Comparative assessment of Fixed Dose Combinations of Indacaterol/Glycopyrronium versus Formoterol/Tiotropium in terms of Pulmonary Function Tests in mild to moderate Chronic Obstructive Pulmonary Disease patients: An Open Label Pilot Study

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ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) is a serious global healthcare problem. WHO predicts COPD as a leading cause of death by 2030. It is commonly diagnosed via spirometry also known as Pulmonary Function Test (PFT). Long Acting Beta Agonist/Long Acting Muscarinic Antagonist (LABA/LAMA) fixed dose combinations (FDC) remains the cornerstone in treatment of COPD. A FDC of IND/GLY was recently approved for COPD. This FDC induces dual bronchodilation.

Material and methods: A total of 90 patients were screened as perinclusion and exclusion criteria, 60 eligible patients were selected and randomised into 2 groups, 30 patients were randomly allocated to group I (Indacaterol/glycopyrronium) and the other 30 were allocated to group II (formoterol/tiotropium). Spirometric evaluations were done at -15 min, baseline 1 hour, 6 hour and 24 hours and then subsequently at 4, 8 and 12 weeks.

Results: The improvement in FEV_1 and FEV_1/FVC was similar in both the FDCs showing an equal efficacy.

Conclusion: Both theLABA/LAMA FDCs are pharmacologically valid, synergistic combination and are equiefficacious.

Keywords:LABA/LAMA, COPD, FDC, PFT, IND/GLY.

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INTRODUCTION: Chronic obstructive pulmonary disease (COPD) is a serious global healthcare problem. The GOLD initiative defines COPD as a common, preventable, and treatable disease which affects both men and women worldwide, it is characterised by persistent respiratory symptom that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.[1] COPD is further classified into chronic bronchitis and emphysema. WHO predicts COPD as a leading cause of death by 2030.[2] Evolution of COPD is multifactorial including both genetics and environmental risk factors. Genetics include alpha 1 antitrypsin deficiency (AATD), the most frequent cause of severe AAT deficiency is homozygosity for the SERPINA1*Z allele, which is brought on by a single base pair change in the SERPINA1 gene's coding sequence and results in a single amino acid substitution that results in the formation of AAT polymers in the hepatocytes that produce the majority of AAT, this aberrant protein synthesis leads to decreased circulating

AAT levels.[3] Othergenetic factor include matrix metalloproteinases 12 (MMP12) deficiency, MMP-12 overexpression may play a significant role in the development of COPD as it might result in abnormal extracellular matrix protein breakdown and excessive airway remodelling.[4] and glutathione S transferase. Clinical features of COPD are shortness of breath and chronic cough, with or without sputum, frequent chest infections in winter, easy fatigability, weight loss. Signs include wheezing, pursed lip breathing, barrel shaped chest, dyspnoea, prolonged expiratory time, cyanosis, and peripheral oedema in advanced cases.

It is commonly diagnosed via spirometry also known as Pulmonary Function Test (PFT). Cessation of smoking and lifestyle modifications is the most effective way to prevent COPD from getting worse. Pharmacological treatment includes short acting beta agonists (SABA's) like salbutamol, terbutaline, long acting beta agonist (LABA's) such as salmeterol, formoterol and indacaterol. Long acting antimuscarinic agents (LAMA's) like tiotropium, glycopyrronium and aclidinium, LABAs are keystone treatment for COPD, whereas SABAs are meant for symptom control and are mainly used as rescue medication in case of inadequate control or when the exacerbation happens.

With the arrival of combination inhaler such as LABA/LAMA, the treatment options in COPD are continually expanding. These FDC inhalers improve the patient compliance by decreasing the number of medications and dose. Indacaterol is a fast-acting, ultra-long-acting $\beta_2$adrenoceptor agonist that was recently added to the LABA family.[5] Currently available β_2 agonists are used numerous times per day, reduction in frequency is a crucial step in simplifying the treatment regimen and improving patient adherence, sparking interest in the creation of once-daily LABAs or ultra-LABAs.[6]Indacaterol has the potential benefit of once-day dosing, and the drug's safety profile was similar to that of other bronchodilators.[7]Glycopyrronium is a relatively new member to the LAMA family, with the highest affinity for M_1 receptors and a wider therapeutic window than tiotropium. Glycopyrronium dissociates slowly from muscarinic receptors, resulting in a prolonged effect.[8] A FDC of IND/GLY was recently approved for COPD.[9] The indacaterol-induced bronchodilation is greatly enhanced by glycopyrronium, which provides a prolonged competitive blockade of M3 muscarinic receptors, whereas it quickly detaches from M_2 receptors thereby providing a very good pattern of cardiovascular safety.[10]

The LABA/LAMA regimen has superior and more consistent effects with regard to COPD exacerbations of all severities, including exacerbations requiring the use of health care services. This represents two distinct classes of medications, each with a distinct and additive effect on clinical and physiological indices. The efficacy and safety of this recently approved FDC has been fairly established but the studies comparing this FDC with other FDC's have not been done. On that account, a short-term, randomised, prospective, parallel, open label pilot study was planned to assess the efficacy of FDC of IND/GLY in the Indian population, and to compare it to the very commonly used FDC of FOR/TIO.

