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Comparative Study to Evaluate the Effect of Tiotropium and Formoterol versus Glycopyrronium and Formoterol Combination on Pulmonary Functions in Patients with Chronic Obstructive Pulmonary Disease

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ABSTRACT

Background: Chronic Obstructive Pulmonary Disease (COPD) is characterized by persistent airflow limitation with symptoms such as dyspnea, sputum production and cough reported by patients. It is the 4th leading cause of death worldwide and 2nd in India. Bronchodilator agents, Long-Acting β-2 Agonists (LABA) and Long-Acting Muscarinic Antagonists (LAMA) are the cornerstone of all stages of COPD treatment. Long-acting bronchodilator therapy is known to improve lung function and quality of life in patients with COPD.

Aim: To Evaluate the effect of Tiotropium and Formoterol Vs Glycopyrronium and Formoterol Combination on Pulmonary Functions in Patients with Chronic Obstructive Pulmonary Disease

Objectives: The primary objective is to compare the pulmonary function parameters (FEV1 and FEV1/FVC) in COPD patients treated with TFF (Tiotropium and Formoterol) versus GFF (Glycopyrronium and Formoterol). The secondary objective is to compare the quality of life in COPD patients treated with TFF versus GFF.

Methodology: This comparative, two-group, single-centre observational longitudinal study included patients with COPD who were already receiving either Tiotropium and Formoterol (TFF) or Glycopyrronium and Formoterol (GFF) treatment for more than 3 months before enrolment. Patients were classified into the TFF or GFF group according to the treatment combination they were already receiving; no investigator-directed random allocation was performed. A total of 280 eligible patients were enrolled at baseline, with 140 patients in each group. Follow-up assessments were performed at baseline, 3 months and 6 months. Pulmonary function parameters (FEV1 and FEV1/FVC) and health-related quality of life (SGRQ; St. George's Respiratory Questionnaire score) were assessed.

Results: Follow-up data were available for 262 patients at 3 months (130 in the TFF group and 132 in the GFF group) and 252 patients at 6 months (126 in each group). FEV1, FEV1/FVC and SGRQ scores improved over time in both treatment groups. Longitudinal analysis demonstrated a significant effect of time for FEV1, FEV1/FVC and SGRQ ($p<0.001$ for each) and a significant group × time interaction for FEV1 ($p<0.001$), FEV1/FVC ($p<0.001$) and SGRQ ($p=0.005$), indicating that the pattern of change over time differed between the treatment groups.

Conclusion: Both Tiotropium/Formoterol and Glycopyrronium/Formoterol were associated with significant improvement in pulmonary function and health-related quality of life over the 6-month follow-up period. The longitudinal analysis indicated differences in the pattern of response between the two treatment groups. As this was an observational study, these findings do not establish equivalence or non-inferiority between the two treatment combinations.

Keywords: Chronic Obstructive Pulmonary Disease, Tiotropium, Glycopyrronium, Formoterol Fumarate, Forced Expiratory Volume in 1 second, Forced Vital Capacity, St. George's Respiratory Questionnaire

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a lung condition marked by chronic respiratory symptoms like shortness of breath, cough, and sputum production, caused by airway abnormalities leading to persistent, progressive airflow obstruction. It is a common, preventable, and treatable public health issue. [1] According to the World Health Organization (WHO), chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide, accounting for approximately 3.23 million deaths in 2019. [2] In India, data from the Global Burden of Disease (GBD) study indicate that COPD is the second leading cause of both mortality and disability-adjusted life years (DALYs). Among individuals aged >40 years in India, the prevalence of spirometrically defined COPD has been reported to be 17.3% in men and 14.8% in women.[3]

COPD is primarily caused by tobacco and cigarette smoking, biomass fuel smoke, tuberculosis history, and inhaling toxic particles from air pollution. Other factors, like abnormal lung development and accelerated lung aging, also contribute. Smoking is a major environmental risk factor for COPD.[4] Patients with shortness of breath, persistent cough, sputum production, recurrent lower respiratory infections, or exposure to risk factors should be evaluated for COPD. Diagnosis is confirmed by spirometry showing post-bronchodilator FEV1/FVC <0.7, indicating airflow obstruction.[1]

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, inhaled bronchodilators, particularly long-acting muscarinic antagonists (LAMAs) and long-acting β_2-agonists (LABAs), constitute the cornerstone of pharmacological therapy for COPD management across disease stages.[1] LAMAs and LABAs represent the two principal classes of long-acting bronchodilators and are currently the mainstay of maintenance pharmacotherapy for patients with COPD, providing sustained bronchodilation and symptomatic relief. LAMA such as Tiotropium, Umeclidinium, and Glycopyrronium and LABA namely as Indacaterol, Olodaterol, and Vilanterol, Formoterol Fumarate, Salmeterol.[5] LAMA/LABA fixed-dose combinations (FDCs) improve lung function, exercise capacity, lung hyperinflation, and quality of life, helping to slow COPD progression. These combinations work synergistically.[6] LAMA/LABA combinations optimize bronchodilation by targeting adrenergic and cholinergic pathways in airway smooth muscle. LAMAs block muscarinic receptors to inhibit bronchoconstriction, while LABAs stimulate beta-2 adrenergic receptors to relax airway muscles. This

complimentary action enhances bronchodilation and improves lung function, making these combinations effective in treating COPD's airflow limitation and respiratory symptoms.[7]

