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Review Article

Effectiveness and safety of bronchodilators and inhaled corticosteroids in the management of chronic obstructive pulmonary disease

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a lung condition marked by restricted lung airflow. It is a globally prevalent condition affecting almost 300 million individuals. COPD is linked to a significant burden of morbidity and mortality thus necessitating early diagnosis and management. Rising COPD treatment options complicate care and necessitate a review of clinical data to guide treatment choices. Corticosteroids and bronchodilators are the mainstay of treatment for COPD due to their safety and efficacy. Compared to inhaled corticosteroids or long-acting β-agonist therapy alone, inhaled corticosteroids plus long-acting β-agonist lower the risk of exacerbations and enhance lung function and health status in patients with COPD. Patients who experience frequent exacerbations despite taking long-acting bronchodilators and those who have evidence of eosinophilic bronchial inflammation, as shown by high blood eosinophil levels and/or a history of asthma or asthma-COPD overlap, may both benefit greatly from inhaled corticosteroids therapy. Although not widespread, inhaled corticosteroid use is linked to an elevated risk of pneumonia and may vary depending on the particular corticosteroid utilized. Recent research on combination therapy of inhaled corticosteroids and long-acting β-agonist has shown significant advantages and supports its widespread use in COPD patients who experience frequent exacerbations however some clinical studies and trials have also demonstrated quite conflicting outcomes to this therefore necessitating the need for further clinical trials to exhibit conclusive results. The purpose of this research is to review the available information about the effectiveness and safety of bronchodilators and inhaled corticosteroids in the management of COPD.

Keywords: COPD, Inhaled, Corticosteroid, Long-acting, Beta-agonist

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a pathological condition that is linked to increased morbidity and mortality rate. Around 300 million individuals worldwide suffer from COPD, with a frequency of 12.2%. Currently the fifth-leading cause of mortality globally, this disease is predicted to overtake all others by the year 2030. Almost 80% of COPD fatalities take place in developing and affluent nations. Additionally, the condition imposes a significant economic burden, which rises in proportion to the disease's severity.[1] COPD is defined by poorly reversible airway blockage, which can be diagnostically confirmed by spirometry. This includes obstruction of the small airways referred to as chronic obstructive bronchiolitis and emphysema, which results in air trapping and shortness of breath in response to physical activity. Smoking cigarettes is the most frequent risk factor for the onset of COPD, although other environmental factors, such as exposure to indoor air pollutants particularly in developing countries may also affect COPD risk. Chronic inflammation, which is typically corticosteroid resistant, is linked to the condition. Furthermore, COPD causes premature aging of the lungs and has an unusual healing system that may be triggered by oxidative stress. Acute exacerbations are significant because they are associated with a poor prognosis. They are typically caused by viral or bacterial infections.[2]

The foundation of the current COPD management strategy combines symptomatic control with a decrease in exacerbation risk. The essential elements of managing COPD include pulmonary rehabilitation, smoking cessation promotion, an appropriate medication that targets both symptom management and exacerbation prevention, and routine follow-up monitoring for disease progression. At all levels of severity, bronchodilators are essential to the therapy of COPD. Depending on the patient's classification, the global initiative for chronic obstructive lung disease (GOLD) advises particular initial therapeutic options. After assuring appropriate use of inhalers and compliance to the initial treatment regimen, the follow-up therapy, which relies on present medication(s) and the most treatable features, such as dyspnea or exacerbation, differs from the original therapy.[3,4] Pharmacological management strategies for COPD are illustrated in (Figure 1).

Long-acting β-2 agonists and long-acting muscarinic antagonists can effectively decrease the frequency of exacerbations, relieve symptoms, and enhance the quality of life, and lung function in COPD patients, according to evidence-based findings from extensive clinical trials and real-world studies. They are suggested as the initial COPD maintenance therapy.[5] For individuals with a history of exacerbations, inhaled corticosteroids (ICS) are also considered a cornerstone of treatment for COPD. Although in spite of improvements in symptoms and decreases in exacerbations, early studies evaluating their usage as monotherapy were unable to demonstrate an impact on the rate of pulmonary function deterioration in COPD. Later, it was shown that using ICS and long-acting β-agonists helped improve exacerbations, lung function, and general health. Presently, ICS- long-acting β-agonists combination therapy is advised for patients who have experienced exacerbations despite receiving long-acting bronchodilator medication alone.[6]

