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Original Article

Observational, Concurrent Study to Assess Safety and Efficacy of Glycopyrronium and Arformoterol Home Nebulization in High-risk, Symptomatic Acute Exacerbation of Chronic Obstructive Pulmonary Disease Cases: SYMPTOM Study

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is one of the most important reasons for hospitalization worldwide with high 30-day readmission rates. Although the prognostic significance of early readmission is not fully understood, they are often associated with poor outcomes including high mortality rates of 4%–19% at 30 and 365 days, respectively. Similarly, in acute exacerbations of COPD (AECOPD) cases receiving emergency department care, current status on lung function and cardiovascular comorbidities are considered as best predictors for both 30- and 90-day COPD readmission rates. Dual bronchodilator strategy with long-acting muscarinic antagonist (LAMA)/long-acting beta-agonists (LABA) is therefore recommended by GOLD (2019) in the postdischarge phase following an acute exacerbation.

Aim: To further assess the clinical impact of dual bronchodilators including glycopyrronium and arformoterol as home nebulization in the post-discharge phase of AECOPD, the current postapproval, observational study was conducted.

Materials and Methods: An observational, concurrent, and non-inferiority study with glycopyrronium and arformoterol home nebulizing solutions on patients with moderate and severe COPD was conducted at two centers in India. An estimated sample size of 40 patients involving moderate and severe COPD cases was factored for per-protocol analyses with $P < 0.05$ considered as statistically significant. A concurrent study analysis for the follow-up visit was conducted as per the principles of International Conference of Harmonization for Good clinical practice and Declaration of Helsinki while ensuring confidentiality during access of patient support registration sheets.

Results: Per protocol analyses for consecutive 46 cases from two centers receiving Nebulized glycopyrronium (25 mcg) and arformoterol (15 mcg), as separate formulations are given as admixed solution with follow-up visit for at least 4 weeks was carried out. Baseline demographics for the overall group showed exacerbation history (46, 100%), hospitalization for AECOPD (21, 45.6%); ED visit (25, 54.3%), forced expiratory volume in one second (FEV_1) 1.2 ± 0.6 L/min; FEV_1/FVC64.8% ± 10.6; reversibility 8.4% ± 11.8; CAT 34.6 ± 2.3; and vibrating mesh nebulizer (46, 100%). The mean predose FEV_1 (Δ) at the end of 4 weeks for overall, moderate and severe COPD cases were observed as of 9.6±3.1%, 11.8% ± 3.1, and 8.4% ± 1.6, respectively ($P < 0.0001$). Similarly, the mean CAT(Δ) score at the end of 4 weeks was observed as of 18.1 ± 0.69, 20.6 ± 0.69, and 18.26 ± 0.6 for overall, moderate and severe COPD cases, respectively ($P < 0.0001$). The intergroup differences for rescue medication use for a lone case with severe COPD (1, 2.04%) complied with the suggested non-inferiority margin between the groups. There were no other treatment-emergent adverse events or serious adverse events that warranted treatment modification or withdrawals in both groups.

Conclusion: Glycopyrronium and arformoterol home nebulization with Vibrating mesh nebulizer (VMN) offers bronchodilation that is clinically significant with successful use of the drugs as "Rescue Medication" in post-discharge high-risk symptomatic AECOPD cases.

Key words: Acute exacerbation of chronic obstructive pulmonary disease, Arformoterol, Glycopyrronium, Home nebulization, High risk COPD, Vibrating mesh nebulizer

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the most important reasons for hospitalization worldwide with 1 in 5 patients readmitted within 30 days. Notwithstanding, the various reasons for the readmission rate including patient adherence to device and formulation use, clinical comorbidities for hypertension, cardiovascular disease (CVD), bronchiectasis, Type 2 diabetes, and high-risk status for prior exacerbations play a pivotal role in above readmission rates for acute exacerbations of COPD (AECOPD) cases. Although the prognostic significance of early readmission is not fully understood, they are often associated with poor outcomes including high mortality rates of 4%–19% at 30 and 365 days, respectively.[1]

Similarly, in AECOPD cases receiving emergency department (ED) care were often associated higher readmission rates due to the inappropriate therapy received at most of these centers. In a 1-year long retrospective study conducted among AECOPD cases receiving ED care, current status on lung function and cardiovascular comorbidities are considered as best predictors for both 30- and 90-day COPD readmission rates were the best predictors for both 30- and 90-day COPD readmission rates in these cases. Only 50% of the ED group patients received bronchodilators, oral steroids, and antibiotics inclusively, and the need for oral steroids to treat AECOPD predicted future 90-day COPD readmissions in the ED group ($P < 0.003$).[2]

