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Review Article

Role of Corticosteroids in Treatment of Chronic Obstructive Pulmonary Disease (COPD)

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ABSTRACT

All patients with Chronic Obstructive Pulmonary Disease (COPD), a multifactorial illness, have decreased post-bronchodilator lung function. While it was once believed that hyperresponsiveness and acute bronchodilator reversibility were characteristics of asthma, it is now generally acknowledged that these clinical features also occur in COPD. The current review provides an overview of corticosteroids' role in treating COPD signs. Both localized and systemic inflammations are key components of the pathophysiology of COPD. Inflammation occurs during an exacerbation and has been linked to a quicker course of COPD. Both systemic and local inflammations have been linked to COPD and using both Inhaled and Systemic Corticosteroids (ICS) has been found to be important when treating COPD. According to several current international documents on the management and therapy of COPD, patients at high risk of exacerbations-those with a Forced Expiratory Volume in one second (FEV1) of a fifty percent probability of exacerbation or more than one exacerbation per year-should receive ICS in addition to long-acting bronchodilators as maintenance treatment. In summary, systemic corticosteroids are the gold standard for treating Acute Exacerbations of COPD (AECOPD). Research has shown that using these drugs can improve lung function in the short term while reducing the likelihood of treatment failure, 30-day recurrence rates and length of hospital stay.

Keywords: COPD, Corticosteroids, Chronic Inflammation, Inhaled Corticosteroids, Systemic Corticosteroids.

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INTRODUCTION

By 2030, COPD is predicted to surpass smoking as the third leading cause of death worldwide, continuing its long-standing history of contributing to both mortality and morbidity.[1] 3.23 million COPD-related deaths occurred in 2019, up more than 23% from 1990, based to the Global Burden of Disease Study.[2] The following is the Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition of COPD: An enhanced chronic inflammation in the lungs and airways to harmful particles or gases and progressive airflow restriction are the hallmarks of COPD, a common preventable and treatable condition. Exacerbations and comorbidities affect an individual's overall severity.[3] Chronic bronchitis and lung emphysema are common conditions that result in increasing airway blockage and are primarily brought on by cigarette smoking. As a matter of fact, two main phenotypes have been identified on the basis of clinical, pathological and radiological features: type B patients, also known as blue-bloaters (chronic bronchitis) and type A patients, also known as "pink puffers" (emphysema).[4,5] In addition to physical disability, COPD includes extra pulmonary and pulmonary consequences that affect stress levels on a mental, physical and emotional level due to the illness and its symptoms.[6] Cigarette smoking is the primary pathophysiological factor contributing to the development of COPD. It also encourages aberrant inflammation, oxidative stress, apoptosis and imbalances between the protease and anti-protease and increased deterioration of the lungs.[7,8] The ageing of the world's population and pollution, both indoors and outdoors, have been identified as additional causative factors. Theoretically, chronic inflammation is the cause of structural changes in the airway, airway blockage and respiratory symptoms. These, in turn, sustain chronic inflammation by releasing chemotactic mediators that attract more inflammatory cells into the lung, such as neutrophils, monocytes, lymphocytes and CD8+ T cells.[9]

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The primary risk factor for COPD that is not brought on by Alpha-1 Antitrypsin Deficiency (AATD) is smoking. COPD is hereditary and is caused by AATD.[10] Neutrophil elastase is a serine Protease Inhibitor (PI) that protects lung tissue from proteolytic injury. AAT is a strong enzyme with broad substrate specificity. As such, individuals with autosomal codominant disorder have an increased risk of acquiring COPD.[11,12] The Centers for Medicare and Medicaid Services and the National Committee for Quality Assurance's Healthcare Effectiveness Data and Information Set both list spirometry as a performance metric for COPD patients.[13] The Global Initiative for COPD 2018 Global Strategy for the Diagnosis, Management and Prevention of COPD[14] assesses the volume of air forced out during the first second of this maneuver (i.e., Forced Expiratory Volume in 1 second, or FEV1), the volume of air expelled from the point of maximal inspiration (i.e., Forced Vital Capacity, or FVC) and the ratio of these two measurements (FEV1/FVC). New spirometry guidelines have been approved by the American Thoracic Society and European Respiratory Society (ATS/ERS), emphasizing a one-second plateau or 15 sec of expiration, instead of 6 sec. Since spirometry had no bearing on therapy recommendations, it was excluded from the GOLD-ABCD evaluation of COPD. It has been found, nevertheless, that even ABCD is not very good at predicting effects and mortality. As a result, all COPD patients must use both classes at the same time as a compromise. Updated categories for the previous classification are 1A, 1B, 1C, 4A, 4B, 4C and 4D. The specific function of this modification is currently unknown because the ABCD method is still used to make treatment decisions. Spirometry is necessary, nevertheless, for decisions regarding surgical procedures like lung transplants and bullectomy.[15] Although a postbronchodilator ratio of FEV1/FVC 0.70 is used to diagnose COPD, the pathophysiologic changes in the lung tissue and airways that cause COPD start much earlier criteria is attained.[16]

Over the past 20 years, oral and inhaled corticosteroids have become increasingly significant in the therapy of COPD. As they alleviate symptoms and lessen exacerbations, inhaled corticosteroids are administered to more than half of COPD patients in certain clinical settings-a notable increase from only a few years ago.[17] Systemic corticosteroids are the gold standard of care for treating an Acute Exacerbation of COPD (AECOPD). Studies show that using them reduces treatment failure rates, 30-day recurrence rates and length of hospital stay in addition to improving short-term lung function.[18] But since corticosteroids can have major side effects, particularly when utilized systemically, the effectiveness question is crucial. Just finished or almost finished are a number of important clinical trials that should provide more information for clinicians making decisions about the use of systemic and inhaled corticosteroids in COPD. The doctor must decide whether the benefits of such therapy outweigh the possibility of side effects while the analyses and publication of these studies are still pending.[19]

Nature of inflammation in COPD

Airway inflammation is a recurring characteristic of COPD that results from an inflammatory response to noxious foreign particles such as cigarette smoke and burning biomass. It is also connected to the beginning and progression of the illness.[20] The continuous deterioration of the lung is connected to the production of inflammatory mediators (Figure 1) and destructive enzymes by immune systems, which is a major cause in the genesis of COPD.[21] Long-term cigarette smoke exposure damages the mucociliary carpet and the tight connections between epithelial cells, which constitute the pulmonary airway defence system. This damage aggravates the damage and leads to epithelial injury. Macrophages, lymphocytes and neutrophils become locally infiltrated due to the intoxication-related lesions. The mediators that are subsequently released by these cells act on the airway walls, resulting in constriction of the airways, increased muscle mass, fibrosis and limited breathing flow.[22] Patients with COPD have a wide variety of inflammatory cells living in their airways. Important players in the inflammatory processes associated with COPD have been identified, including neutrophils, macrophages, eosinophils and CD8+ lymphocytes.[23]