Previous clinical trials evaluating LAMA/LABA combination therapy have demonstrated that these agents are generally well tolerated and provide clinically significant improvements in lung function and respiratory symptoms among patients with COPD. However, based on the available literature reviewed, no relevant studies were identified that directly compared the specific LAMA/LABA combination evaluated in the present study. This lack of comparative evidence highlights the need for further investigation of the efficacy and tolerability of the specific combination used in the current study. [8-9] Therefore, the present study was conducted to evaluate the comparison of effect of Tiotropium and Formoterol versus Glycopyrronium and Formoterol combination on pulmonary functions in patients with COPD.

Aim

The aim of current study is to compare the effectiveness of Tiotropium and Formoterol vs Glycopyrronium and Formoterol combination on pulmonary functions in patients with COPD.

Objectives

(1.) Primary outcome is to compare the pulmonary function parameters (FEV1 and FEV1/FVC) in patients with COPD receiving TFF (Tiotropium and Formoterol) and GFF (Glycopyrronium and Formoterol) treatment.

(2.) Secondary outcome is to compare the quality of life in patients with COPD receiving TFF (Tiotropium and Formoterol) and GFF (Glycopyrronium and Formoterol) treatment.

METHODOLOGY

This was a comparative, two-group, single-centre observational longitudinal study conducted in the Department of Pharmacology in collaboration with the Department of Respiratory Medicine at Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, after obtaining ethical clearance from the Institutional Ethics Committee (IEC No. 118/22). The study was conducted from October 2022 to March 2024. All participants were already receiving either Tiotropium/Formoterol (TFF) or Glycopyrronium/Formoterol (GFF) combination treatment for more than 3 months before enrolment and were classified into the respective group according to their pre-existing treatment. No investigator-directed random allocation was performed. A total of 280 eligible patients were enrolled at baseline, with 140 patients in each group.

Follow-up assessments were planned at 3 months and 6 months. At 3 months, follow-up data were available for 130 patients in the TFF group and 132 patients in the GFF group (total n=262). At 6 months, follow-up data were available for 126 patients in each group (total n=252). Thus, 28 patients did not have 6-month follow-up data. The specific reasons for loss to follow-up were not documented in the available patient-level dataset.

A total of 280 eligible participants were included in the study, with 140 participants in each treatment group. The sample size was determined considering a two-sided significance level of 5%,80% statistical power, and an equal allocation ratio between the two treatment groups.

Inclusion Criteria:

(1.) Participants of age ≥40 years with prior history of smoking (calculated according to pack-years) assessed with moderate COPD (Stage 2 according to GOLD 2022 guidelines)

(2.) Participants were also enrolled with proven and confirmed case of COPD such as shortness of breath, cough, with or without expectoration.

(3.) Participants with respiratory examination suggestive of airway

obstruction such as rhonchi, decreased intensity of breath sounds and prolonged expiration.

(4.) Patients who had COPD history and were already receiving treatment of TFF (Tiotropium and Formoterol) and GFF (Glycopyrronium and Formoterol) combination for more than 3 months.

Exclusion Criteria:

(1.) All patients with insufficient mental capacity who could not give an informed consent

(2.) Patients with urinary retention, cancer, thyroid disease, severe liver disease, chronic kidney disease, congestive heart failure, rheumatoid arthritis, narrow-angle glaucoma

(3.) Pregnant or nursing mothers

(4.) Women of child bearing potential not taking adequate contraceptive measures

(5.) Contraindications and hypersensitivity to any of the study drugs

(6.) History of adverse reactions to inhaled anticholinergics/any of the study drugs

Data Analysis:

Data were entered into Microsoft Excel and analyzed using SPSS software version 21.0. Continuous variables were summarized as mean ± standard deviation, and categorical variables were summarized as frequencies and percentages. Baseline categorical characteristics were compared using the Chi-square test, as appropriate, and baseline continuous variables were compared using an independent-samples Student's t-test. For repeated measurements of FEV1, FEV1/FVC and SGRQ scores obtained at baseline, 3 months and 6 months, a longitudinal linear mixed-effects model was used with treatment group, time and the group × time interaction as fixed effects and patient as the repeated-measures subject. Effect estimates with 95% confidence intervals were reported together with p-values. No values were imputed for missing follow-up observations. A two-sided p-value ≤0.05 was considered statistically significant.

