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A Comparative Study on the Combination Use of Indacaterol with Glycopyrronium and Formoterol with Tiotropium in COPD Patients in a Tertiary Care Hospital

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ABSTRACT

Chronic Obstructive Pulmonary disease(COPD) is a lung disease characterized by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible. It is a common preventable and treatable disease characterized by persistent limitation in airflow, leading to reduced ventilatory capacity and is associated with shortness of breath. It is associated with an enhanced chronic inflammatory response in airways and the lungs to noxious particles or gases. Emphysema and Chronic Bronchitis are the two most common conditions that contribute to COPD. Chronic bronchitis is the inflammation of the lining of the bronchial tubes. It is characterized by a daily cough and sputum production. Emphysema is a condition in which the air sacs at the end of the smallest air passages of the lungs are destroyed as a result of damaging exposure. Dual bronchodilation with the long-acting muscarinic antagonist(LAMA)& long-acting β_2-agonist (LABA) is always more effective than the LAMA or LABA. Indacaterol/Glycopyrronium is a fixed-dose combination of two long-acting bronchodilators. Indacaterol is the LABA and Glycopyrronium is the LAMA. A combination of Tiotropium and Formoterol is more effective than single drugs alone in inducing bronchodilation and a bronchodilator-mediated symptom benefit in patients suffering from COPD.

INTRODUCTION

Chronic Obstructive Pulmonary disease(COPD) is a lung disease characterized by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible.[1] It is a common preventable and treatable disease characterized by persistent limitation in airflow, leading to reduced ventilatory capacity and is associated with shortness of breath. It is usually progressive and associated with an enhanced chronic inflammatory response in airways and the lungs to noxious particles or gases.[9,14] Emphysema and Chronic Bronchitis are the two most common conditions that contribute to COPD. Chronic bronchitis is the inflammation of the lining of the bronchial tubes, which carry air to and from the air sacs, of the lungs. It is characterized by a daily cough and sputum production. Emphysema is a condition in which the air sacs at the end of the smallest air passages of the lungs are destroyed as a result of damaging exposure.[10]

COPD is a complex syndrome comprised of airway inflammation, mucociliary dysfunction, and consequent airway structural changes. **Airway Inflammation:-** COPD is characterized by chronic inflammation of the airways, lung tissue and pulmonary blood vessels as a result of exposure to inhaled irritants such as tobacco smoke. The inhaled irritants cause inflammatory cells such as neutrophils, CD8+ T- lymphocytes B cells and macrophages to accumulate.When activated, these cells initiate an inflammatory cascade that triggers the release of inflammatory mediators such as tumor necrosis factor alpha (TNF-α), interferon gamma (INF-$^{\gamma}$), matrix metalloproteinases (MMP-6, MMP-9), C-reactive proteins (CRP), interleukins (IL-1, IL-6, IL-8) and fibrinogen.[7] **Structural Changes:-** Airway remodeling in COPD is a direct result of inflammatory response associated with COPD and leads to narrowing of the airways. Three main factors contribute to this: peribronchial fibrosis, build up of scar tissue from damage to the airways and the over multiplication of the epithelial cells lining the airways.[8] **Mucociliary Dysfunction:-** Smoking and inflammation enlarge the mucous glands that line airway walls in the lungs causing globlet cell metaplasia and replacement of healthy cells by more mucous secreting cells.[11] Additionally, inflammation associated with COPD causes damage to the mucociliary transport system which is responsible for clearing mucus from the airways[12,15]. Symptoms of COPD are Persistent Dyspnoea: progressive (worsens over time), worse with exercise, Chronic cough: Maybe intermittent or may be unproductive, Chronic sputum production: Any pattern of chronic sputum production may indicate COPD.[1,6] Indacaterol/Glycopyrronium is a fixed-dose

combination of two long-acting bronchodilators.Indacaterol is a long-acting β2 adrenergic agonist (LABA) and Glycopyrronium is the long-acting muscarinic antagonist(LAMA). Indacaterol/ glycopyrronium significantly reduced the rate of moderate or severe exacerbations, improvement in lung function (forced expired volume in 1 second [FEV_1]), dyspnoea, health status and use of rescue medication compared with glycopyrronium alone in people with severe or very severe COPD.[2] Indacaterol is a long-acting β2 adrenoceptor partial agonist with a high intrinsic activity that stimulates intracellular adenylyl cyclase, which converts adenosine triphosphate to cAMP. The resulting increased intracellular cAMP levels lead to relaxation of the bronchial smooth muscle.[3]