MATERIALS AND METHODS

A total of 90 patients were screened as perinclusion and exclusion criteria laid down for the study. 60 eligible patients of COPD who fulfilled the criteria were selected, informed consent was taken, with IEC approval number IEC/Th/19/Pharm03 & CTRI registration number CTRI/2020/06/025652. All the selected patients were randomised into 2 groups, 30 patients were randomly allocated to group I i.e. the study group and the other 30 were allocated to group II i.e. the control group. Both male and female adults aged 40 years and above with clinical diagnosis of COPD or moderate to severe COPD according to GOLD Criteria were included. Patients having COPD exacerbations 4 weeks prior, active TB and ILD were excluded. At the commencement of the study, all the participants had undergone a general physical examination, and spirometry which were recorded on first visit. The patients were followed up at 4 weeks, 8 weeks and 12 weeks. Spirometric evaluations were done at -15 min, baseline 1 hour, 6 hour and 24 hours and then subsequently at 4, 8 and 12 weeks. Patients were evaluated at each visit regarding improvement in symptoms.

All the eligible patients were randomly allocated to one of the two treatment groups- GROUP I or GROUP II.

- **GROUP I –** A fixed dose combination of Indacaterol+ Glycopyrronium, 110/50 mcg OD.
- **GROUP II –** A fixed dose combination of Formoterol + Tiotropium, 12/18 mcg 1 puff BD.

Efficacy of both the FDCs were assessed by doing PFT i.e. FEV_1 and FEV_1/FVC at -15 minutes, 0 hour, 1 hour, 6 hours and 24 hours to see the short term efficacy of the drug treatment and then at each follow up visit i.e. 4, 8 and 12 weeks to evaluate the efficacy of maintenance treatment.

Data was tabulated in Microsoft Excel Sheet. Data was expressed as Mean ± SD. Data was subjected to descriptive statistical analysis. Both intragroup and intergroup analysis was done. All the statistical analysis was performed using Microsoft excel. P-value < 0.05 was considered significant. The intra-group outcomes were compiled and analysed using ANOVA test. Inter-group analysis between 2 groups was analysed using unpaired "t" test.

RESULTS

The demographics of patients are shown in table 1. It was observed that no statistically significant difference ($p>0.05$) in any of the baseline parameters among the two groups was found, thereby showing that the study outcomes were not affected by any of the demographic parameters. (Table 1).

Table 1: Demographic Features of Patients

Variables		**Group I (n=26) Indacaterol/Glycopyrronium**	**Group II (n=24) Formoterol/Tiotropium**	**p value****
Age (years)		56.30 ± 1.99*	57.83 ± 1.90*	0.58
Sex	**Male**	22	19	0.62
	Female	4	5	
FEV1		57.84 ± 1.32*	56.95 ± 1.13*	0.62
FEV1/FVC		67.76±0.75*	69.97 ± 0.94*	0.09

3-D stacked column depicts the short term efficacy in both the groups at -15 minutes, 1 hour, 6 hour and 24 hours. (figure 1). The observations indicate that both the FDCs caused a significant increase at 1 hour, 6 hour and 24 hour ($p<0.00001$). These findings of group I and group II suggest that there was a good short term efficacy of both the combinations.

Figure 2 depicts the long term efficacy in both the groups. These findings of group I and group II suggest that there was a good long term efficacy of both the combinations. ($p<0.00001$)

On intergroup comparison the baseline values for FEV_1 were comparable ($p=0.61$). There was no significant difference in the FEV_1 values at any of the time point ($p>0.05$). This is indicating that the improvement in FEV_1 was similar in both the FDCs showing an equal efficacy in this regard.

Figure 3 shows that both the FDCs caused a significant increase in FEV_1/FVC at 1 hour, 6 hour and 24 hour ($p<0.00001$). These findings of group I and group II suggest that there was a good short term efficacy of both the combinations.

Figure 4 indicates long term efficacy of both the FDCs which was done at 4, 8 & 12 weeks. The findings are significant for both the groups. However, on intergroup comparison it was found that There was no significant difference in the FEV_1/FVC values at any of the time point ($p>0.05$).