OBSERVATION AND RESULTS

This observational longitudinal study compared the effectiveness of Tiotropium and Formoterol (TFF) versus Glycopyrronium and Formoterol (GFF) on pulmonary function in COPD patients. Conducted at Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, after IEC approval, at baseline, 280 patients were enrolled (140 TFF and 140 GFF). At 3 months, data were available for 130 TFF and 132 GFF patients (n=262). At 6 months, data were available for 126 patients in each group (n=252). Therefore, 28 patients lacked 6-month follow-up data. Group A received TFF (9µg/6µg) and Group B received GFF (25µg/12µg) via Revolizer twice daily. Baseline and clinical characteristics were assessed at baseline, 3 months, and 6 months. Data analysis results are below.

The general characteristics of the study participants are as follows: In the Tiotropium and Formoterol Combination (TFF) group (n=140), 122 (87.15%) were male and 18 (12.85%) were female, with an average age of 57.73±5.48 years and a BMI of 22.53±0.96. In the Glycopyrronium and Formoterol Combination (GFF) group (n=140), 128 (91.43%) were male and 12 (8.57%) were female, with an average age of 59.07±4.46 years and a BMI of 23.16±0.75. Additionally, 102 patients (72.86%) of the TFF group were from rural areas, while 38 patients (27.14%) were from urban areas. In the GFF group, 88 (62.86%) were from rural areas, while 52 (37.14%) were from urban areas. The p-values for these comparisons were 0.098 for gender distribution, 0.088 for age, 0.738 for BMI, and 0.056 for the rural-urban distribution, indicating no statistically significant differences between the groups.

In the TFF group, 64 (45.71%) experienced shortness of breath and 113 (80.71%) had a cough with expectoration. In the GFF group, 79 (56.4%) experienced shortness of breath and 109 (77.85%) had a cough with expectoration. The p-values were 0.069 and

0.087, respectively, indicating no significant differences between the groups.

The history of smoking among participants is as follows: In the TFF group (n=140), 17 (12.14%) had 0 pack years, 6 (4.28%) had 10 pack years, 65 (46.42%) had 15 pack years, and 52 (37.14%) had 20 pack years. In the GFF group (n=140), 13 (9.28%) had 0 pack years, 6 (4.28%) had 10 pack years, 79 (56.42%) had 15 pack years, and 42 (30%) had 20 pack years. The p-value was 0.064, indicating no significant difference between the groups.

In the TFF group, 49 (35%) had a history of biomass fuel exposure, 38 (27%) had tuberculosis, 29 (20.71%) had diabetes, 29 (20.71%) had hypertension, and 30 (21.43%) had a history of alcohol use. In the GFF group, 60 (42%) had a history of biomass fuel exposure, 24 (17.14%) had tuberculosis, 18 (12.85%) had diabetes, 23 (16.42%) had hypertension, and 34 (24.28%) had a history of alcohol use. The p-values indicate no significant differences: 0.065 for biomass fuel exposure, 0.065 for tuberculosis, 0.058 for diabetes, 0.097 for hypertension, and 0.088 for alcohol use. The severity of the disease in both groups was classified as moderate.

Table 1: Comparison of clinical characteristics between the TFF and GFF group

S. No.	Parameters	Time Period	TFF	GFF	p-value
1.	FEV1	At Baseline (n=140 per group)	55.12±2.91	54.65±2.12	0.099
		At 3 months (n=130 in TFF, n=132 in GFF)	59.52±2.14	58.54±2.30	0.325
		At 6 months (n=126 per group)	65.07±2.14	62.83±1.30	0.245
2.	FEV1/FVC	At Baseline	65.03±3.96	64.45±4.55	0.087
		At 3 months	68.34±3.53	67.84±3.98	0.125
		At 6 months	73.24±1.88	71.24±3.75	0.059
3.	SGRQ	At Baseline	44. 21±1.52	44. 21±1.52	1.00
		At 3 months	29.95±1.86	30.37±1.37	0.078
		At 6 months	22.32±1.43	23.14±0.84	0.088