Neutrophils

A defining feature of COPD is lung inflammation and smokers still have increased lung counts of inflammatory cells.[24] When COPD first appears, there is a correlation between increased neutrophil numbers in the conducting airway lumen and maybe in the airway wall. In the tracheobronchial lumen of COPD patients, neutrophils outnumber macrophages.[25] A common feature of many long-term inflammatory lung diseases, airway neutrophilia is associated with the advancement of the illness, sometimes without regard to the underlying cause. Multiple clinical characteristics of COPD, including as mucus hypersecretion and emphysema, have been linked to neutrophils and their products. As mediators of the inflammatory alterations in the airways of people with COPD, these cells are thought to be important.[26] As shown by the degree of airway blockage, FEV1 decline, or emphysema severity, the amount and makeup of these compounds in sputum and airway lavage fluid are related to the disease's severity. Raised concentrations of Neutrophil Elastase (NE), Interleukin 6 (IL-6), IL-17 and Matrix Metalloproteinase 9 (MMP-9) are among the markers of neutrophilic airway inflammation.[27]

Monocytes/ macrophages

Nearly half of COPD patients have Lower Airway Bacterial Colonization (LABC), which is linked to increased inflammation, more frequent exacerbations and a faster rate of lung function decline. Alveolar macrophages are the primary phagocytic cell of the lungs throughout homeostasis; in charge of eliminating invasive pathogens.[28] The Bronchial Alveolar Lavage fluid (BAL) of smokers with and without COPD contains more

macrophages than that of nonsmokers.[29] It has been suggested that elevated blood monocyte recruitment causes much greater lung macrophage levels in COPD. However, exposure to cigarette smoke increases the synthesis of anti-apoptotic genes in macrophages. Furthermore, COPD macrophages have been shown to express anti-apoptotic proteins more highly, indicating that prolonged apoptosis is a probable source of macrophage accumulation in COPD.[30] Because of their increased activation of Nuclear Factor-kappa-B (NF-kB), macrophages have been demonstrated to have a significantly longer lifespan than neutrophils. This may also apply to the alveolar macrophages found in the lungs of cigarette smokers and COPD patients. Emphysema may arise as a result of the elastolytic enzymes released by alveolar macrophages in COPD, including MMP-9, neutrophil elastase and cathepsins.[31]

Lymphocytes

The initiation and progression of COPD are thought to be significantly influenced by lymphocytes. Interest has been particularly piqued in CD8+ cells. When a person has stable COPD, the quantity of CD8+ cells, which are increased in the peripheral blood and the submucosa of the airway, is connected with the degree of airflow limitation.[32] CD8+ cells generate Th1 cytokines, such as IP-10 (interferon-Inducible Protein-10), increased IFN-alpha and chemokines such as CXCL10 and CCL5 produced by Interferon-Gamma (MIG). These mediators can increase the immune system's ability to produce MMP from macrophages and other consequences, which can lead to tissue damage. All of these mediators, which affect the immune system and the aetiology of the disease, are more prevalent in COPD patients. CD8+ cells release granzyme B, TNF-ά and perforins, which cause alveolar epithelial cells to be cytolyzed and die, leading to the development of emphysema.[33,34] Compared to healthy nonsmokers or COPD patients, AECOPD patients showed significantly lower percentages of CD8+ T cells. Disorders in peripheral blood CD8+ T cells were the source of immune response failure in the pathogenesis of COPD. COPD exacerbations are associated with increases in sputum CD8+ T cells and a relative drop in the ratio of CD8+ T lymphocytes producing IFN-γ/IL4.[35]

Systemic inflammation

Systemic inflammation, which includes elevated levels of circulating inflammatory cytokines, activation of circulating inflammatory cells and systemic oxidative stress, is linked to COPD, along with an abnormal inflammatory response in the lungs.[36] The mechanisms underpinning the systemic inflammation linked to COPD are the subject of multiple theories. It is believed that systemic inflammation is brought on by tobacco use. Given that smoking tobacco has been connected to other systemic inflammatory diseases, such as coronary artery disease and atherosclerosis, this is an intriguing theory.

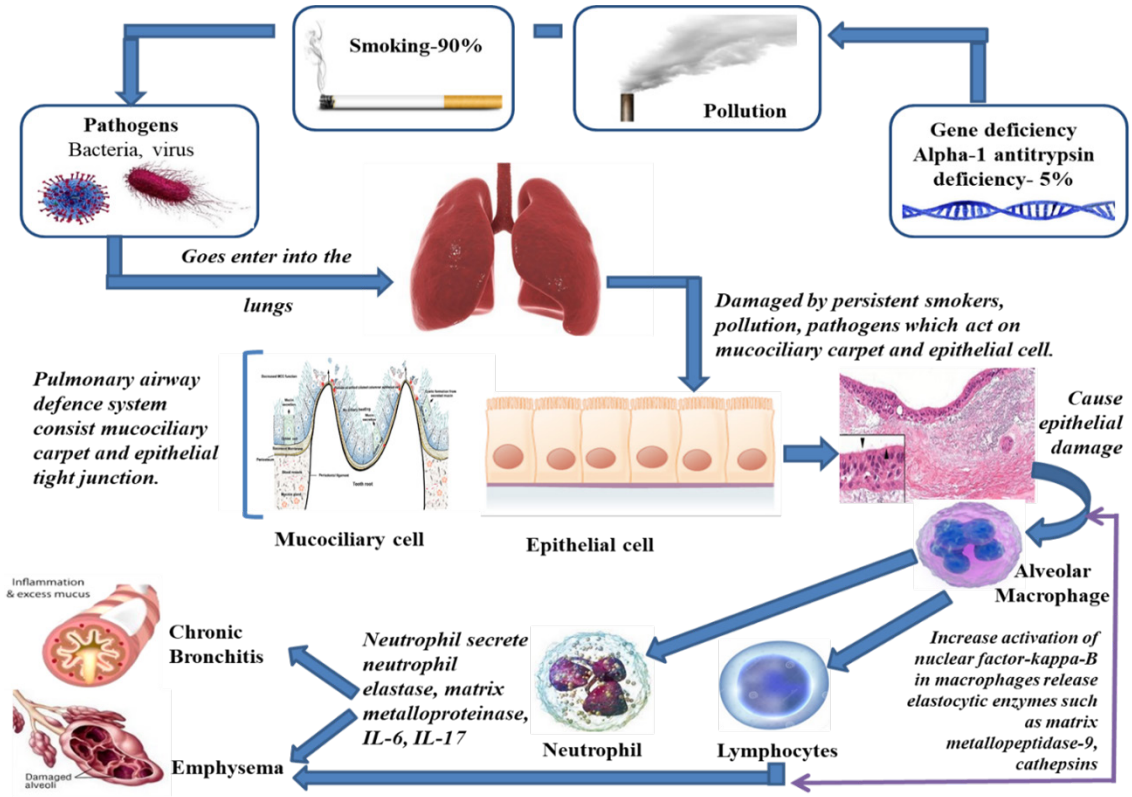

Figure 1: The figure represents the chronic inflammation by releasing different inflammatory cells or mediators due to smoking, pollution, pathogens or also by alpha-1 antitrypsin deficiency which cause emphysema and chronic bronchitis which leads to COPD (Chronic Obstructive Pulmonary Disease).