Formoterol (beta(2)-agonist) and Tiotropium (anticholinergic) are long-acting bronchodilators Formoterol has a fast onset and a bronchodilator effect of approximately 12 h, while Tiotropium has a 24-h bronchodilator effect . A combination of Tiotropium and Formoterol is more effective than single drugs alone in inducing bronchodilation and a bronchodilator-mediated symptom benefit in patients suffering from COPD. [4]Formoterol is a potent, selective long-acting beta agonist that acts locally in the lungs and work as a bronchodilator, by relaxing the smooth muscle in the airway walls to widen the airways. Tiotropium is a long-acting anticholinergic that acts on specific receptors (muscarinic receptors) in the bronchioles of the lung and inhibits the interaction of acetylcholine, with muscarinic receptors, which prevents spasm of the airway wall caused by the acetylcholine.[5]

REVIEW OF LITERATURE

1. Peter Kardos, Ina Hagedorn-Peinz(2018)[33] conducted a randomized crossover study on the impact of Indacaterol with Glycopyrronium FDC Vs Tiotropium monotherapy on lung function and treatment preference. The aim of the study was to evaluate the effect of Indacaterol with Glycopyrronium Vs Tiotropium on peak forced expiratory volume and also to investigate patient satisfaction and physician's treatment preference. 88 patients were enrolled and 87 completed the study and showed significantly higher lung function after four weeks of treatment with Indacaterol with Glycopyrronium Vs Tiotropium. A higher proportion of the patients stated that they were satisfied with Indacaterol with Glycopyrronium Vs Tiotropium, with regard to dyspnoea reduction. Indacaterol with Glycopyyronium demonstrate good safety and tolerability profile. LAMA-LABA demonstrates a significant and clinically important improvement in lung function and reduction in the use of rescue medication along with favorable long-term safety profile.

Taking patient's treatment preferences into consideration,may help to improve treatment adherence and consequently treatment outcomes. The study states that treatment improvement could influence patients's preference for medication. Hence, we compare Indacaterol with Glycopyyronium and Tiotropium, the two single dose and bronchodilator treatments based on their potential for lung function improvement and the subsequent impact on patients overall treatment preference. The study demonstrated the benefit of Indacaterol with Glycopyrronium 110/50µg OD combined therapy Vs Tiotropium 18µg o.d monotherapy for treating stable COPD patients with persistent complaints based on the patient reported outcomes and lung function. The study suggests that individual patients felt the lung function benefits with Indacaterol with Glycopyrronium compared with Tiotropium which in turn may also have contributed to the preference for Indacaterol with Glycopyrronium.

2. Donald Banerji, Robert Fogel, Francesco Patalano(2018)[34] conducted a study on the Indacaterol with Glycopyrronium bronchodilator combination for COPD. Indacaterol with Glycopyrronium was developed to improve the standard of care for patients with this disease in terms of symptom control and exacerbation frequency. An adaptive comprehensive and innovative phase 3 development programme demonstrated the efficacy of Indacaterol with Glycopyrronium in optimizing bronchodilator by reducing the symptoms and exacerbations in COPD. The study enrolled more than 2100 patients and it states that Indacaterol with Glycopyrronium provided superior and sustained improvement in lung function and symptom score compared with placebo. Also the study states that a significant reduction in rescue medication use with Indacaterol with Glycopyrronium versus active comparators as well as an improvement in health status measures ,a reduction in symptoms and a similar incidence of adverse events.Indacaterol with Glycopyrronium is a safe and effective maintenance treatment for moderate to severe COPD. The study conclude that Indacaterol with Glycopyrronium is an effective well tolerated FDC with positive effects on lung function,rescue medication use,and exacerbation compared with placebo and its monocomponents .

3. Mina Gaga et al. (2017)[36]conducted an open-label randomized trial on Efficacy and safety of direct switch to Indacaterol with Glycopyyronium in patients with moderate COPD. LABA and LAMA is the preferred choice of treatment for moderate to severe COPD patients as recommended by GOLD guidelines. They conducted an open-label trial that evaluated the efficacy and safety of a direct switch from previous treatment to Indacaterol with

Glycopyrronium 110/50µg on lung function, dyspnoea in patients with moderate COPD and a history of up to one exacerbation in the previous year. The patients were divided into 2 groups according to the background therapy and symptom scores and were randomized to Indacaterol with Glycopyrronium or to continue with previous treatment. The study enrolled 4389 patients of whom 2160 were in groups switched to Indacaterol with Glycopyrronium. The effect of indacaterol with glycopyrronium was superior to LABA +ICS on forced expiratory volume. Improvement in health status and lower rescue medication use were also observed with Indacaterol with Glycopyrronium. The study conclude that a direct switch to Indacaterol with Glycopyrronium demonstrates significant improvement in lung function and dyspnoea after treatment in moderate to severe COPD patients compared to the continuation of previous treatment with LABA or LAMA or LABA+ICS.