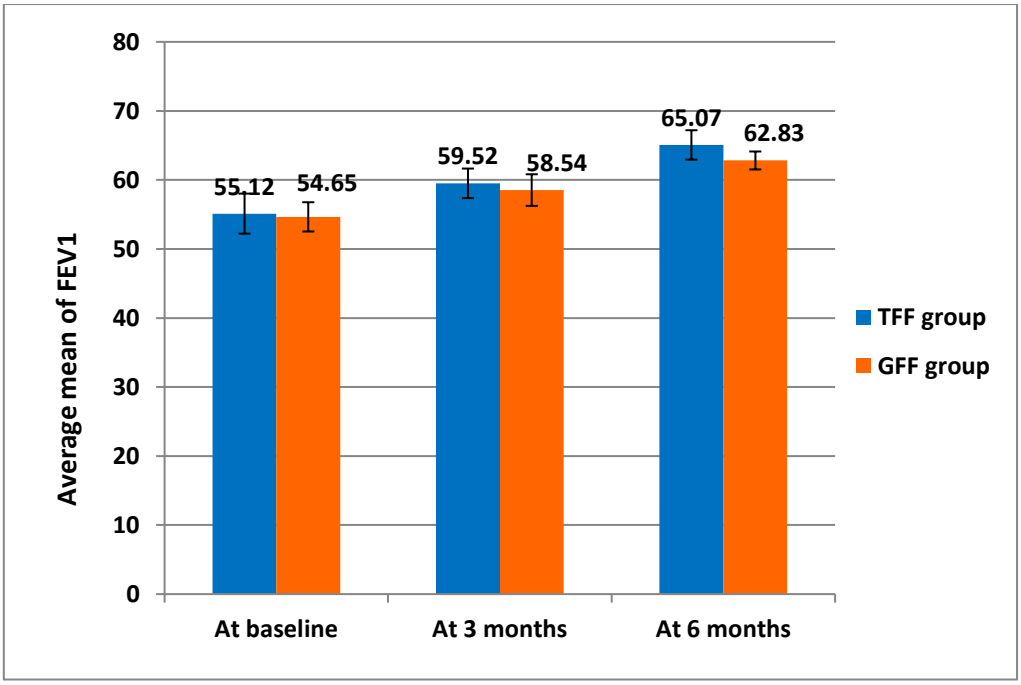

Fig 1: Comparison of average mean of FEV1 in patients between both the groups

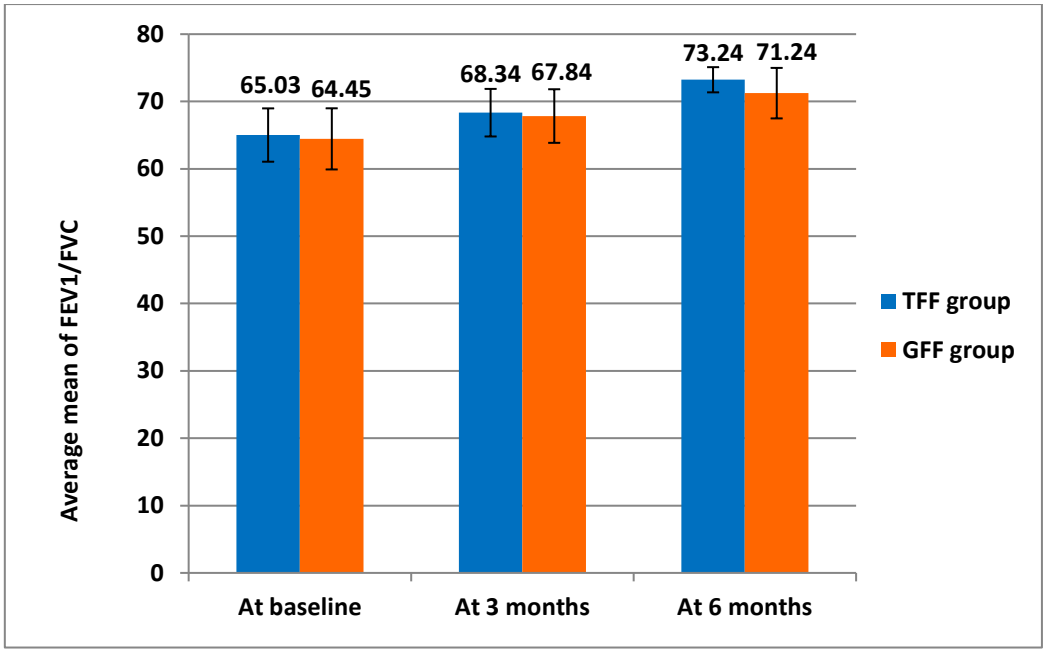

Fig 2: Comparison of average mean of FEV1/FVC in patients between both the groups