DISCUSSION

COPD is a chronic, progressive, and debilitating respiratory disorder that affects people all over the world. COPD is ranked third among India's top five chronic diseases.[11] Spirometry, also known as the Pulmonary Function Test (PFT) is commonly used to diagnose it. LABA/LAMA FDCs remains the cornerstone in treatment of COPD. By reducing the number of medications and doses, these FDC inhalers improve patient compliance. The most recent LABA/LAMA approved by CDSCO for COPD is IND/GLY.

Efficacy assessment was done by evaluating lung functions: FEV_1 and FEV_1/FVC at baseline and then at various time intervals i.e. 0 min, 15 min, 1 hour, 6 hour and 24 hour to evaluate short term efficacy and then at each follow up visit i.e. 4, 8 and 12 weeks to evaluate efficacy of maintenance treatment.

Although exact similar studies were not available in which similar treatment groups were compared for observing improvement in FEV_1 values, though few studies had mentioned comparison of IND/GLY with TIO or GLY alone and comparison of FOR/TIO with FOR alone.

In a multicenter study, 2138 pts were randomized to receive IND/GLY (110/50 mcg) or tiotropium (18mcg) or glycopyrronium (50 mcg) or placebo alone for 26 weeks. Trough FEV_1 at week 26 was significantly improved with IND/GLY compared with both indacaterol and glycopyrronium, with treatment differences of 0.07 L and 0.09 L, respectively (both $p<0.001$). IND/GLY also provided significantly higher improvement in trough FEV_1 compared with tiotropium and placebo at week 26, with treatment differences of 0.08 L and 0.2 L, respectively ($p<0.001$). All active treatments at week 26 had an increase from baseline in trough FEV_1, the mean increase being highest for the IND/GLY group. IND/GLY provided rapid bronchodilation following the first dose on day 1, with significantly higher FEV_1 compared with placebo, glycopyrronium and tiotropium (all $p<0.01$).[12] The study clearly indicated superiority of the FDC over individual drugs.

In another 26 weeks multicenter, randomized, triple blinded study 934 patients were randomized to receive either FDC of IND/GLY or free dose combination of formoterol and tiotropium. It was concluded that the values of FVC post bronchodilation showed no significant differences between the treatment groups as as both LABAs (indacaterol and formoterol) are potent bronchodilators with a fast onset of action.[13]

In another study 78 eligible patients were randomized to receive IND/GLY or IND/placebo. A statistically significant adjusted treatment difference in FEV_1 was noted at all-time points in favour of IND/GLY treatment ($p<0.001$ for all comparisons).[14] The results reflect of improved efficacy on addition of glycopyrronium to indacaterol.

The findings in the present study are quite consistent with the above mentioned studies with regard to improvement in FEV_1 with IND/GLY at the end of treatment.

In the present study, both the groups showed statistically significant improvement in FEV_1/FVC values starting with effect from 0 minutes post administration with further improvement up to 12 weeks. This statistically significant increase was observed starting from week 4 which gradually increased further in the subsequent weeks indicating that the improvement was ongoing throughout the study period. The improvement

is on the expected lines as combining two bronchodilators with different mechanisms of action has the potential to enhance efficacy more so in improving the FEV_1/FVC.

In both groups, the improvement was determined to be statistically significant. However, both the groups were found to be equi-efficacious in causing this improvement. No studies could be found observing the effect of these combinations on FEV_1/FVC.

CONCLUSION:

Both the FDCs were found to be safe and well tolerated by the patients. The findings are clearly indicating that combination of LABA with LAMA is a pharmacologically valid and synergistic combination with a much better efficacy. The IND/GLY FDC provides an additional alternative to the clinician for treating the COPD patient with the advantage of once daily dosing as well as the likelihood of an increased patient compliance.

Conflict of interest: None

Acknowledgement: None

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Figure 1: SHORT TERM EFFICACY IN TERMS OF FEV1 IN BOTH THE GROUPS