In addition to causing damage to peripheral vascular endothelial cells, passive smoking exposure raises systemic oxidative stress.[37] During exacerbations, systemic inflammation is increased. There have been reports of elevated blood levels of C-Reactive Protein (CRP), IL-8, TNF-ά, leptin, endothelin-1, eosinophil cationic protein, myeloperoxidase, fibrinogen, IL-6, a1-antitrypsin and leukotriene E4 and B4 during an exacerbation in comparison to baseline.[38]

The term "systemic inflammation" refers to two things: (a) the most likely major common mechanism through which significant threat factors, such as overweight, smoking, hyperlipidemia and hypertension, lead to chronic diseases, including COPD; and (b) nearly half of all individuals 65 years of age or older have at least three chronic illnesses, with comorbid circumstances accounting for more than 50% of COPD patients' medical care resources.[39] When combined with other risk factors like obesity, hyperlipidemia and elevated blood pressure, smoking can cause a number of chronic diseases, including metabolic syndromes, cardiovascular disease and certain cancers. These diseases can all be precipitated by the systemic effects of smoking. These long-term conditions may develop in conjunction with COPD or apart from it.[40]

Tissue inflammation

While COPD undoubtedly causes systemic inflammation, the inflammatory cascade may have its origin in local inflammation within the lung parenchyma and airways.[41] During COPD exacerbations; there is a noticeable increase in airway inflammation along with enhanced neutrophils, lymphocytes and eosinophils in the sputum and airways. In macrophages, cigarette smoke activates posttranslational Histone Deacetylase (HDAC) activation, p38 Mitogen-Activated Protein Kinase (MAPK) and nuclear factor-B (NF-β). By lowering HDAC efficiency and raising histone acetyltransferase activity, oxidative stress-induced damage encourages the expression of pro-inflammatory enzymes in COPD patients.[42,43]

Two distinct stages of GC-mediated gene suppression require HDAC2. To enable binding to pro-inflammatory transcription factors like nuclear factor-B (NF-β), HDAC2 must first remove this acetyl group. Secondly, HDAC2, which deacetylates histones and thereby inhibits transcription, is drawn to active GR.[44] Alveolar macrophages from cigarette smokers have lower levels of HDAC, which also reduces the macrophages' production of inflammatory cytokines. Figure 2 illustrates how higher exacerbations and the severity of COPD disease are associated with decreased HDAC activity and raised histone acetyltransferase activity. Less than 5% of smokers' HDAC2 is reportedly expressed by patients with severe COPD. It is advised to use this decreased expression of HDAC2, which is HDAC4 close to the IL-8 promotor, as a gauge of the severity of symptoms as the condition progresses.[45]

It has been demonstrated that Cigarette Smoke Extract (CSE) exposure decreases HDAC3 expression and activity in bronchial epithelial cells and alveolar macrophages. HDAC6 protein levels were not altered in cultured lung endothelial cells exposed to CSE *in vitro*, but were markedly reduced in the lung tissues of mice exposed to CS for three weeks.[46] This finding contrasts with other HDACs, such as elevated cytoplasmic HDAC6 expression

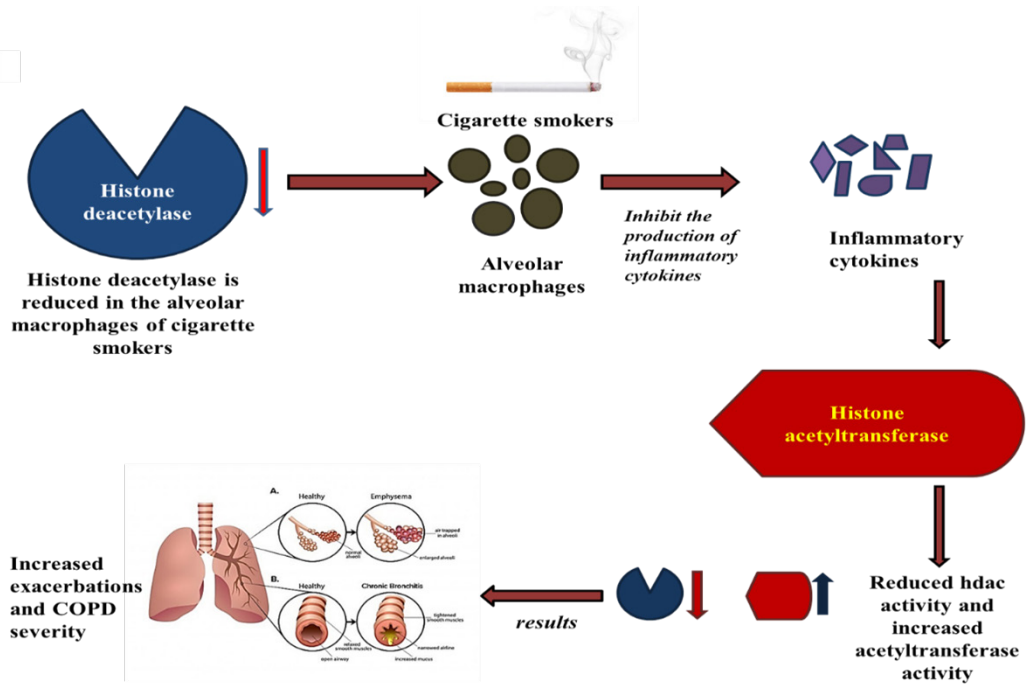

Figure 2: Represents the role of Histone Deacetylase (HDAC) activity in tissue inflammation which results in exacerbations and COPD severity.

in the lung tissues of chronic smokers with COPD, which may be caused by HDAC6 hypomethylation.

Inflammatory role of corticosteroids in COPD

The effectiveness of corticosteroids in treating COPD patients over the long term is a topic of significant controversy. Corticosteroids may lessen bronchial hyperreactivity, lessen the duration of exacerbations and limit the rate of worsening of the individual's health situation, according to recent studies, even though they may not slow down the rate of deterioration in lung function.[47] A longer time to first exacerbation or lower rates of exacerbation were observed in patients with greater serious airflow restriction (mean FEV1 50% expected) in subsequent ICS studies. These trials' meta-analyses revealed that ICS decreased Acute Exacerbations of COPD (AECOPD) by 30%.[48] Neutrophils, macrophages and CD8+T cells are more prevalent in COPD4 and the disease is less sensitive to the impact of inhalation corticosteroids on airway inflammation evident than in asthma. In spite of this, inhaled corticosteroids were prescribed for COPD even before the clinical benefit was demonstrated; in fact, 54% of patients enrolled in one of the first clinical trials of inhaled corticosteroids for COPD had previously employed inhaled corticosteroids. Inhaled corticosteroids were found to have a therapeutic benefit in COPD after clinical trials.[49]

