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TRIPLE THERAPY IN COPD: A GAME-CHANGER? - EXAMINING ETHOS, IMPACT &TRIBUTE STUDIES

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disease affectingmillions worldwide. In recent years, the use of triple therapy, which combines an inhaled corticosteroid (ICS), a long-acting beta-agonist (LABA), and a long-acting muscarinic antagonist (LAMA), has most recommended for the management of COPD. Triple therapy has been shown toimprove lung function, reduce exacerbations, and improve quality of life compared to other treatments, especially in patients with more severe COPD. This study aims to compare dual therapiesand triple therapies according to the pivot studies namely IMPACT, TRIBUTE, and ETHOS. This reviewshows the safety and effectiveness of triple therapy. However, as with any medication, there are potential side effects and risks associated with triple therapy, and it is important for healthcare providers to carefully consider each patient's individual needs and risks before prescribing this treatment. Overall, triple therapy has emerged as a valuable treatment option for patients withCOPD.

KEYWORDS:- ***COPD, triple therapy, safety, effectiveness, exacerbation, pneumonia.***

INTRODUCTION

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023 report defines Chronic Obstructive Pulmonary Disease (COPD) as "a heterogeneous lung condition characterized by chronic respiratory symptoms (shortness of breath, cough, expectoration, exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow hindrance." [1] The GOLD initiative defines COPD as "a disease state that differentiates by airflow limitation that is not fully reversible [2]. For high-risk patients withsevere symptoms (GOLD GROUP D) who experience subsequent exacerbations after receiving dual bronchodilation (the preferred initial therapy) or LABA/ICS (the alternate initial therapy), GOLD currently advises triple therapy (ICS plus LABA plus LAMA). This suggestion is based on investigations that used previous GOLD guidelines to determine "high-risk" patients (those with severe-to-very serious airway obstruction or a history of exacerbation). According to WHO, around 65 million peoplehave moderate to severe COPD Mortality: COPD is the third leading cause of death globally, accounting for 3 million deaths in 2019, which represent 5% of all deaths globally.

COPD is more common in older adults and is usually diagnosed after the age of 40. The disease is more prevailing inmales than in females. Global burden: COPD is a major public health problem worldwide, and its burden is expected to increase in the coming years due to aging populations, increased tobacco uses in developing countries, and exposure to air pollution. [3]. A Few of the symptoms such as dyspnea, cough, and sputum production worsen during exacerbations of COPD, which are associated with accelerated mortality [4]. To lower the symptoms and the exacerbation, triple or dual - inhaled bronchodilators are recommended for the treatment depending on the severity. If the patients havesevere symptoms and a history of exacerbations, the inclusion of inhaled corticosteroid (ICS) to the long-acting muscarinic antagonist (LAMA) and long-acting beta-agonist (LABA) combination therapy has been recommended because it lowers the incidence of exacerbations [5]. Triple fixed-dose combination therapies providing an ICS, a LAMA, and LABA in a single inhaler are a recent addition tothe range of available treatment options for COPD [6-7]. A study examining the efficacy of triple therapy with fixed-dose ICS/LAMA/LABA showed positive effects on lung function, quality of life, and exacerbation rates compared to dual therapy with LAMA/LABA and ICS/LABA. [8,9]. In patients receiving ICS the blood eosinophils levels should be monitored. The cost-effectiveness analysis of triple therapy (LAMA /LABA/ICS) compared with dual therapy (LAMA/LABA OR LABA/ICS) shows economic benefits by the decrease in moderate to severe exacerbation and shows significant

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improvement in quality of life and improvement in FEV1 function.[10]

OBJECTIVE

A Review of the study to compare the efficacy of triple with dual combination therapiesin COPD is the primary objective of the study.

DISCUSSION

Triple inhaled therapy is used for chronic obstructive pulmonary disease which includes an inhaledLAMA, LABA, and a glucocorticoid (ICS) [11]. The GOLD guidelines suggested the inclusion of ICS- induced bronchodilation (LAMA + LABA) for patients with symptomatic disease and a history of frequent exacerbations [12]. The recent studies conducted on the availability of triple therapy combinations are IMPACT, ETHOS, and TRIBUTE [11,12,13].

According to the IMPACT study, the total number of populations involved in the randomized trial is 10,355. Compared to a period time of 52 weeks. The patients included in the impact trial who had moderate to severe COPD, if the Fev1 is lesser than 50% (Fev1 < 50%) and history of more than one (>1) moderate or severe COPD exacerbation in the past 12 months (GOLD B) or the patients with 50-80% of Fev1 predicted and a history of more than 2 (>2) moderate exacerbations (GOLD D) or thepatients with the history of more than 1 (>1) severe COPD exacerbations. Involved the comparison of fluticasone furoate (ICS), umeclidinium (LAMA), and vilanterol (LABA) in the doses of 100 µg, 62.5µg,and 25 µg respectively with ICS+LABA (fluticasone furoate + vilanterol) in doses of (100 µg+ 25 µg) and with another dual bronchodilator LAMA + LABA (umeclidinium + vilanterol) in the doses of (62.5ug +25 ug) respectively. This study documented the outcomes such as exacerbations, mortality, and safety-related issues like pneumonia. Results have shown triple therapy has a significantly lowerrate of moderate or severe COPD exacerbations, improved lung function, and enhanced quality of lifethan other dual therapies i.e., ICS+LABA and LAMA+LABA combinations. By evaluating the above results, we determined that triple therapy and dual therapy (ICS+LABA) showed a decreased rate of mortality than umeclidinium + vilanterol [11]. However, the decrease in mortality rate with triple therapy might be mainly due to a lower rate of fatal cardiovascular events [14].