4.Jadwiga A Wedzicha et al. (2016),[37] conduct a Randomized double-blind,placebo-controlled clinical study on Indacaterol –Glycopyrronium versus Salmeterol-Fluticasone for COPD patients.A total of 1680 patients were assigned to the Indacaterol-Glycopyrronium group and 1682 to the salmeterol-fluticasone group.Indacaterol-Glycopyrronium shows not only non inferiority but also superiority to salmeterol –fluticasone in reducing the annual rate of all COPD exacerbations. The rate was 11% lower in the indacaterol-glycopyrronium group than in the salmeterol fluticasone group. The study conclude that,among patients with COPD,who had a history of exacerbation during the previous year ,Indacaterol-Glycopyrronium was consistently more effective than salmeterol-fluticasone in preventing exacerbation and was associated with no detectable increase in adverse events. The Indacaterol-Glycopyrronium group had a longer time to the first exacerbation than did the salmeterol –fluticasone group. The annual rate of moderate or severe exacerbations was lower in the Indacaterol-Glycopyrronium group than in the salmeterol-fluticasone group.

5. Mohammed Imran et al(2015),[39] conducted a Randomized, Double-blind, Placebo-Controlled Clinical Study on An Acute Therapeutic Evaluation of Three Regimens of Tiotropium and Formoterol in COPD Patients: A total of 60 patients with COPD, were identified.The 3 regimens were , Tiotropium 18µg once a day in the morning along with the Formoterol matched placebo in the evening, the FDC of Tiotropium 18µg plus Formeterol 12 µg once a day in the morning and Formeterol matched placebo in the evening and the same FDC of two drugs once a day in the morning and once a day Formeterol 12µg in the evening in patients of COPD without any comorbidity. The study concludes that addition of

Formoterol to Tiotropium as fixed-dose combination once a day in the morning has shown improvement in the lung function in COPD. Addition of second dose of Formoterol in the evening in addition to the FDC'S of Tiotropium and Formeterol once in the morning have shown the superior effects than the Tiotropium alone implying the role of sympathetic component . The study shows that Tiotropium alone is as good as the FDC once a day obviating the need for such prescription. It may be because of the predominance of the parasympathetic system in COPD patients.

6. Claus Vogelmeier et al,(2008)[41] conducted a study on Formoterol- mono and combination therapy with Tiotropium in patients with COPD.This study deals with the clinical efficacy and safety of Formoterol,Tiotropium and their combination in patients with COPD. 847 patients with COPD is enrolled in the study. They were randomized to receive either of the treatment, Formoterol 10µg bid+Tiotropium 18µg OD, Formoterol10µg bid and Tiotropium 18µg odor placebo. They examined that all the three treatment were superior to placebo,and the combination was superior to monotherapy. Symptom score, use of rescue medication and peak expiratory flow and health-related quality of life were improved for the combination. Combined therapy did not appear to confer any increased risk compared to individual therapy. There were no indication of safety concerns affecting particular organ systems. Most adverse drug events were mild to moderate in severity. The combination of Formoterol and Tiotropium provided an improvement on either monotherapy. It is possible that advantages of combination therapy would be more apparent in severe stages of COPD.The study concludes that the addition of Formoterol to Tiotropium treatment conferred the advantage in terms of bronchodilator effect, lung function and exacerbation.

CONCLUSION

This study ended with the conclusion that Indacaterol with Glycopyrronium and Formoterol with Tiotropium have a significant effect. Indacaterol with Glycopyrronium was found to be more efficacious in COPD patients in this study. Indacaterol/ glycopyrronium significantly reduced the rate of moderate or severe exacerbations, makes improvement in lung function, health status and reduces the use of rescue medication. It provides the quick 24-hour bronchodilation effect, with the once-daily administration. It was assessed using SGRQ-C questionnaire. The COPD patients have improvement in the symptom score, activity score, impact score and total score with the course of treatment with a decrease in SGRQ-C scores.

Health-related quality of life is assessed using the EQ-5D-5L questionnaire. Mobility, Self-care,usual activities, discomfort/pain, anxiety/depression was assessed. There is significant increase in quality of life for both groups, significantly greater difference was seen with Ind/Gly group.

Patients medication adherence had improved after effective patient counseling. Patient knowledge about the disease and medication had been increased.

Adverse reactions like dry mouth and urinary retention had reported during the study. But the incidence of occurrence of ADR is more with Formoterol/Tiotropium compared to Indacaterol/Glycopyrronium. This study emphasizes on the fact that Indacaterol with Glycopyrronium should be preferred over Formoterol with Tiotropium in patients with COPD.

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