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SINGLE-INHALER TRIPLE THERAPY FOR COPD EXACERBATION

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ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is a progressive lung disease that includes chronic bronchitis and emphysema and is characterized by airflow limitation. Triple inhaled therapy consists of inhaled corticosteroids (ICSs), long-acting β2-agonists (LABAs), and long-acting muscarinic receptor antagonists (LAMAs) has been recommended for COPD patients who still have clinically significant symptoms following the use of a dual inhaler with LABA plus LAMA or LABA plus ICS and those who have a higher risk of exacerbation. Studies have shown that triple inhaled therapy has positive effects on lung function and COPD symptoms as compared with dual therapy. This review concludes that triple inhaled therapy is more effective than dual therapy for COPD patients.

KEYWORDS: Chronic Obstructive Pulmonary Disease, Inhaled corticosteroid, Long-acting β2-agonists, Long-acting muscarinic receptor antagonists.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a lung disease characterized by chronic obstruction of lung airflow limitation that is not fully reversible.[1] COPD is not just a "smoker's cough" but an under-diagnosed, life-threatening lung disease.[2]

Chronic bronchitis and emphysema are the most common conditions comprising COPD. Chronic bronchitis is a condition with chronic or recurrent excessive mucus secretion into the bronchial tree with cough that is present on most days for at least 3 months of the year for at least 2 consecutive years in a patient in whom other causes of chronic cough have been excluded.[3] Emphysema, an anatomically defined condition characterized by destruction and enlargement of the lung alveoli. COPD is present only if chronic airflow obstruction occurs; chronic bronchitis without chronic airflow obstruction is not included within COPD.[1]

COPD is currently the 4th leading cause of death in the world but is likely to be the 3rd leading cause of death by 2020.[4] More than 3 million people died of COPD in 2012 accounting for 6% of all the deaths globally.[5] COPD is a leading cause of morbidity and mortality worldwide that induces an economic and social burden that is both substantial and increasing.[6] A systematic review and meta-analysis, including studies carried out in 28 countries between 1990 and 2004, provided evidence that the prevalence of COPD is higher in smokers and ex-smokers compared to non-smokers, in those ≥40 years of age compared to those < 40, and in men compared to women.[7]

The most common risk factors for COPD is cigarette smoking and other epidemiological studies with reliable evidence shows that chronic airflow limitations can also be developed in non-smokers. The complex interaction between the genes and environment can also result in COPD. The most significant leading environmental risk factor is Cigarette smoking; however in heavy smokers less than 50% of them develop COPD during their lifetime. Exposure to particles, age and sex, lung growth and development, asthma and airway hyper-activity are the other causes that influences the disease development and progression.[5]

PATHOPHYSIOLOGY OF EXACERBATION

Inflammation of Cigarette smoke or smoke from the noxious particles causes the inflammation of lungs. This lung inflammation is a normal response in patients who develop COPD and the chronic inflammatory response may include parenchymal tissue destruction (leading to emphysema) and disruption of normal repair and defence mechanism (resulting in small airway fibrosis). Oxidative stress and excess of proteinases in the lungs are likely to further modify the lung inflammation. These pathological changes leads to gas trapping and progressive airflow limitation.[5]

The natural history of COPD is characterized by recurrent exacerbations associated with increased symptoms and a decline in overall health status. Because many patients experience chronic symptoms, the

diagnosis of an exacerbation is based, in part, on subjective measures and clinical judgment. There are limited data about pathology during exacerbations owing to the nature of the disease and the condition of patients; however, inflammatory mediators including neutrophils and eosinophils are increased in the sputum. Chronic airflow limitation is a feature of COPD and may not change remarkably even during an exacerbation. The primary physiologic change is often a worsening of arterial blood gas results owing to poor gas exchange and increased muscle fatigue. In a patient experiencing a severe exacerbation, profound hypoxemia and hypercapnia can be accompanied by respiratory acidosis and respiratory failure.[3]

Need of inhaled treatments for COPD

Many factors contribute to poor adherence among COPD patients including treatment complexity such as dosing frequency, the number of medications, and ease of use of the inhalers. The growing choice of drugs for COPD delivered using a variety of inhalers allows health care professionals (HCPs) to individualize treatment. In addition to the number of inhalers, HCPs need to consider the ease of use of any device prescribed. Ease of use is an influential factor that determines adherence. Poor inhaler technique might contribute to symptoms and exacerbations and HCPs should ensure that patients are able to use any device prescribed.

Many patients can be adequately treated with long-acting bronchodilator monotherapy with either a long-acting beta2 - agonist (LABA) or a long-acting muscarinic antagonist (LAMA). Other patients may require a double combination inhaler containing an inhaled corticosteroid (ICS) and a LABA (ICS plus LABA) or two long-acting bronchodilators (LAMA plus LABA).[8]

Triple inhaled therapy comprised of ICSs, LABAs, and LAMAs (ICS plus LABA plus LAMA)[9] due to the clinical need to prevent further exacerbations, alleviate symptoms or both despite using monotherapy or a double combination inhaler.