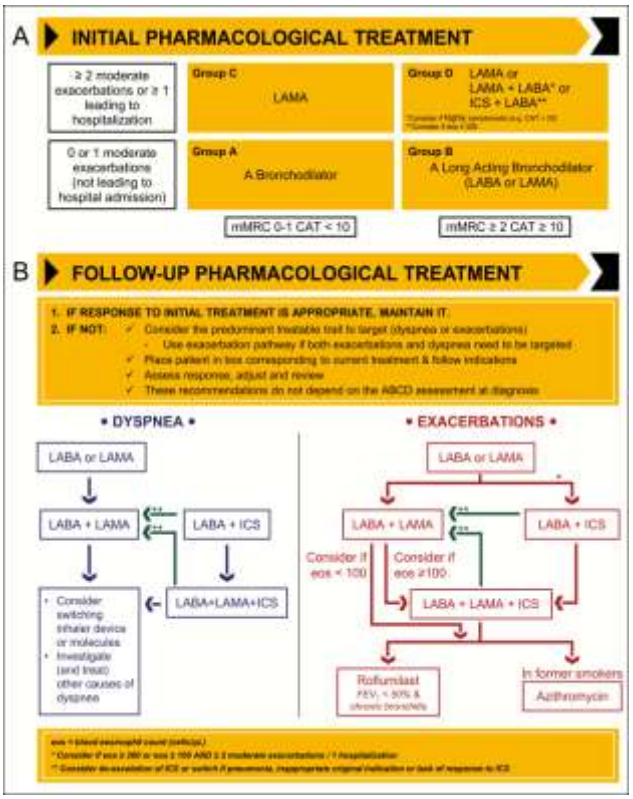

Figure 1: Pharmacological management strategies for COPD.[3]

*CAT = COPD assessment test, **COPD = chronic obstructive pulmonary disease, ***eos = eosinophil counts (cells/µL), ****FEV1 = forced expiratory volume in 1 second, *****ICS = inhaled corticosteroid, ******LABA = long-acting β2-agonist, *******LAMA = long-acting muscarinic antagonist, ********mMRC = modified Medical Research Council.

Although the use of ICS in the treatment of asthmatic airway inflammation has been demonstrated to be beneficial, there are still concerns over its administration in COPD patients. For symptomatic COPD patients with forced expiratory volume in one second (FEV1) less than 50% expected and recurrent exacerbations, the GOLD recommendations for COPD advocate adding ICS long-acting β-2 agonists. However, much debate has surrounded the use of ICS in the treatment of COPD. Important international standards advocate the sparing use of ICS. The outcomes of inhaled steroid therapy for COPD have been the subject of inconsistent findings in recently published meta-analyses and studies.[7] The purpose of this research is to review the available information about the effectiveness and safety of bronchodilators and ICS in the management of COPD.

LITERATURE SEARCH

This study is based on a comprehensive literature search conducted on June 1, 2023, in the Web of Science, Medline, and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed the information about effectiveness and safety of bronchodilators and ICS in the management of COPD**.** There were no restrictions on date, language, participant age, or type of publication.

DISCUSSION

The management of asthma and COPD commonly involves the use of bronchodilator medications. Both sympathetic system activation, notably of beta-2 receptors, and parasympathetic system inhibition methods are used to maintain bronchodilation. In obstructive pulmonary disorders, bronchodilator therapy did not alter significantly over a 20-year period. However, a single-dose inhaler treatment per day in the management of stable COPD became a topical concern in recent years after the development of new extremely long-lasting bronchodilator medication.[8] With the development of long-acting anticholinergics, long-actingβ-agonists, and ICS, there have been significant adjustments in the comprehensive understanding and management of the disease. The use of ICS is recommended by the current GOLD guidelines for patients with severe and very severe airflow limitations, as well as for patients who experience frequent exacerbations. Even though this group only accounts for 20% of all COPD patients, recent studies indicate that up to 70% of them receive ICS prescriptions. Clinical studies on the effectiveness of ICS in COPD have, despite being widely utilized, proven unclear or even conflicting to date. As a result, there is much misunderstanding and disagreement about their function in the treatment of COPD.[9]

Evidence from literature

Agusti et al described that ICS could have significant clinical benefits in certain individuals with COPD, but they can also be ineffective or even have serious adverse effects, such as pneumonia, in other patients. As a result, there is substantial dispute about the effectiveness, safety, and positioning of ICS in the treatment of COPD patients. Therefore, ICS should not be used as a sole, stand-alone treatment for COPD; patients who are most likely to benefit from the addition of ICS to long-acting bronchodilators include those who have a history of multiple or severe exacerbations despite appropriate maintenance bronchodilator use, especially if blood eosinophils are >300 cellsL-1; and patients with a history of and/or concomitant asthma are at an increased risk. Before adding ICS to the maintenance bronchodilator regimen of a specific COPD patient, all of these aspects must be carefully weighed and balanced.[10]

Findings of population cohort study demonstrated that in individuals with asthma alone, ICS was linked to a reduction in obstructive lung disease hospitalizations, albeit the advantage was mitigated by the presence of COPD. Subjects with COPD and concurrent asthma showed a similar relationship, but not those with COPD alone, where ICS use had minimal effect on hospitalizations. Regarding safety, individuals with COPD and no asthma had a slightly higher risk of pneumonia hospitalizations after receiving ICS than the other groups.[11] However, results of a meta-analysis concluded that long-acting β-agonists was associated to a lower risk of myocardial infarction, while ICS/ long-acting β-agonists combination therapy was linked to a lower risk of hospitalization or mortality from asthma-COPD overlap.[12] Similarly, Larsson and Selroos reported that a single inhaler with an ICS/ long-acting β-agonists combination is a convenient, safe, and effective way to treat patients who have asthma and COPD.[13]