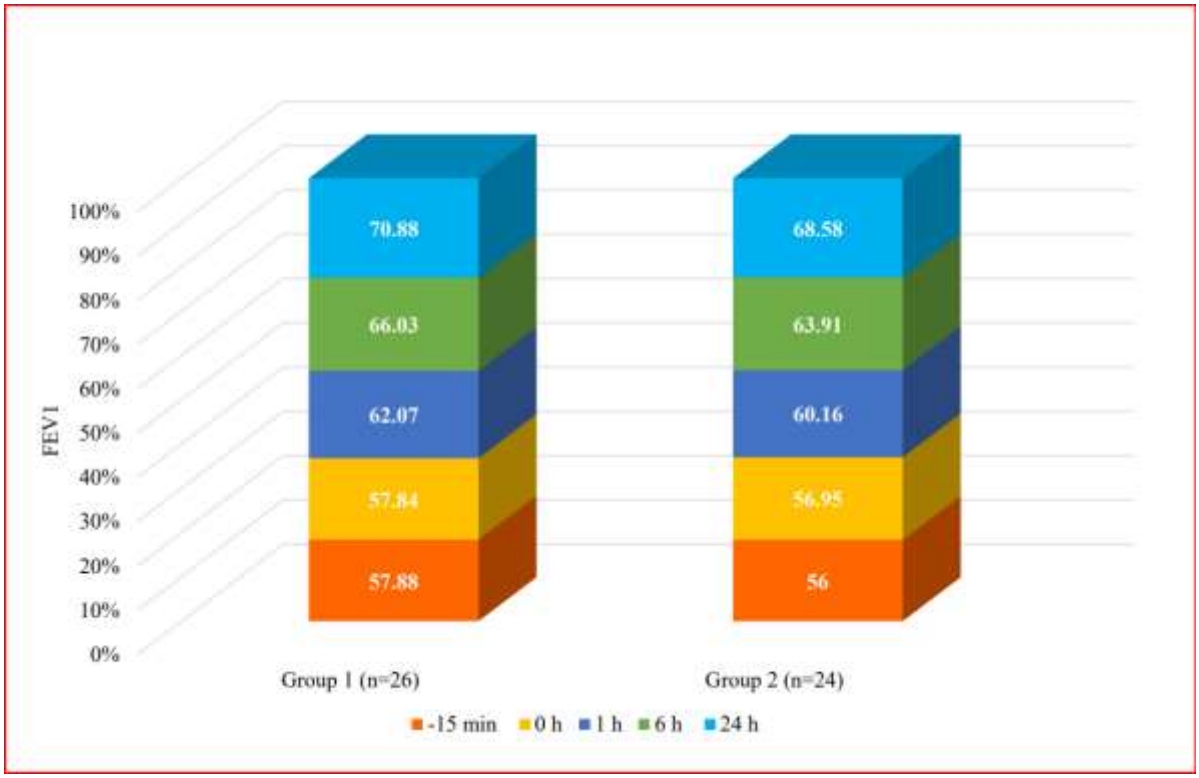

Figure 2: LONG TERM EFFICACY IN TERMS OF FEV1 IN BOTH THE GROUPS

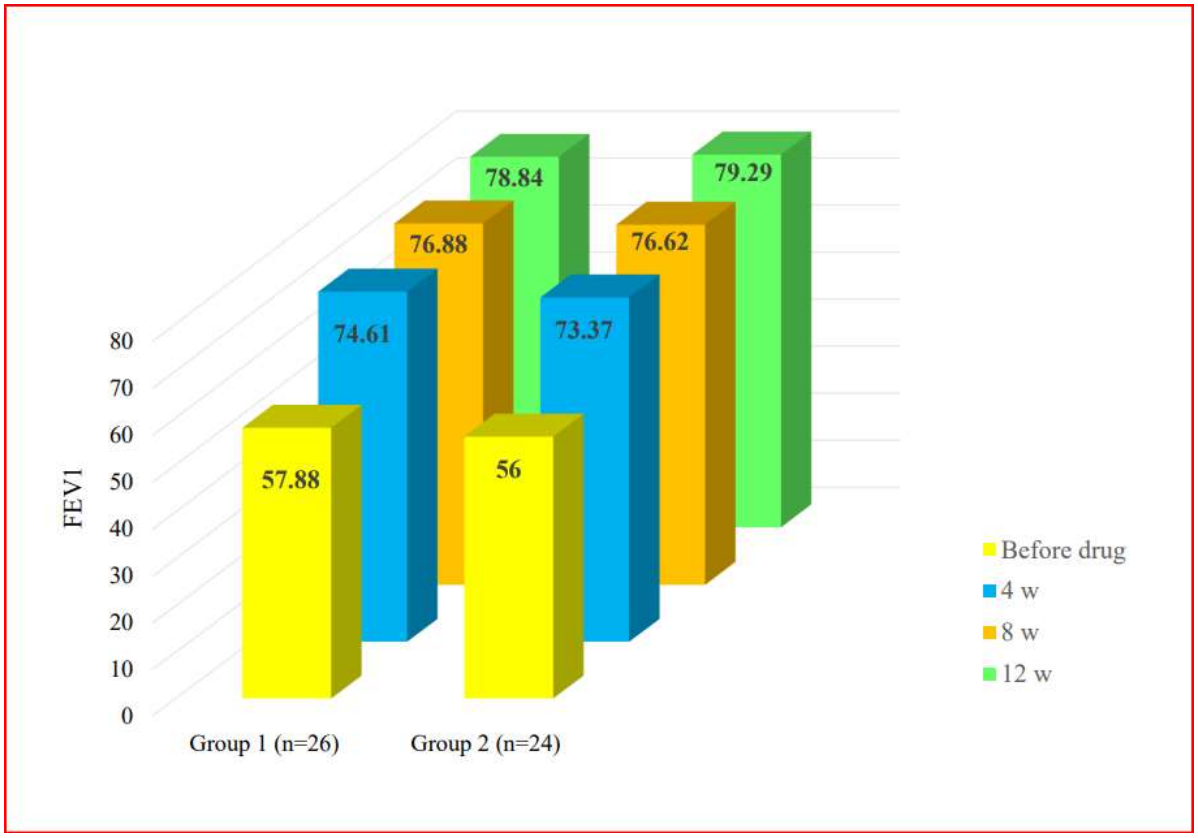