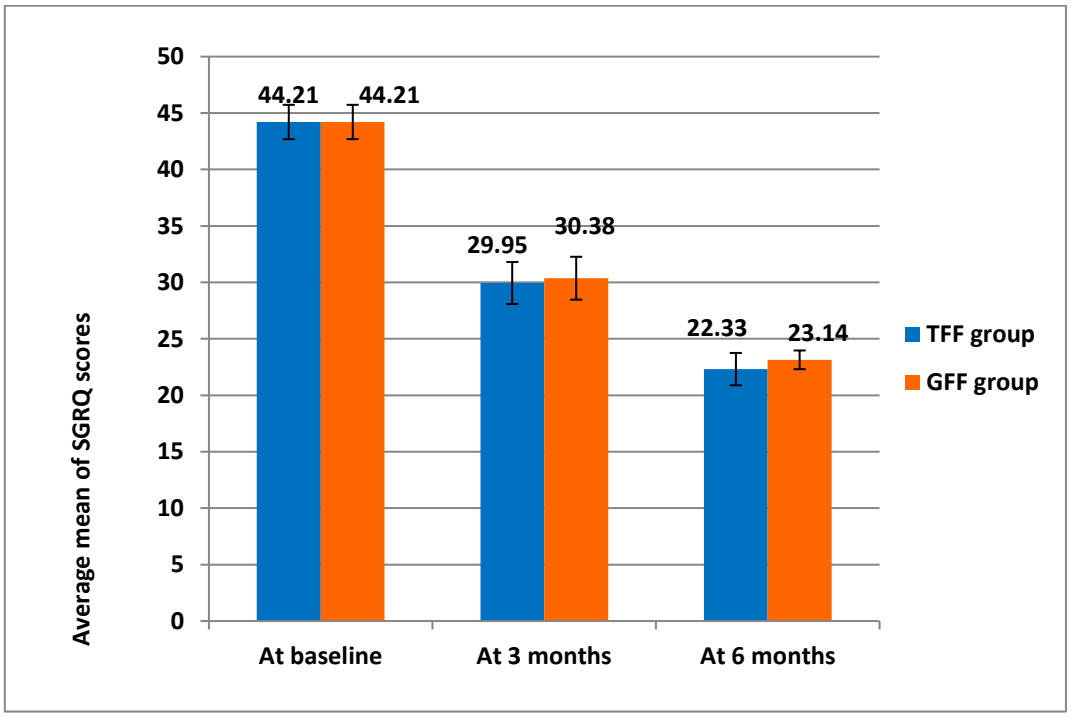

Fig 3: Comparison of average mean of SGRQ scores in patients between both the groups

Table 2: Comparison of clinical characteristics from baseline to the three-month and six-month follow-up periods for both groups

S. No.	Parameters	Groups	Baseline	Follow-up period		p-value
1.	FEV1	TFF	55.12±2.91	At 3 months	59.52±2.14	0.054
				At 6 months	65.07±2.14	0.012
		GFF	54.65±2.12	At 3 months	58.54±2.30	0.062
				At 6 months	62.83±1.30	0.023
2.	FEV1/FVC	TFF	65.03±3.96	At 3 months	68.34±3.53	0.066
				At 6 months	73.24±1.88	0.014
		GFF	64.45±4.55	At 3 months	67.84±3.98	0.074
				At 6 months	71.24±3.75	0.013

3.	SGRQ scores	TFF	44. 21±1.52	At 3 months	29.95±1.86	0.021
				At 6 months	22.33±1.43	0.011
		GFF	44. 21±1.52	At 3 months	30.38±1.37	0.026
				At 6 months	23.14±0.84	0.013

Table 3: Longitudinal analysis of FEV1, FEV1/FVC and SGRQ scores over time

Outcome	Time effect	Group × time interaction
FEV1	p<0.001	p<0.001
FEV1/FVC	p<0.001	p<0.001
SGRQ	p<0.001	p=0.005

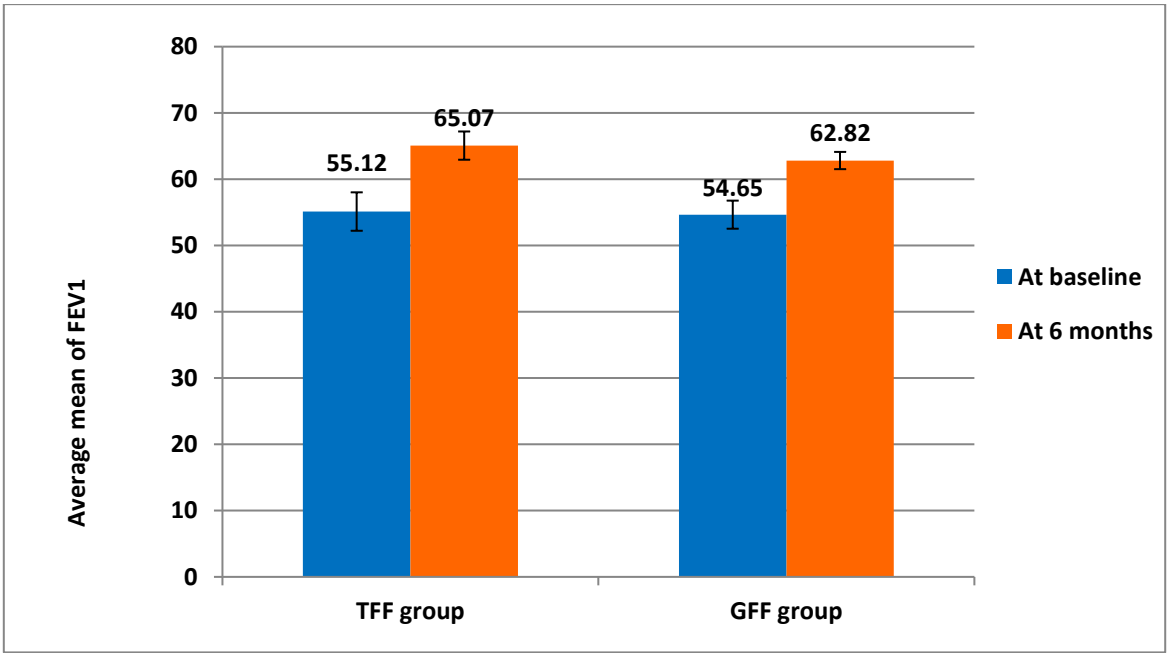

Fig 4: Comparison of the average FEV1 values at baseline and after six months of follow-up in both groups