In severe COPD patients, the add-on of ICS would lead to an increased incidence of pneumonia [14]. The results showed a greater incidence of pneumonia in the groups containing inhaled glucocorticosteroids than in the umeclidinium and vilanterol groups. In glucocorticoid groups also, triple therapy has a higher incidence of pneumonia than the ICS+LABA combination. But still, triple therapy is taken into consideration because of lower exacerbation, a better quality of life score, and higher trough Fev1 [11]. Triple therapy has resulted in more clinical benefits and health outcomes and has a moderatecost increment than dual therapy. Triple therapy more chosen in the case of cost-effectiveness because of greater fev1 benefit, quality of life, and exacerbations led to improved survival and decreased overall lifetime cost by reducing frequent hospitalizations [15].

In the ETHOS study, the total population involved is 8509 patients compared to 52 weeks. this trialcomprises the comparison of a single inhaler twice daily triple therapy with two different doses of ICS (BUDENOSIDE) along with twice daily dual therapy. The therapy consists of budesonide (320 /160µg), glycopyrrolate (18µg), and formoterol (9.6µg). the dual therapies consist of LABA +LAMA (formoterol 9.6µg + glycopyrrolate 18µg) and LABA +ICS (formoterol 9.6µg + budesonide 320µg) theoutcomes evaluated in this study are moderate to severe exacerbations, mortality, quality of life and adverse events like pneumonia and bronchitis. The exacerbations seen in patients treated with triple therapy (budesonide 320µg) have no exacerbations. The patients treated with triple therapy (budesonide 160µg) had one exacerbation in a year. the patients treated with LAMA +LABA (glycopyrrolate 18µg +formoterol fumarate 9.6µg) and LABA +ICS (formoterol fumarate 9.6µg + budesonide 320µg) have experienced less than one exacerbation. Overall, patients receiving tripletherapy (budesonide 320µg) have no exacerbations seen compared to other triple and dual therapies.

The rate of mortality seen in patients with triple therapy is less when compared with otherdual therapies. The rate of mortality in triple therapy in a dose of ICS (budesonide 320µg) is less when compared with triple therapy in a dose of ICS (budesonide 160µg). The majorly seen risk factors in the patients in the study are pneumonia and bronchitis. The incidence of pneumonia in the patients receiving ICS+LABA is high and low in patients receiving LAMA+LABA when compared with the other therapies in the study. The incidence of bronchitis in the patients receiving LAMA+LABA is high compared with the other therapies. The patients receiving triple therapy have shown improved quality of life in a year compared with the other dual therapies [12]. The total expense of triple therapy (BGF) was higher than that of dual therapy (GFF or BFF) but BGF was more cost-effective
over a patient's lifetime. BGF is preferable therapy to other therapies because it abateshospitalizations and enhances the quality of daily life [16].

In the TRIBUTE study total number of populations involved is 1532 with symptomatic COPD, severe airflow obstruction (fev1 <50%), and at least one moderate or severe exacerbation in a year. This study involves the comparison of twice daily single inhaler triple therapy (SITT) consisting of ICS+LABA+LAMA [beclomethasone dipropionate (BDP) 87µg+ formoterol fumarate (FF)5µg+ glycopyrrolate (GLY)9µg] versus once-daily single inhaler dual therapy consists of LAMA+LABA [indacaterol (IND)85 µg+glycopyrrolate (GLY)43µg].

Patients were priorly receiving IND/GLY for a run period of 2 weeks. later the patients were divided into two groups in a ratio of 1:1. One group started receiving triple therapy and the other group withdual bronchodilator therapy. The findings evaluated in this study were, that triple therapy reduced the annual rate of severe or moderate exacerbations by 15% when compared with dual therapy. The SGRQ score has significantly enhanced in triple therapy when compared with dual therapy, but thereis no notifiable improvement in the Fev1 value. The incidence of risk of pneumonia in both groups shows identical outcomes [13,17].

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CONCLUSION

The analysis of the ETHOS, IMPACT, and TRIBUTE studies demonstrates that triple therapy can be an effective option for controlling exacerbations and improving lung function in patients with moderateto severe COPD. However, the use of inhaled corticosteroids in triple therapy may increase the risk ofpneumonia and careful consideration of the benefits and risks is required before making a treatment decision. Regular monitoring and follow-up are essential to ensure the therapy is effective and well- tolerated over time.

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