The 2008 Canadian Thoracic Society guidelines recommend that patients with AECOPD be treated with combined, increased doses of inhaled, short-acting beta-agonists, and an anticholinergic to improve dyspnea and pulmonary function. However, their use as long-term maintenance therapy may be fraught with several challenges including cardiac side effects or tachycardia that may be detrimental particularly in patients with cardiac comorbidities.[3,4] Moreover, in patients with moderate to severe AECOPD, oral or parental corticosteroids for 7–14 days are recommended. The treatment of AECOPD with systemic corticosteroids has been shown to improve airflow limitations, decrease treatment failure rates, and decrease the risk of relapse.[5] The GOLD guidelines in this line recommend the use of corticosteroids as maintenance therapy only in cases with elevated sr. eosinophils (≥300 cells/μL) due to the risk of pneumonia and immunosuppression leading to TB reactivation. In the postdischarge phase following an acute exacerbation, dual bronchodilator strategy with LAMA/LABA is therefore recommended in such cases by GOLD guidelines.[6]

In most of the high-risk or severe COPD cases, the poor inspiratory flow rate observed is often associated with related noncompliance toward conventional devices.[7] In ambulatory patients of COPD, again, poor inspiratory flow rates (<45 L/min) were observed for about 20% cases.[8] Low peak inspiratory flow rate (PIFR) (<60 L/min), especially in post-discharge settings following an exacerbation, was observed in nearly 31.7% of the patients.[9]

In a systematic review of randomized controlled trials implementing AECOPD rehospitalization reduction interventions failed to find clinical trials targeting a 30-day readmission outcome, especially when the rehospitalization rates have been as high as 58.4%.[1] In most of the cases NIV plays a significant role in hypercapnic COPD while delivering oxygen or short-acting bronchodilators including short-acting muscarinic antagonist (SAMA)/short-acting beta2-agonists (SABA) combinations for patient a tune to tidal breathing.

In this line, glycopyrrolate 25 mcg and arformoterol (15 mcg) nebulizing solutions remain as the only US FDA approved formulations for use in clinical practice that may be nebulized in home settings with new generation advanced ultra-compact, noiseless, portable vibrating mesh nebulizers (VMNs) further improving the patient compliance and adherence to therapy that is vital for long-term beneficial outcomes. In both the cases, the long-term studies involving nebulized glycopyrronium and arformoterol have successively highlighted the safety profile of these formulations even when coprescribed with ancillary bronchodilators including beta2-agonists or anticholinergics.[10]

Aim

To further assess the real-world use and clinical impact of nebulized glycopyrronium 25 and arformoterol 15 mcg given as separate formulation when delivered through new-generation active VMNs in high-risk COPD cases on 30-day relapse or readmission rates, the current observational, concurrent clinical study was planned.

MATERIALS AND METHODS

An observational, concurrent, noninferiority clinical study i.e. SYMPTOM study on Glycopyrronium and Arformoterol Nebulizing solutions for High risk COPD was conducted after obtaining approval from an Independent Institutional Ethics committee with registration in the Clinical Trial Registry of India (Clinical Trial Registry of India CTRI/2019/07/020144). Consecutive patient records for High risk COPD with above formulations that utilized Spirometric assessment of Lung function and CAT symptom score for Moderate

to Severe COPD cases were collated. A concurrent study analyses for the follow-up visit was conducted as per the principles of International Conference of Harmonization for Good clinical practice and Declaration of Helsinki while ensuring confidentiality of patient identifiers before analyses. Patient support provided was accessed from the Patient access registration sheets.

The inclusion criteria included Post discharge cases of Acute Exacerbation of COPD (AECOPD) following ED visit or hospitalization; GOLD defined COPD cases with history of ≥1 exacerbation in past year with smoking or nonsmoking risk factors; and patients willing for follow-up visit while receiving glycopyrronium 25 mcg and arformoterol 15 mcg nebulizing solutions admixed and delivered as one nebulization twice a day for at least 4 weeks were assessed and analyzed.

The exclusion criteria included patients with <1 follow-up visit to be excluded from the analyses; personal history of bronchial asthma; patients with history on use of oxygen therapy >12 h/day; patients with any history of unstable disease and/or recent hospitalization due to COPD before 6 weeks of study observation.