The number of eosinophils in the blood has been shown in multiple studies to be predictive of a patient's prognosis for ICS therapy.[50] Bafadhel *et al*. identified a number of subcategories that were linked to high eosinophil counts, bacterial or viral infections and were responsible for 55%, 29% and 28% of exacerbations, respectively. Moreover, some COPD patients experience elevated eosinophil levels in their sputum during exacerbations. Significantly, responsiveness to systemic Corticosteroids (CSs) for exacerbation therapy and ICSs for preventing exacerbations may be predicted by sputum and/or blood eosinophilia in COPD patients. Current COPD care guidelines recommend the use of Inhaled Corticosteroids (ICS). For instance, the GOLD Guideline states that breathed-in corticosteroids should only be given to patients who have a severe illness (FEV 1 <50% projected normal, GOLD stage III) and have experienced two or more exacerbations annually.[51] Although early research has not consistently shown a positive effect on FEV1 decrease, a larger study titled "Towards a Revolution in COPD Health" showed evidence that prolonged therapy with ICS and/or LABA attenuates FEV1 loss in COPD. All severity levels of COPD patients' mortality were shown to be lowered by ICS treatment, with a particularly significant effect in stages III and IV (15% in stage I, 49% in stage II, 28% in stage III and 9% in stage IV).[52] The results of this meta-analysis, which included seven prospective investigations with intermediate- and long-term follow-up, were corroborated. The mainstay of COPD treatment is long-acting bronchodilators; however, even with maximal bronchodilation, some patients continue to have severe or frequent exacerbations. These patients pose a substantial challenge to clinical treatment and have an increased risk of death. In addition to being helpful for some COPD patients, ICS is the cornerstone of treatment for asthma. ICS are generally advised for people with COPD in all severity levels and exacerbation risk and they are especially suitable for those with exacerbations who are not responding to bronchodilator therapy. In most developed countries, 40% of COPD patients are expected to be candidates for ICS, based on the GOLD criteria, though prescribing rates may reach 80%.[53,54]

Systemic corticosteroids in COPD

Systemic corticosteroids were often and uniformly prescribed to all patients experiencing acute exacerbations.[55] The use of systemic steroids in COPD is recommended differently depending on the stage of the disease.[56] Systemic steroids were investigated in mild and severe acute exacerbations. Systemic corticosteroids enhance airflow, lower the incidence of treatment failure and the likelihood of recurrence and may improve symptoms and shorten hospital stays when compared to placebo. As a result, corticosteroids are advocated for use in the treatment of AECOPD by all major recommendations. Existing research demonstrates that low-dose oral corticosteroid regimens are equally effective as high-dose intravenous corticosteroid regimens while causing fewer side effects.[57] On the other hand, systemic corticosteroids, did not reduce mortality and caused a considerable increase in adverse effects (in particular a five-fold increase in hyperglycaemic episodes). In contrast, favorable benefits of systemic steroids in stable COPD are limited: there is some indication that larger doses (30 mg prednisolone/day) may enhance lung function for a short period, however, this was not found in doses less than 10-15 mg prednisolone/day.[58]

In nine studies (n=917) compared to placebo, systemic corticosteroids significantly decreased the likelihood of treatment failure by more than half. The trials had a median treatment duration of 14 days and an odds ratio (or) of 0.48 (95% Confidence Interval (CI) 0.35 to 0.67). The quality of the evidence was high and the administration of systemic corticosteroids to nine individuals (with a 95% confidence interval of 7 to 14) was necessary to prevent one treatment failure. Systemic corticosteroid treatment reduced the incidence of recurrence by one month in two studies (n=415); the evidence was of intermediate quality (Hazard Ratio (HR) 0.78; 95% Confidence Interval (CI) 0.63 to 0.97).[59] Researchers looked at how well oral prednisone worked to reduce the likelihood of recurrence after an outpatient exacerbation of COPD. After releasing patients from the emergency room, they randomly allocated them to receive either a placebo or prednisone for a period of 10 days. They found that at 30 days, there was a lower chance of recurrence (27% vs. 43%; p=0.05), more time was spent without relapse (p=0.04) and there was a non-significant drop in COPD hospitalizations (11% vs. 21%; p=0.11). They also discovered that after 10 days of therapy, individuals given systemic corticosteroids had improved

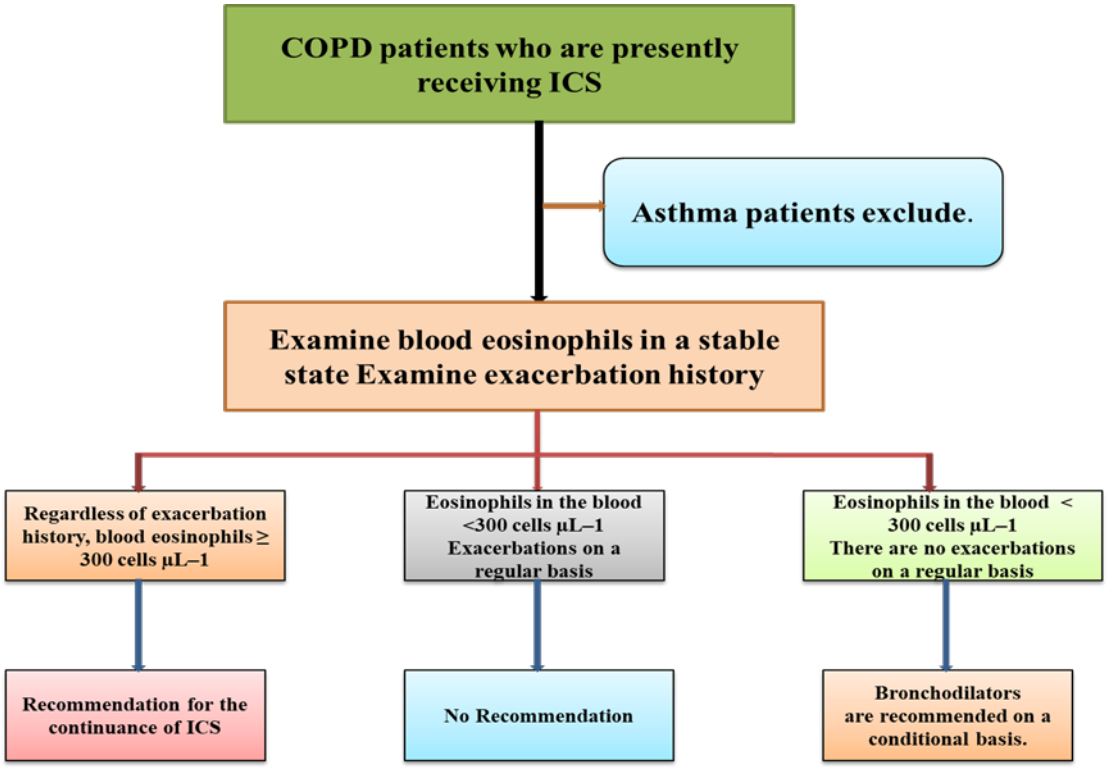

Figure 3: Represents the European Respiratory Society's (ERS) in patients with Chronic Obstructive lung Disease (COPD) that systemic corticosteroids reduce eosinophil levels in the blood and withdrawal algorithm for Inhaled Corticosteroids (ICS).