Figure 3: SHORT TERM EFFICACY IN TERMS OF FEV1/FVC IN BOTH THE GROUPS

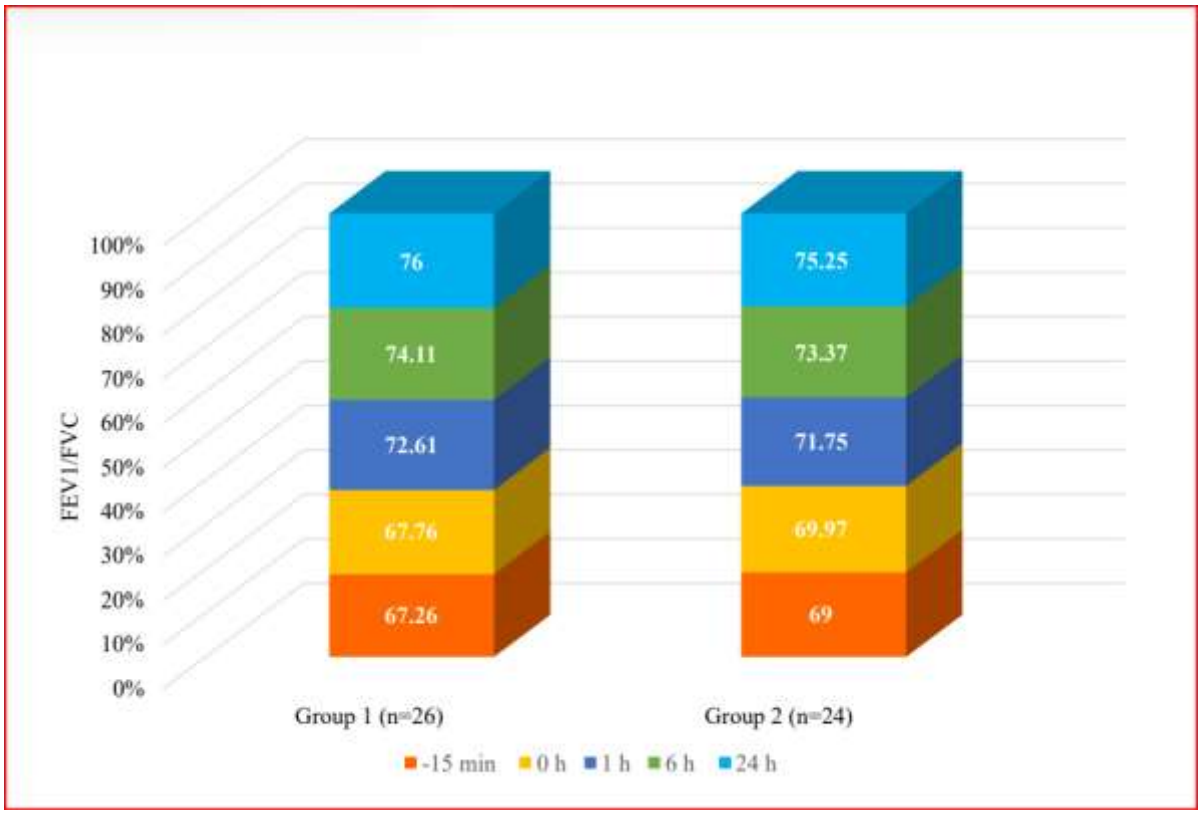

Figure 4: LONG TERM EFFICACY IN TERMS OF FEV1/FVC IN BOTH THE GROUPS