The study endpoints included: Intergroup differences for percentage patients requiring additional anticholinergics and beta2-agonist dosages in hospitalized and outpatient cases of moderate or severe COPD; prebronchodilator forced expiratory volume in one second (FEV_1) improvement at 4 weeks; common adverse events (>1%) at 4 weeks; and change in CAT score at 4 weeks.

Safety variables were assessed as treatment-emergent adverse event (TEAE) rate at 4 weeks with severity classification as mild, moderate or severe. In case of any of these serious adverse events (SAEs), appropriate notification records on notification to the National Coordination Centre, PvPI (CDSCO) utilizing Suspected Adverse Drug Reaction Reporting form on pvpi@ipcindia.net was also assessed for analyses.

Statistical considerations with an estimated sample size of 40 patients involving moderate and severe COPD cases with dropout rate of 25% were factored for analyses with $P < 0.05$ considered as statistically significant. The sample size for a non-inferiority study was based on the assessment of primary endpoint. Percentage patients requiring rescue medication use for exertional or acute symptoms in both arms for a proportion size difference of 20% at the end of 4 weeks. Based on NI margin of 10%, the current sample size was calculated assuming 80% power to detect a difference in two arms with a two-sided alpha of 5%.

RESULTS

The intent to treat and per-protocol analyses for 49–46 cases, respectively, receiving nebulized glycopyrronium (25 mcg) and arformoterol (15 mcg) with follow-up visit for at least 4 weeks were carried out. Baseline demographics included high-risk COPD, i.e., patients with at least one prior history of exacerbation in the past year [Table 1]. In all of the cases, glycopyrronium (25 mcg) and arformoterol (15 mcg) were admixed and inhaled as one inhalation twice a day using a VMN following hospitalization or ED visit for AECOPD.

Clinical records with follow-up data for at least 4 weeks receiving nebulized bronchodilators exclusively during the continuation phase (on 3rd day of discharge or 7th day of moderate exacerbation) following completion of steroid course were included in the analyses as per protocol analyses. Post-discharge cases of ED or hospitalized cases receiving SAMA/SABA background therapy were also included in the analyses.

Efficacy variables for FEV_1 and CAT score

A significant improvement in FEV_1 and CAT score at the end of 4 weeks was observed as the mean change of 9.6 ± 3.1% [Figure 1] and 18.1 ± 0.69, respectively ($P < 0.0001$).

Table 1: Baseline demographics for overall group with moderate or severe COPD

Parameters	N (%)
Per protocol analysis set	46
Mean Age (Years)	64±16.9
Gender	
Male	28 (57.1)
Female	21 (42.8)
Mean Weight (kg)	56±12.2
Airway obstruction	
FEV_1 (%)	44.1%±16.2
FEV_1 (L/min)	1.2 L/min±0.6
FEV_1/FVC (%)	64.8%±10.6
Reversibility	8.4%±11.8
CAT	34.6±2.3
Risk factors	
Hospitalization history	21 (45.6)
ED visit history	25 (54.3)
Current/Ex-smoker	
Cig/day	17±5.5
Years	13.6±7.2
Treatment arms	
Moderate COPD (FEV_1≥50%)	12 (24.5)
Severe COPD (FEV_1<50%)	37 (75.5)
Comorbidities	
Hypertension	30 (61.2)
ASCVD	2 (4.1)
Type 2 diabetes	7 (14.2)

COPD: Chronic obstructive pulmonary disease, FEV1: Forced expiratory volume in oe second, CVD: Cardiovascular disease

Moderate COPD

The mean change in FEV_1 and CAT score showed significant improvement with glycopyrronium 25 and arformoterol 15 mcg nebulization given twice a day as maintenance therapy at the end of 4 weeks [Figure 2 and 3].

Severe COPD

The mean change in FEV_1 and CAT score showed significant improvement with glycopyrronium 25 and arformoterol 15 mcg nebulization given twice a day with VMN as maintenance therapy at the end of 4 weeks [Figure 4 and 5].

The intergroup differences for pre-bronchodilator FEV_1 and CAT score improvement in the moderate and severe COPD groups are highlighted in Table 2. The efficacy variables including intergroup differences for FEV_1 improvement in the moderate and severe groups were not significant (P = NS)

The intergroup differences for rescue medication use for a lone case with severe COPD (1, 2.04%) complied with the suggested non-inferiority margin between the groups.