lung function, less dyspnea and a higher quality of life, according to the Chronic Respiratory Illness Questionnaire (CRQ).[60] Eosinophilic airway inflammation is linked to around 30% of COPD exacerbations. Exacerbations of COPD with sputum eosinophilia have been reported to have the best response to systemic corticosteroid treatment in terms of FEV1.[61,62]

A single-center prospective randomized study was conducted to determine the appropriate course of systemic corticosteroid therapy based on the circulating eosinophil count (relative count of 2%) during an exacerbation. This study found that the ability to exercise and a quicker recovery from symptoms, as well as a lower rate of treatment failures (defined as re-treatment, hospitalization, or death), were associated with eosinophilic COPD exacerbations.[61] A subgroup with eosinophilic inflammation known as a peripheral blood eosinophil count of less than 2% of total leukocyte count those benefits from systemic corticosteroid therapy is emerging and during a COPD exacerbation, the peripheral blood eosinophil count is a reliable proxy for sputum eosinophilic airway inflammation.[63,64]

Researchers found that stopping inhaled corticosteroids for four weeks was linked to a 70% increase in serum CRP levels in a study of forty-three patients (ages 45 to 80) who had stable COPD symptoms during the previous three months. In contrast, CRP levels in subjects who had never taken corticosteroids did not change significantly during the same time period. Significantly, CRP levels were lowered by 50% when fluticasone (1 mg/day) was started and by 62% when prednisone (30 mg/day) was started. The reductions in CRP levels brought about by either systemic or inhaled corticosteroids were sustained over the course of the four months that fluticasone was administered.[65]

Inhaled corticosteroids in COPD

The Global Initiative for Treatment for Chronic Obstructive Lung Disease 2021 Report suggests ICS-containing regimens as part of pharmacological treatment for patients with COPD who have recurrent exacerbations, particularly when there is eosinophilic inflammation.[66] Because ICSs are not very successful at treating COPD, all national and international COPD recommendations prescribe them only for patients with severe symptoms and a higher risk of exacerbation. Treatment with these drugs, however, improves the quality of life associated with health for some subgroups of COPD patients (e.g., reduced exacerbation rate, slower progression of pulmonary function loss).[67] Patients with COPD/asthma overlap and frequent exacerbators with predominant chronic bronchitis make up these patient subgroups. More and more studies point to the potential advantages of corticosteroids for the cardiovascular system, particularly at low dosages. Over a three-year period, individuals allocated to inhaled budesonide had a 40% reduced risk of cardiovascular events compared to those assigned to placebo, according to a post-hoc analysis of a major randomized controlled study conducted by the EUROSCOP trial investigators.[68] It is essential to bear in mind, nevertheless, that not every COPD patient will see

advantages from ICS therapy. The GOLD approach reserves the use of ICS as part of the first treatment in COPD group D patients with two or more mild exacerbations, one exacerbation that lead to hospitalisation in the preceding year and a blood eosinophil count exceeding 300 cells/L. Intra-abdominal cardiopulmonary bypass (LABA) patients with COPD who experience recurrent exacerbations should only take ICS as part of their follow-up care.[69] Subanalyses of major randomized studies have demonstrated that ICS reduces the risk of exacerbation in individuals with increased blood eosinophil counts. It is most effective in those with the highest blood eosinophil counts.[70] When prednisone was administered to individuals with sputum eosinophilia, sputum eosinophil levels were shown to decrease seven-fold more than when budesonide medicine was used.[71] The threshold for an ICS benefit on exacerbation, 300 cells/mL, is shown in Figure 3.[72]

Present guidelines, however, suggest using Immunosuppressive medicine (ICS) for patients with severe and very severe COPD who have frequent exacerbations. A number of trials assessing the anti-inflammatory benefits of ICS in patients with COPD have not employed bronchial biopsies or Bronchoalveolar Lavage (BAL). According to a recent meta-analysis, bronchial biopsies showed less CD4+ and CD8+ cells in patients receiving ICS therapy for 12-26 weeks. Additionally, while neutrophil and lymphocyte counts were down, ICS raised macrophage levels in BAL. Previous studies have demonstrated that a 30-month course of inhaled fluticasone medication reduces the numbers of mast cells, CD3+, CD4+, CD8+, neutrophils, lymphocytes and macrophages in sputum.[73,74] In patients with moderate-to-severe COPD, fluticasone medication decreased sputum neutrophils, macrophages and lymphocyte counts for 30 months, but stopping fluticasone after six months increased bronchial CD^{3+}, mast and plasma cell counts (Groningen Leiden Universities Corticosteroids in Obstructive Lung Disease, or GLUCOLD)-1 trial data. In a long-term observing follow-up study, patients who stopped taking fluticasone after 30 months of treatment reported an increase in mast cells, bronchial T-lymphocytes and sputum inflammatory cells (GLUCOLD-2). A correlation between higher numbers of sputum macrophages and a quicker rate of lung function loss was also found in the GLUCOLD-2 study. According to these trials, at least some COPD patients may benefit from taking ICS medication, especially if they have significant airway inflammation.[75] Several randomized clinical trials have shown that quitting corticosteroids abruptly might cause adrenal insufficiency, poor lung function, increased exacerbations and other concerns that COPD patients experience.[76,77] Many studies also suggest that in the majority of these patients, particularly those with mild to moderate COPD, no history of exacerbations and a history of pneumonia, ICSs should be regularly withdrawn.[78] Even though comparable outcomes have been documented since 2007, it is still unknown how ICS affects pneumonia mortality. Another study found no connection between the risk of pneumonia and the usage of ICS. Furthermore, no connection was found in another investigation between the use of ICS and an increased risk of pneumonia in individuals with COPD. Compared to Fluticasone/Salmeterol (FP/SM), using Budesonide/Formoterol (BUD/FM) is associated with a decreased incidence of pneumonia. As such, there is ongoing controversy over the correlation between ICS and pneumonia.[79] The SUMMIT sub-study indicates that ICS may be helpful for individuals with FEV1 values greater than 60% of predicted and no history of exacerbations. ICS are normally recommended for patients with a FEV1 value of less than 60% of expected and a history of exacerbations.[80]

