாட்பட்ட நுரையீரல் அடைப்பு நோய்களில் லாபா/ லாமா/ ஐ.சி.எஸ் மற்றும் ரோசுவாஸ்டேட்டின் மருந்துகளில் பலாபலன் மற்றும் பாதுகாப்பு குறித்த ஆய்வு.

ஆராய்ச்சி நிலையம் : அரசு ஸ்டான்லி மருத்துவக்கல்லூரி மற்றும் மருத்துவமனை சென்னை – 600001

பங்குபெறும் நோயாளியின் விவரங்கள்:

பெயர் : பிறந்த தேதி :

வயது: பாலினம்: ஆ / பெ மருத்துவமனை எண்:

பங்குபெறுபவர் இதனை ( ) குறிக்கவும்.

- மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது என்னுடைய சந்தேகங்களை கேட்கவும் அதற்கான தகுந்த விளக்கங்களைப் பெறவும் வாய்ப்பளிக்கப்பட்டது.

- நான் இவ்வாய்வில் தன்னிச்சையாகத்தான் பங்கேற்கிறேன் எந்த காரணத்தினாலோ எந்தக் கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகிக் கொள்ளலாம் என்று அறிந்து கொண்டேன்.

- இந்த ஆய்வு சம்மந்தமாகவோ இதைச் சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும்போது இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளைப் பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன் நான் ஆய்வில் இருந்து விலக்கொண்டாலும் இது பொருந்தும் என அறிகிறேன்.

- இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும் பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான முடிவுகளையும் மருத்துவர் மேற்கொள்ளும் மருத்துவருக்கு உண்மையாக இருப்பேன் என்றும் உறுதியளிக்கிறேன் என் உடல் நலம் பாதிக்கப்பட்டாலோ அல்லது எதிர்பாராத நோய்க்குறி தென்பட்டாலோ உடனே அதை மருத்துவ அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்கிறேன்.

- இந்த ஆய்வில் எனக்கு தேவையான இரத்த பரிசோதனை செய்து கொள்ள நான் முழு மனதுடன் சம்மதிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம் ..... இடம் .....தேதி.....

கட்டைவிரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

ஆய்வாளரின் கையொப்பம்.....இடம்.....தேதி.....

ஆய்வாளரின் பெயர்.....

நோயாளி அறிய வேண்டிய விவரங்கள்

ஆய்வின் பெயர் :

நாட்பட்ட நுரையீரல் அடைப்பு நோயில் லாபா/ லாமா/ ஐ.சி.எஸ் மற்றும் ரோசுவாஸ்டேட்டின் மருந்துகளின் பலாபலன் மற்றும் பாதுகாப்பு குறித்து ஆய்வு

ஆய்வாளர் :

மரு.கோ.வனிதா
பட்ட மேற்படிப்பு மருத்துவர்,
மருந்தியல் துறை,
அரசு ஸ்டான்லி மருத்துவ கல்லூரி
சென்னை – 600001

வழிகாட்டி :

பேராசிரியர் மரு.ரா.சிவகாமி,
மருந்தியல் துறை,
அரசு ஸ்டான்லி மருத்துவ கல்லூரி
சென்னை – 600001

துணை வழிகாட்டி :

பேராசிரியர் மரு.நான்சி குளோரி
சுவாச மருத்துவ துறை
அரசு ஸ்டான்லி மருத்துவ கல்லூரி
சென்னை – 600001

இந்த ஆய்வின் நோக்கமும் பயன்களும் யாவை?

நாட்பட்ட நுரையீரல் அடைப்பு நோய் உலக அளவில் மனித இறப்பிர்கு நான்காவது காரணியாக இருக்கிறது.2012 ஆம் ஆண்டு இந்நோயால் 3 மில்லியன் மக்கள் இறந்துள்ளனர். இந்த இறப்பு விகிதத்தில் இந்நோய் 6% சதவித பங்களிக்கிறது. 2020 ஆம் ஆண்டில் இந்நோய் இறப்பிற்கு மூன்றாவது காரணியாக மாறும் சூழ்நிலை உள்ளது.

இந்த ஆய்வில் பங்கேற்றால் என்ன செய்யவேண்டி வரும்?

இந்த ஆய்வில் பங்கேற்க சம்மதித்தால் உங்கள் நோய் மற்றும் அதைச் சார்ந்த விவரங்கள் பெறப்படும் தேவையான இரத்த பரிசோதனைகள் செய்யப்படும் மாதம் ஒரு முறை மருத்துவமனைக்கு வரவேண்டி வரும்.

இந்த ஆய்விற்கான பணசெலவு செய்ய வேண்டி வருமா?

இல்லை தேவைப்படாது. அனைத்து மருந்துகளும் இலவசமாக் மருத்துவமனையில் வழங்கப்படும் பரிசோதனைகளும் செய்யப்படும்.

இந்த ஆய்வில் பங்கேற்றால் ஏதேனும் இடர் வருமா?
இப்பொழுது கிடைக்கும் சிகிச்சை முறையில் மாற்றம் வருமா?
உங்கள் வழக்கமான சிகிச்சை முறையில் மாற்றம் எதுவும் கிடையாது. இந்த மருந்தினால் எப்பொழுதாவது இலேசான உடல் அசதி ஏற்பட வாய்ப்பு உள்ளது என்பதால் பயப்பட தேவையில்லை பக்கவிளைவுகள் ஏற்பட்டால் உடனே எங்களை தொடர்பு கொள்ளலாம்.

இந்த ஆய்வில் பங்கேற்றால் எனது தனிப்பட்ட விவரங்கள் பாதுகாக்கப்படுமா?
உங்கள் தனிப்பட்ட விவரங்கள் மற்றும் மருத்துவ பரிசோதனை விவரங்கள் இரகசியமாக வைத்துக்கொள்ளப்படும் இந்த ஆய்வின் விவரங்கள் மருத்துவ பதிப்பிதழ்களில் வெளியிடப்படும் ஆனால் உங்களது பெயர் தனிப்பட்ட விவரங்கள் வெளியிடப்படமாட்டாது.

இந்த ஆய்வில் இருந்து இடையில் நான் விலகிக்கொள்ள முடியுமா?
இந்த ஆய்வில் இருந்து ஆய்வு செய்யப்படும் காலத்தில் எந்த நிலையிலும் விலகிக்கொள்ளலாம். இது உங்களது மருத்துவ மற்றும் சட்ட உரிமைகளை எந்த விதத்திலும் பாதிக்காது.

ஆய்வினை பற்றி மேலும் விவரங்கள் அறிய கீழ்கண்ட அலைபேசி எண்ணிலும், மின்னஞ்சலிலும் முதன்மை ஆய்வாளரை (மரு.கோ.வனிதா) தொடர்பு கொள்ளலாம்.

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