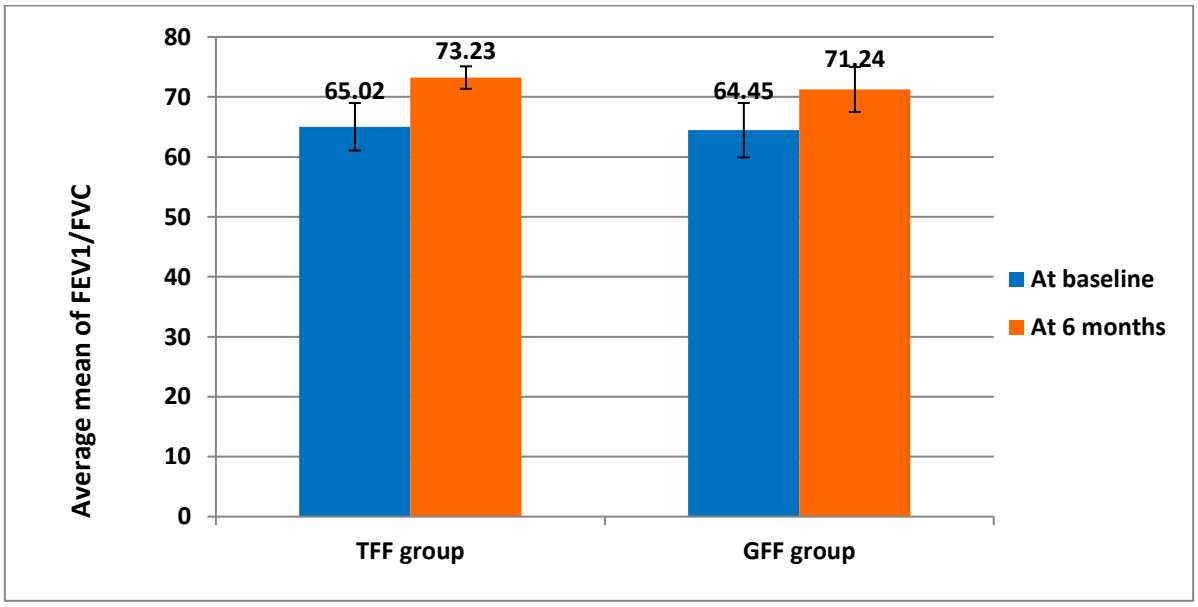

Fig 5: Comparison of the average FEV1/FVC values at baseline and after six months of follow-up in both groups

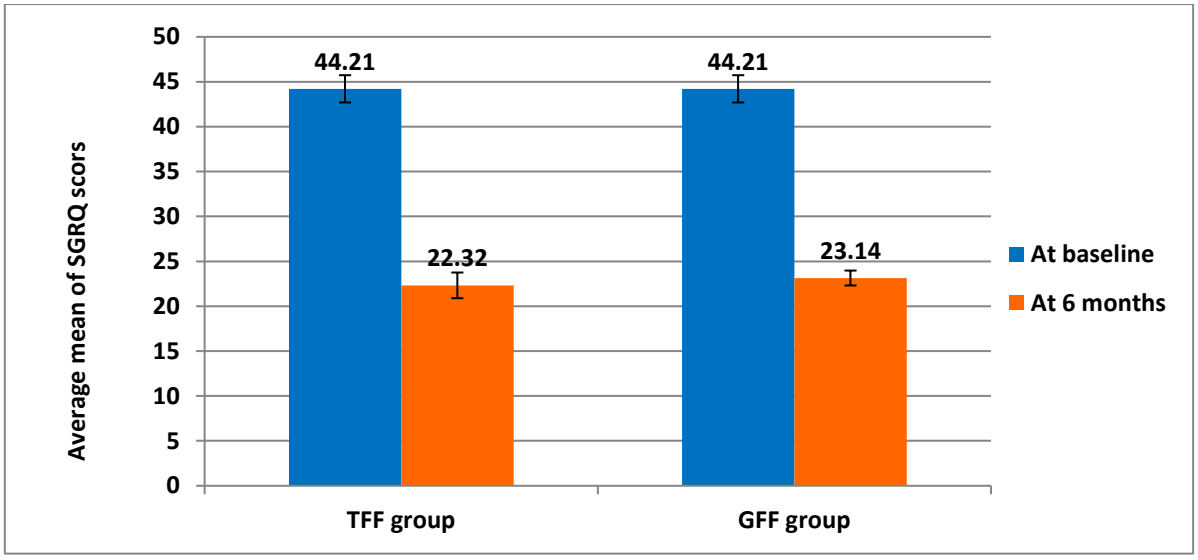

Fig 6: Comparison of the average SGRQ scores at baseline and after six months of follow-up in both groups

DISCUSSION

Of the 280 patients enrolled at baseline, follow-up data were available for 262 patients at 3 months and 252 patients at 6 months, with 126 patients in each group at 6 months. Thus, 28 patients did not have 6-month follow-up data. The specific reasons for loss to follow-up were not documented in the available patient-level dataset.