Mechanisms of corticosteroids in COPD

Liposoluble hormones, Glucocorticoids (GCs) and CSs, readily penetrate cell membranes and bind to Glucocorticoid Receptors (GR) in the cytoplasm. Depending on the receptor's function, these GRs can be identified as either the less common GRβ isoform or the GRα isoform of GR.[81] By blocking the receptor's sites necessary for passage over the nuclear membrane and into the nucleus, Hsp90, p23 and FK-binding protein dissociate after the corticosteroid connects to GR, protecting the receptor and inhibiting nuclear localization. This interacts with import proteins such importin α to allow the activated GR-corticosteroid complex to localize inside the nucleus and bind to DNA.[82-84] In the responsive gene promoter region, activated GRs homodimerize and attach to certain genomic DNA sequences called Glucocorticoid Responses Elements (GREs). After binding, the ligand frees the receptor from its complex of proteins, allowing the activated GR-ligand complex to quickly translocate into the nucleus. Here, they have the ability to stimulate or inhibit the transcription of different molecules, including mediators of inflammation.[85] Gene transcription is altered when two homodimers of glucocorticoid receptor molecules bind to GRE. Interaction between GR and GRE often results in increased transcriptional activity (transactivation) and decreased production of pro-inflammatory cytokines from genes encoding transcription factors that generate anti-inflammatory compounds (e.g., lipocortin 1 and IκB).[86-88] HDAC must be engaged for the CS-GR complex to work. By de-repressing nuclear sequence transcription and altering the local chromatin structure, this permits transcription to take place. What gives CS its effect apart from direct DNA binding is the ability of the CS-GR complex to bind particular signal-dependent transcription factors, like NF-κB, Activator Protein 1 (AP-1), or Interferon Regulatory Factor-3 (IRF-3). These factors are usually activated by signal transduction cascades that begin when circulating cytokines bind to specific cell receptors. These transcription factors decrease their capacity to transactivate genes transmitting proinflammatory substances (trans-repression) when bound by CSGR, as seen in Figure 4.[89,90] Glucocorticoids inhibit proinflammatory transcription factors like AP-1 by activating genes that produce β2-adrenergic receptors and anti-inflammatory proteins like Secretory Leukoprotease Inhibitor (SLPI), Glucocorticoid-Induced Leucine Zipper

(GILZ) and Mitogen-activated protein Kinase Phosphatase-1 (MKP-1).[90,91] These outcomes might help to explain some of the glucocorticoids' anti-inflammatory qualities. One possible role for GR interaction-mediated decrease of gene transcription in the regulation of osteocalcin, an enzyme involved in bone formation is to mediate a range of glucocorticoid side effects. This includes GREs that cross the transcriptional start site and negative GREs.[92] This is how corticosteroids work to reduce inflammation. Nonetheless, research on the mechanisms underlying COPD has demonstrated the crucial roles HDAC plays in the disease.[93] Alveolar macrophages from COPD patients exhibited reduced HDAC activity compared to healthy controls.[94] Some of this lack of responsiveness to corticosteroids may be explained by the inhibitory effects of smoking cigarettes and oxidative and nitrative stress, which speed up the production of peroxynitrite and nitrate certain tyrosine residues on particular proteins.

Figure 5 shows that in COPD patients' peripheral lungs and macrophages, HDAC-2, but not other HDAC isoforms, exhibits increased tyrosine nitration.[95] This obstructs the important anti-inflammatory action of HDACs, which is linked to elevated corticosteroid production of IL-8, TNF-ά and MMP-9. In the peripheral lungs of COPD patients, HDAC expression and activity are markedly reduced.[96] High levels of reactive oxygen and nitrogen species develop in COPD, which triggers the production of proinflammatory cytokines and chemokines, mucus hypersecretion, activation of proteases and destruction of cellular components. Histones' acetyl groups are removed by HDAC enzymes which affects how genes are expressed. HDAC2 is downregulated in lung tissue and alveolar macrophages in COPD and it also lowers the expression of inflammatory genes.[97] It is believed that one of the main factors contributing to COPD patients' increasing steroid resistance is reduced HDAC2. For effective protein complex development restriction with NF-kappa B and AP-1, a low acetylated GR is required.[98]

Studies have demonstrated that andrographolide can help reduce inflammation and increase the levels of HDAC2 and Nuclear factor erythroid 2-related factor (Nrf2) in the mononuclear cells seen in Figure 6 as well as corticosteroid responsiveness in COPD.[99] The study employed a model of acute lung damage brought on by cigarettes, human U937 monocytic cells exposed to smoke and Peripheral Blood Mononuclear Cells (PBMCs) from COPD patients. A different study also revealed that andrographolide restored the LPS/IFN-induced IL-27 levels in mice's BAL fluid and AHR, thereby restoring dexamethasone's anti-inflammatory effects. LPS/IFN dramatically reduced the nuclear level of HDAC2, a crucial epigenetic enzyme that helps corticosteroids have their anti-inflammatory effects. Andrographolide significantly decreased the overall HAT/HDAC activity ratio in mouse lungs displayed to LPS/IFN- and restored nuclear HDAC2 levels, most likely by up-regulating the antioxidant transcription factor Nrf2 and inhibiting PI3K/Akt/HDAC2 phosphorylation.[100]

A powerful antioxidant called MnPD and plasmid DNA encoded with HDAC2 were code delivered using core-shell type LPNs into H2O2-treated A549 cells in an *in vitro* model of COPD. This led to the elimination of intracellular ROS and a significant increase in intracellular HDAC2 expression levels, which in turn reduced IL-8 secretion and improved glucocorticoid resistance.[101] There are more methods for recovering HDAC2 activity and corticosteroid sensitivity in COPD and asthma. Researchers have been looking into the possibility of theophylline, a bronchodilator and nonspecific phosphodiesterase (PDE) inhibitor, to increase corticosteroid sensitivity in patients with COPD because it was discovered to increase HDAC2 expression in these patients. Early

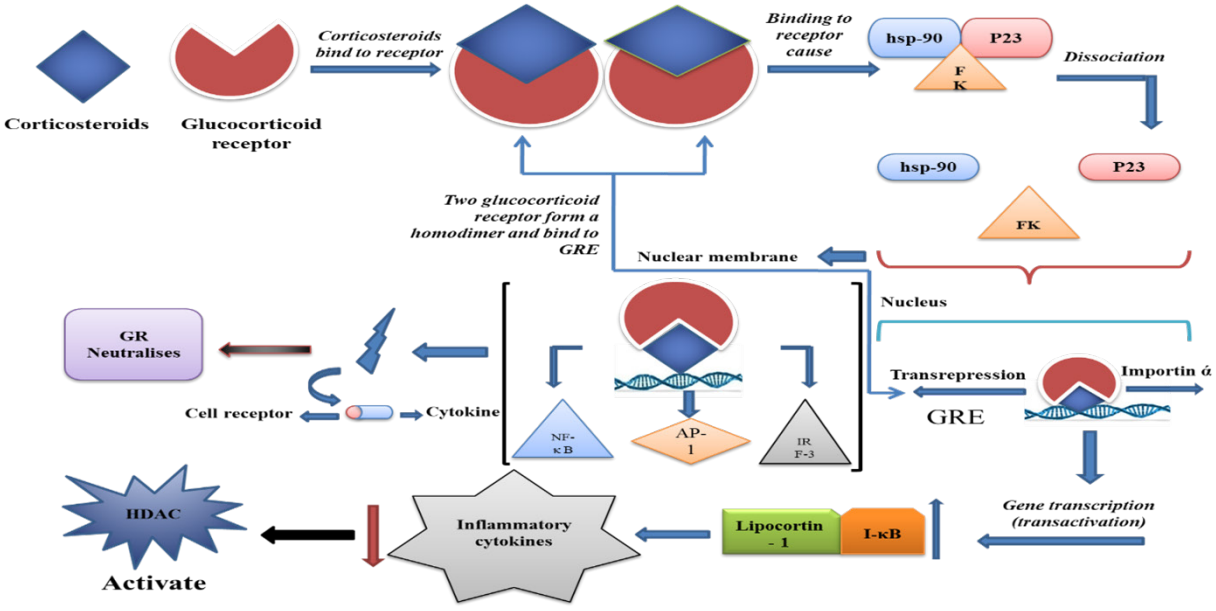

Figure 4: Represents the mechanism of binding of corticosteroids to Glucocorticosteroid receptor and also show transactivation or transrepression process.