Historically, triple therapy has been prescribed with two separate inhalers, namely an ICS plus LABA inhaler and a LAMA inhaler. Single inhaler triple therapy and exacerbations triple therapy with ICS plus LABA plus LAMA is now a mainstay of management for some patients with COPD. Patients who require further treatment for exacerbations, who experience symptoms or both despite treatment with a double combination inhaler (ICS/LABA or LAMA/LABA) are often escalated to triple therapy.[8]

At present, there are three different formulas for single inhaler triple therapy, including fluticasone furoate (FF)/ umeclidinium (UMEC)/vilanterol (VI) in a once daily dry powder inhaler formulation (Trelegy Ellipta; GSK, Uxbridge, UK), extra fine beclomethasone dipropionate (BDP)/formoterol fumarate (FOR)/glycopyrronium bromide (GB) in a twice daily extra fine particle pressurized metered dose inhaler (pMDI) formulation (Trimbow; Chiesi, Parma, Italy), and budesonide (BUD)/GB/FOR in a co-suspension pMDI formulation (Aerosphere; Luton, UK, not approved).

Recently, several randomized controlled trials (RCTs) have shown that extra fine BDP/FOR/GB therapy could be associated with a lower rate of moderate-to-severe COPD exacerbations, as well as improved lung function and health-related quality of life compared with other treatment options. Bremner et al,[10] showed that FF/UMEC/VI therapy was only better than open triple therapy (FF/VI plus UMEC) in terms of changes in lung function, health related quality of life and safety. In contrast, Lipson et al,[11] demonstrated that a single inhaler triple therapy with FF/ UMEC/VI resulted in a lower rate of moderate or severe exacerbations and a lower rate hospitalization due to COPD compared with dual therapy with FF/VI or UMEC/VI. In addition, another RCT showed that single inhaler therapy with FF/UMEC/VI was associated with improved lung function and health-related quality of life compared with BUD/FOR dual therapy. Ferguson et al, demonstrated that single inhaler triple therapy with BUD/ GB/FOR could improve lung function compared with BUD/FOR dual therapy.[9]

SITT devices could help address poor adherence with COPD medications, which is common and may result in increased exacerbations, persistent symptoms, and poor economic outcomes. Traditionally, patients receiving triple therapy need to use multiple inhalers several times a day. Typically, these patients used combined ICS/LABA in one inhaler and LAMA in another inhaler and these inhalers may be of different types and designs. This may lead to incorrect use of the inhalers and affect the patient's adherence to treatment. Recently, a single inhaler containing triple therapy ICS, LABA, and LAMA has been developed as a more practical alternative, which may improve therapy compliance.[9]

Risk associated with moderate or severe COPD exacerbation

3 RCTs conducted by Papi A et al,[12] Lipson DA et al,[11] Ferguson Ga et al,[13] compared single inhaler triple therapy with LABA/LAMA dual therapy. It was found that single inhaler triple therapy was associated with a lower risk of COPD exacerbation compared with LABA/LAMA dual therapy. Another 4 RCTs directed by Sing D et al,[14] Lipson DA et al,[11] Ferguson Ga et al,[13] compared single inhaler triple therapy with ICS/LABA revealed that single inhaler triple therapy could significantly reduce the risk of COPD exacerbations. Vestha J et al[15] and Bremner et al[10] compared single inhaler triple therapy with ICS/LABA plus LAMA separate triple therapy, however, no significant differences in the risk of moderate or severe COPD exacerbations were observed between the groups.

Single inhaler triple therapy was associated with a significantly lower risk of COPD hospitalization compared with LABA/LAMA dual therapy and ICS/LABA dual therapy. However, no significant differences while comparing to single inhaler triple therapy and separate triple therapy.[9]

ADVERSE EVENTS

Single inhaler triple therapy was associated with a significantly higher risk of pneumonia compared with LABA/LAMA dual therapy, but no significant differences were found when it was compared with ICS/LABA dual therapy or separate triple therapy. The risk of lower respiratory tract infection (LRTI) was investigated however, no significant differences were found between single inhaler triple therapy and the three alternative treatments.[9]

CONCLUSION

COPD represents an important public health challenge which is both preventable and treatable. Despite recent advances in pharmacotherapy, COPD remains an important cause of death, disability, and health care expenditure. Triple therapy with ICS plus LABA plus LAMA is a mainstay of COPD management for some patients. The most recent studies of ICS combined with LABA and LAMA in a single inhaler showed that triple therapy represents the most potent pharmacological treatment available for patients with COPD with moderate-to-very severe airflow limitation, particularly those with an exacerbation history. It was found that single inhaler triple therapy was associated with a significantly lower risk of moderate or severe COPD exacerbations compared with dual therapy (ICS/LABA or LABA/LAMA).

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CONFLICT OF INTEREST

There is no conflict of interest between the authors.

ABBREVATIONS

BDP- Beclomethasone Dipropionate
BUD- Budesonide
COPD- Chronic Obstructive Pulmonary Disease
FOR- Formoterol Fumarate
FF- Fluticasone Furoate
GB- Glycopyrronium Bromide
HCPs- Health Care Professionals
ICSs- Inhaled Corticosteroids
LABAs- Long-acting β2-agonists
LAMA- long-acting muscarinic receptor antagonists
pMDI- Pressurized metered dose inhaler
RCTs- Randomized controlled trials
UMEC- Umeclidinium (UMEC)
VI- Vilanterol

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