Gender distribution showed a higher percentage of males in both groups, with no significant difference between them (p-value 0.098). D'Urzo [10] also found in their study that maximum COPD patients were male. Patients were aged 40 and above, with average ages of 57.72 years in the TFF group and 59.07 years in the GFF group, showing no significant age difference (p-value 0.088). The average BMI was slightly lower in the TFF group (22.53) compared to the GFF group (23.15), but this difference was not significant (p-value 0.73). More patients were from rural areas in both groups, with no significant difference in residential distribution (p-value 0.056). Overall, there were no significant differences between the groups in terms of gender, age, BMI, and residential areas.

In the current study, both groups experienced symptoms of shortness of breath and cough with phlegm. Specifically, 64 patients (45.71%) in the TFF group and 79 patients (56.4%) in the GFF group reported shortness of breath, with no statistically significant difference between the groups (p-value 0.069). For cough with expectoration, 113 patients (80.71%) in the TFF group and 109 patients (77.85%) in the GFF group reported symptoms, also showing no statistically significant difference (p-value 0.087). Overall, there were no significant differences between the groups regarding these symptoms.

Smoking history was recorded in both treatment groups. In the TFF group, 17 patients (12.14%) had 0 pack-years, 6 (4.29%) had 10 pack-years, 65 (46.43%) had 15 pack-years, and 52 (37.14%) had 20 pack-years. In the GFF group, 13 patients (9.29%) had 0 pack-years, 6 (4.29%) had 10 pack-years, 79 (56.43%) had 15 pack-years, and 42 (30.00%) had 20 pack-years. Smoking is a major cause of COPD, resulting in chronic inflammation and damage to the airways and alveoli, thereby reducing lung function and causing shortness of breath. Additionally, smoking increases mucus production, leading to congestion and frequent respiratory infections. It also accelerates the progression of COPD and raises the risk of exacerbations.

Patients in both groups had a history of biomass fuel exposure, with 49 patients

(35%) in the TFF group and 60 patients (42.85%) in the GFF group, showing no statistically significant difference (p-value 0.065). Biomass fuel exposure, from sources such as wood and crop residues used for cooking and heating, is a recognized risk factor for COPD due to the release of toxic pollutants during combustion. Inhalation of these pollutants induces lung inflammation, oxidative stress, and structural damage, leading to conditions like emphysema and chronic bronchitis, which contribute to COPD. Long-term exposure results in a progressive decline in lung function and increases susceptibility to respiratory infections, exacerbating COPD symptoms.[11]

In the present study, 38 patients (27.14%) in the TFF group and 24 patients (17.14%) in the GFF group had a history of tuberculosis (TB), with no statistically significant difference between the groups (p-value 0.065). A past history of TB is a key risk factor for COPD, as TB can cause lung inflammation, scarring, and permanent damage, leading to COPD. TB and COPD often coexist, with TB increasing the risk of developing COPD and COPD patients being more susceptible to TB. The combination of both conditions exacerbates respiratory symptoms and complicates treatment.[12]

In the study, 30 patients (21.43%) in the TFF group and 34 patients (24.28%) in the GFF group had a history of alcohol consumption, with no statistically significant difference between the groups (p-value 0.088). Although alcohol does not directly cause COPD, it can exacerbate the condition through related comorbidities and its impact on lung health.[13]

In the study, 29 patients (20.71%) in the TFF group and 18 patients (12.85%) in the GFF group had diabetes mellitus (DM), with no statistically significant difference between the groups (p-value 0.058). Both DM and COPD share common risk factors such as age, smoking, and obesity, and are interconnected through chronic systemic inflammation.[14] DM exacerbates COPD by increasing inflammation, impairing immune function, and raising the risk of respiratory infections and cardiovascular disease. Additionally, shared genetic factors may contribute to the development of both conditions.

In the study, 29 patients (20.71%) in the TFF group and 23 patients (16.42%) in the GFF group had hypertension, with no statistically significant difference between the groups (p-value 0.097). Both hypertension and COPD share common risk factors such as aging, smoking, and obesity.[15] Chronic inflammation is a common feature of both conditions, contributing to vascular and airway damage. COPD increases the risk of cardiovascular diseases, including hypertension, due to chronic hypoxemia and pulmonary hypertension, which strain the heart and elevate blood pressure.

In the study, the initial mean FEV1 values for the TFF (55.12±2.91) and GFF (54.65±2.12) groups showed no statistically significant difference (p-value 0.099). After three months of treatment, FEV1 increased to 59.52±2.14 in the TFF group and 58.54±2.30 in the GFF group, with no significant difference between the groups (p-value 0.32). After six months, FEV1 further improved to 65.07±2.14 in the TFF group and 62.83±1.30 in the GFF group, still showing no significant difference (p-value 0.24). The increases from baseline were significant after six months for both the TFF (p-value 0.01) and GFF (p-value 0.02) groups. These FEV1 improvements indicate effective COPD management with both treatments, enhancing lung function through bronchodilation. The study's findings are consistent with those of previous studies on TFF and GFF.