Ernst, Saad and Suissa narrated that major methodological issues severely restrict the evidence supporting the effectiveness of ICS and, consequently, the long-acting β-agonists /ICS combinations in COPD. There is no survival advantage that is independent of the long-acting bronchodilator effect, no effect on FEV1 decline, and it is uncertain whether there is any benefit to preventing severe exacerbations. The use of ICS in patients with COPD has significant adverse effects, the most notable of which is severe pneumonia that is responsible for increased number of deaths. Currently, the presence of eosinophilic inflammation in the sputum is the most accurate indicator of ICS response in COPD. Better risk and benefit indicators that can be tested in randomised trials are desperately needed for use in standard specialized practice. Although, the use of such medications without an accompanying ICS combination should be encouraged given the general safety and efficacy of long-acting bronchodilators in people without an asthma-COPD overlap.[14]

Zheng et al demonstrated in their findings of a randomized control trial that for COPD maintenance therapy, a single inhaler extrafine constituting of a triple combination of beclometasone dipropionate, formoterol fumarate and glycopyrronium has been developed. Treatment with extrafine beclometasone dipropionate/ formoterol fumarate/ glycopyrronium was more successful at preventing moderate/severe COPD exacerbations than beclometasone dipropionate/ formoterol fumarate in patients with COPD, FEV1 50%, and a history of exacerbations despite maintenance medication.[15] Although Ohar and Donohue suggested that in accordance with current recommendations, combination therapy is advised for COPD patients whose symptoms are not managed by bronchodilator

monotherapy. The use of ICS in conjunction with bronchodilators is essential for the management of COPD.[16]

Campos and Acuna described that guidelines view long-acting bronchodilators as the standard therapy for all patients and clinical phenotypes due to the increase in therapeutic effects and improvements in both treatment adherence and dosage following the introduction of these medications, which are given every 12 or 24 hours. It has been proven that combining long-acting bronchodilators from various families is an innovative therapeutic strategy for patients who experience chronic symptoms while receiving the proper bronchodilator medication. ICS, a form of anti-inflammatory therapy that has been extensively discussed, are recommended by current guidelines for patients who have a high risk of exacerbations because of impaired lung function, a history of exacerbations, or phenotypes that are vulnerable to the effects of corticosteroids.[17] Nannini et al reported that compared to placebo, combined inhaler therapy resulted in around a quarter fewer COPD exacerbations. Although an increased risk of pneumonia is concerning, there were no more hospitalizations, fatalities, or exacerbations as a result. The available information does not point to any significant differences amongst inhalers in terms of effects, but it is also insufficient to prove that they are all similar.[18]

Cazzola and Hanania demonstrated that in the trial investigating the salmeterol/fluticasone combination, combination therapy exhibited an impact comparable to that of its monocomponent. However, when individuals with more severe COPD were evaluated using a combination of budesonide and formoterol as opposed to utilizing a long-acting 2-agonist alone, a definite improvement was noted in the overall exacerbation rates.[19] While Monteagudo et al described that excluding patients with frequent exacerbations and high blood eosinophils, where no differences in the time to first exacerbation were observed, long-acting β-agonists /long-acting muscarinic antagonist was linked to a considerably lower risk of exacerbations and escalation to triple therapy than long-acting β-agonists/ICS.[20] Contrarily, Martino et al revealed that combining ICS with long-acting bronchodilators had a positive impact on mortality. In individuals who experienced frequent exacerbations, the benefit was significantly more obvious.[21]

Calverly narrated that the efficacy of the latte drug is increased in COPD patients by combining an ICS and a long-acting beta-agonist in the same inhaler, with a noticeably increased improvement in FEV1, a marked decrease in reported breathlessness, and a decline in exacerbation numbers in those with more severe symptoms where beta-agonists appear to be less effective. Although they should not be used as a stand-alone treatment for COPD, ICS can be beneficially coupled with an inhaled bronchodilator in individuals with symptomatic illness.[22] Gershon et al. demonstrated that long-acting β-agonists and ICS combination therapy, as compared to long-acting β-agonists alone, was correlated with a significantly reduced likelihood of the composite outcome of death or COPD hospitalization among elderly people with COPD, particularly those with asthma and those not taking a long-acting anticholinergic medication.[23] Studies in literature exhibit quite conflicting results for the safety and efficacy of combination of ICS and bronchodilators additionally randomized control trials present are quite limited.

CONCLUSION

Bronchodilators and corticosteroids are the mainstay of COPD treatment and are highly safe and effective in clinical practice however the use of combination of bronchodilators and ICS is not backed by strong evidence from clinical trials or studies to draw any conclusive outcome hence necessitating the need of further clinical research in recent times.

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