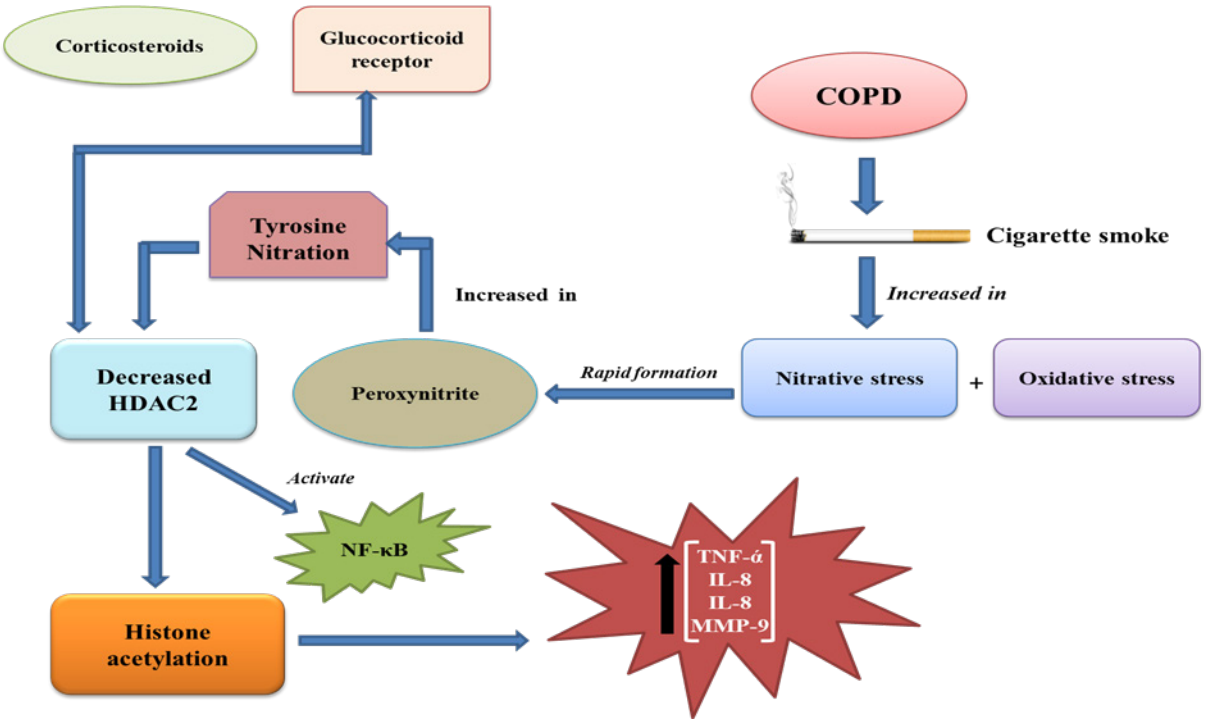

Figure 5: Represent that mechanism of corticosteroid resistance in COPD patients.

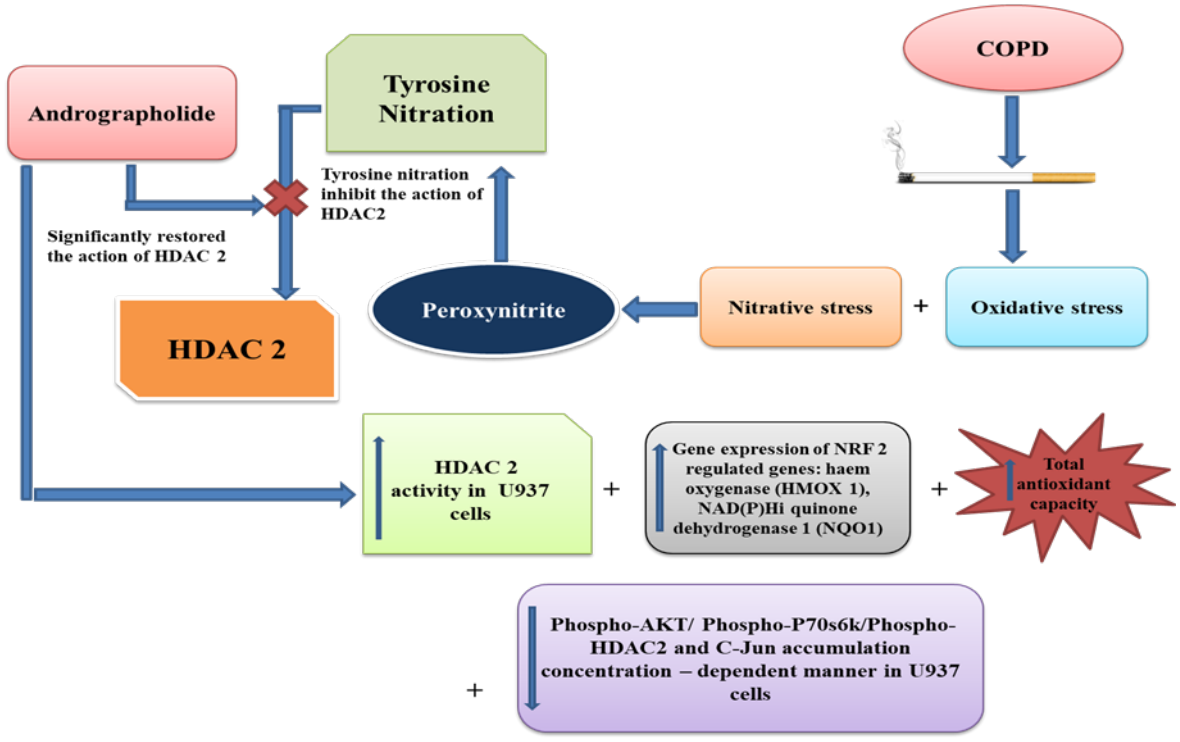

Figure 6: Represent that Andrographolide restored the HDAC2 resistance by enhancing HDAC 2 activity and HDAC 2 level in U937 cells.