For FEV1, both groups improved over follow-up, with a significant group × time interaction ($p<0.001$). For FEV1/FVC, both groups improved over follow-up, with a significant group × time interaction ($p<0.001$). For SGRQ, scores decreased over time in both groups, representing improvement in health-related quality of life, and the group × time interaction was

significant (p=0.005). These findings indicate differences in the longitudinal pattern of response and should not be described as proof of equivalence.

In the study, the initial FEV1/FVC ratio were 65.03±3.96 for the TFF group and 64.45±4.55 for the GFF group, with no statistically significant difference (p-value 0.087). After three months, the FEV1/FVC ratio increased to 68.34±3.53 in the TFF group and 67.84±3.98 in the GFF group, with no significant difference (p-value 0.12). After six months, the FEV1/FVC ratio further improved to 73.24±1.88 in the TFF group and 71.24±3.75 in the GFF group, again showing no significant difference (p-value 0.059). The increase in FEV1/FVC from baseline to six months was significant for both groups (p-value 0.01), indicating improved lung function. The FEV1/FVC ratio is crucial for diagnosing and monitoring obstructive diseases like COPD,[16] with improvements suggesting better airflow and response to treatment. Both TFF and GFF improve lung function by promoting bronchodilation and reducing airway resistance. The study's findings are consistent with those of previous studies on TFF and GFF.

The present study assessed patients with symptoms of COPD, evaluating the severity of these symptoms using SGRQ scores at different time points: baseline, three months, and six months. Higher SGRQ scores indicate worse health, while lower scores signify better health. At the beginning of the study, the average SGRQ scores were 44.21±1.52 in both groups, suggesting comparable respiratory health (p-value = 1). After three months of treatment, the SGRQ scores decreased to 29.95±1.86 in the TFF group and 30.37±1.37 in the GFF group, with no statistically significant difference between the groups (p-value 0.078). However, comparing scores from baseline to the three-month follow-up revealed a significant reduction in both groups (p-values of 0.021 for the TFF group and 0.026 for the GFF group), indicating an improvement in respiratory health and quality of life. After six months of treatment, the mean SGRQ scores decreased to 22.32±1.43 in the TFF group and 23.14±0.84 in the GFF group. With a p-value of 0.088, there was no statistically significant difference between the groups. Nonetheless, comparing the scores from baseline to the six-month follow-up revealed a significant reduction in both groups (p-values of 0.011 for the TFF group and 0.013 for the GFF group), indicating substantial improvement in symptom control, enhanced respiratory health, and improved quality of life. These findings are consistent with previous studies on TFF and GFF treatment.

Severe morning symptoms are a well-known characteristic of COPD patients, significantly interfering with their daily activities. The use of LAMA (Tiotropium and Glycopyrronium) and LABA (Formoterol Fumarate) is crucial for alleviating these symptoms.[17] COPD is a heterogeneous disease with varying degrees of airflow limitation and responsiveness to bronchodilators. Combining LAMA with LABA can enhance bronchodilation, leading to more effective and sustained symptom control, including relief from shortness of breath, cough, and wheezing, as well as a reduced risk of exacerbations.[18] This combination can improve the quality of life for COPD patients by enabling them to perform daily activities with less respiratory discomfort, ultimately resulting in better clinical outcomes and enhanced quality of life.[19]

In the GLOW5 study,[20] researchers compared glycopyrronium with tiotropium in patients with moderate-to-severe COPD in a blinded, double-dummy design. This study demonstrated a statistically significant improvement in health-related quality of life, as measured by SGRQ scores, in both treatment groups, mirroring our results. Our study similarly showed significant improvements from the initiation of treatment, as assessed by SGRQ scores. Larger clinical trials have also reported comparable findings, supporting the

efficacy of these treatments in managing COPD symptoms and improving patient outcomes. [20,21-22]

This study demonstrates significant improvement in pulmonary function parameters (FEV1 and FEV1/FVC) and in health-related quality among stable moderate COPD patients following the administration of TFF and GFF combination. There were limitations in the study that must be acknowledged. These involved one centred study, it was an observational study, long follow up period due to which dropout rate of patients was increased and adverse effects not taken into accountability.

CONCLUSION

Both Tiotropium/Formoterol and Glycopyrronium/Formoterol were associated with improvement in pulmonary function and health-related quality of life over the 6-month follow-up period. Longitudinal analysis demonstrated significant group × time interactions for FEV1, FEV1/FVC and SGRQ, indicating differences in the pattern of response between the treatment groups. The present observational study does not establish equivalence or non-inferiority between the two treatment combinations. Further adequately powered prospective studies are warranted.

Declaration by Authors
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Conflict of Interest: The authors declare no conflict of interest.

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