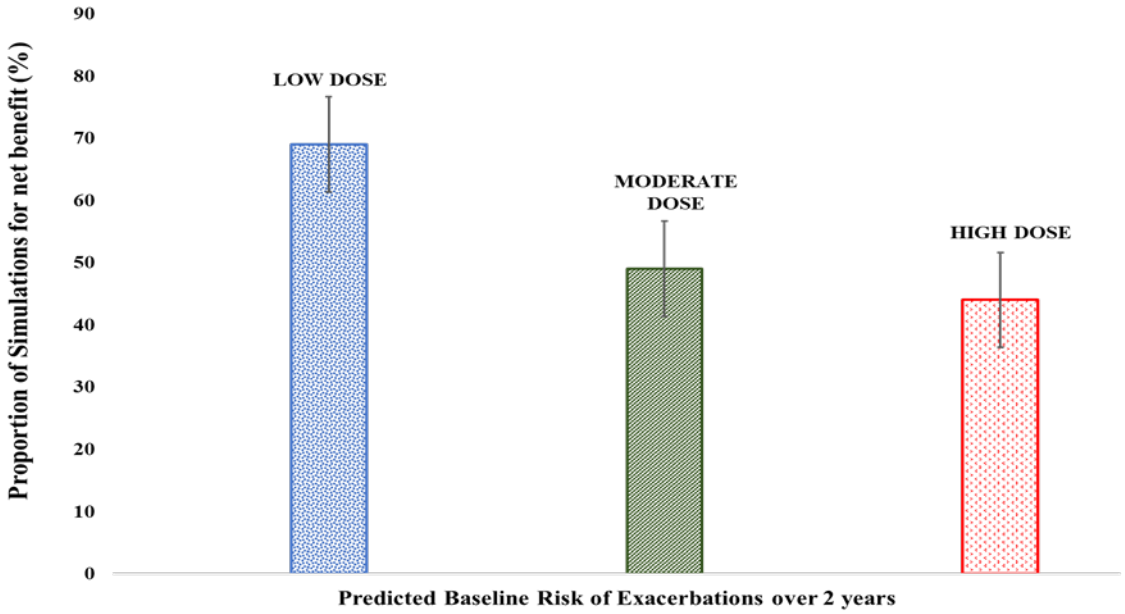

Figure 7: Exacerbation risk over a 2-year baseline: probability of net clinical benefit.

studies discovered that low-dose theophylline and corticosteroids increased HDAC activity and reduced inflammation in COPD patients.[102]

Low dose vs high dose in COPD management

In COPD, corticosteroids can considerably reduce treatment failure, improve lung function, exacerbations and symptoms. However, the appropriate dosage is still debatable.[103] Observational studies show that low-doses of systemic steroids may be preferable to high-doses in individuals with AECOPD, despite the fact that large doses are more often employed.[104] Low dosages (40 mg) for no more than 5 to 7 days for exacerbations are recommended in a 2019 study from the GOLD, based on findings that demonstrate no worse outcome with low-dose oral than with high-dose IV treatment.[105] In research published in 2011, Wang *et al.* found that when compared to high-dose steroid therapy and placebo groups, low-dose steroid treatment resulted in the lowest death rates.[106] Methylprednisolone dosages of less than or equal to 240 mg/day were administered to ICU patient having AECOPD who were taken into one of 473 hospitals and the subjects of the pharmacoepidemiologic cohort investigation. In patients hospitalized to the ICU for AECOPD, smaller doses were observed to be clinically preferable to increased doses. A shorter length of stay in the intensive care unit and hospital, less time spent on invasive ventilation and fewer unpleasant events were among the clinical benefits, even though there was no discernible decrease in mortality.[107]

High doses of ICS have been linked to a higher airway bacterial load and a higher threat of mycobacterial infections, such as pulmonary tuberculosis reactivation. These side effects may be due to impaired function of immune response cells, such as alveolar macrophages, T-cells and other signaling cytokines. Conversely, lesser doses of ICS seem to primarily have anti-inflammatory properties and alter the humoral components of the innate immune reaction potentially lowering the threat of tuberculosis and pneumonia as well as the bacterial load in the airways.[108] A single-center retrospective cohort study was carried out on individuals who met the criteria for AECOPD (Figure 7). Within the three inpatient cumulative dosage range groups, the following are the low: 250 mg prednisone equivalents, medium: 251 to 500 mg and high: 501 mg. 665 records in all were examined. As the corticosteroid dosage ranges increased, the proportion of people with elevated blood glucose levels increased (33.3%, 54.4% and 59.9%). The average length of stay was 21.3 hr longer in the higher-dose group and there was a significant rise in patients with elevated blood glucose in the medium and high-dose groups in comparison with the low-dose group ($p<0.009$, $p<0.001$), all other things being held constant.[107]

CONCLUSION

Over the past 20 years, oral and inhaled corticosteroids have become increasingly significant in the management of COPD. If the patient has simultaneous asthma or elevated eosinophilic levels, the justification for administering ICS in COPD is greater. Aside from lowering the incidence of exacerbations, statistics show that ICS has a minor but substantial favorable effect on lung function decrease and mortality. Systemic steroids were investigated in mild and severe acute exacerbations. Systemic corticosteroids enhance airflow, lower the incidence of therapy failure and the likelihood of recurrence and may enhance symptoms and shorten hospital stays when compared to placebo. Due to the reduced effect of Inhaled Corticosteroids (ICSs) in COPD, all national and international COPD prescribe ICSs

only in individuals who have an elevated threat of exacerbation and serious impairment. Although there is growing evidence suggesting corticosteroids, especially in small doses, may benefit the heart. The most important action is to turn off multiple activated inflammatory genes by inhibiting HDAC2 activity to the inflammatory gene transcriptional complex, as well as to restore HDAC 2 resistance by andrographolide, code delivery of antioxidant MnPD and HDAC2-encoded plasmid DNA into H2O2-treated A549 cells utilizing core-shell type LPNs or by theophylline.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

COPD: Chronic obstructive pulmonary disease; **ICS:** Inhaled corticosteroids; **FEV1:** Forced expiratory volume in one second; **AECOPD:** Acute exacerbation of COPD; **AATD:** Alpha-1 antitrypsin deficiency; **PI:** Serine protease inhibitor; European Respiratory Society; **MMP-9:** Matrix metalloproteinase 9; **ATS/ERS:** American Thoracic Society; **NE:** Neutrophil elastase; **IL-6:** Interleukin 6; **LABC:** Lower airway bacterial colonization; **BAL:** Bronchial alveolar lavage fluid; **NF-Kb:** Nuclear Factor-kappa-B; **HDAC:** Histone deacetylase; **CSE:** Cigarette smoke extract; **CSs:** Systemic corticosteroids; **CRQ:** Chronic respiratory illness questionnaire; long-acting bronchodilator monotherapy; **GLUCOLD:** Groningen Leiden Universities Corticosteroids in Obstructive Lung Disease; **CRP:** C-reactive protein; **FP/SM:** Fluticasone/salmeterol; **BUD/FM:** Budesonide/formoterol; **GCs:** Glucocorticoids; **GR:** Glucocorticoid receptors; **GREs:** Glucocorticoid response elements; **AP-1:** Activator protein 1; **IRF-3:** Interferon regulatory factor-3; **PBMCs:** Peripheral blood mononuclear cells; **SLPI:** Leukoprotease inhibitor; **MKP-1:** Mitogen-activated protein kinase phosphatase-1; **GILZ:** Glucocorticoid-induced leucine zipper; **Nrf2:** Nuclear factor erythroid 2- related factor; **PDE:** Phosphodiesterase.

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