Safety Analyses

In a lone case of severe COPD with baseline FEV_1 20% and history of one exacerbation in the last year, patient-reported exertional symptoms or dyspnea that warranted additional dosage of glycopyrronium 25 mcg and arformoterol 15 mcg as a rescue medication with further continuation as one inhalation 4 times a day before de-escalation to twice daily dosage in the next few weeks. The event resolved without any sequelae or further events that required any additional therapy. There were no other TEAEs or SAEs that warranted treatment modification or withdrawal in either of the patients with moderate or severe COPD.

Table 2: Intergroup differences for FEV_1 and CAT score change between moderate and severe COPD at 4 weeks

Mean change at 4 weeks	Moderate COPD (Mean Δ±SE)	Severe COPD (Mean Δ±SE)	*P* value
FEV_1 (%)	11.8%±3.1	8.4%±1.6	*P*=NS
CAT score	20.6±0.69	18.26±0.6	*P*<0.05

COPD: Chronic obstructive pulmonary disease, FEV1: Forced expiratory volume in one second

DISCUSSION

This real-world, observational, concurrent, noninferiority study highlights the clinical efficacy and safety of nebulized glycopyrronium in AECOPD cases when coadministered with arformoterol.

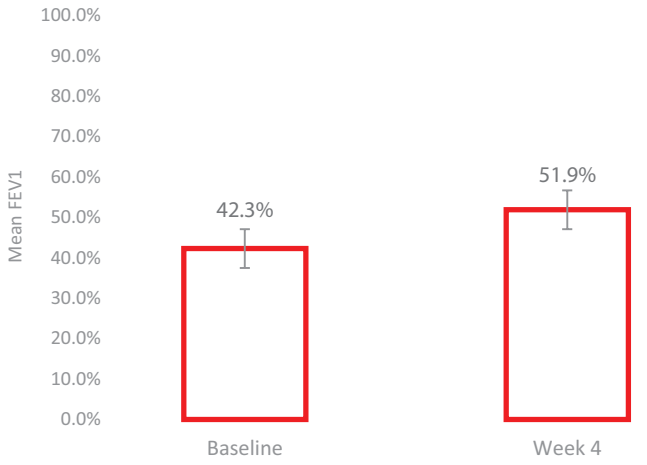

Figure 1: Mean FEV_1 in Overall group with Moderate or Severe COPD at four weeks (P* < 0.0001 vs. baseline)**

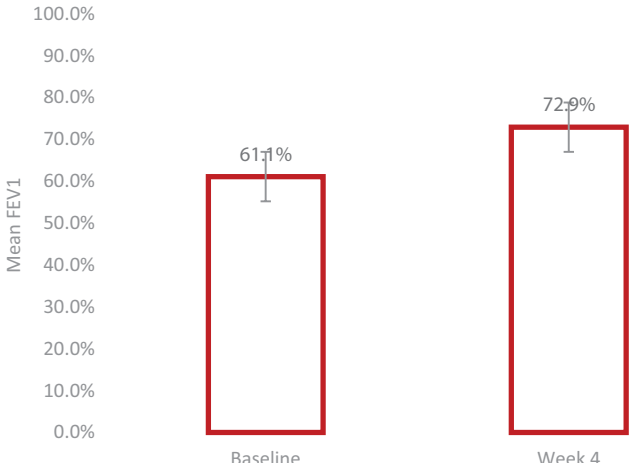

Figure 2: Mean FEV_1 in Moderate COPD group at four weeks (P* < 0.0001 vs. baseline)**

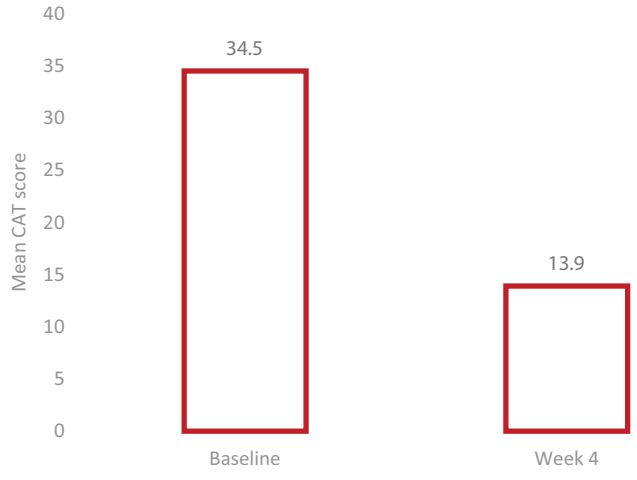

Figure 3: Mean CAT score for Moderate COPD group at four weeks (P* < 0.0001 vs. baseline)**

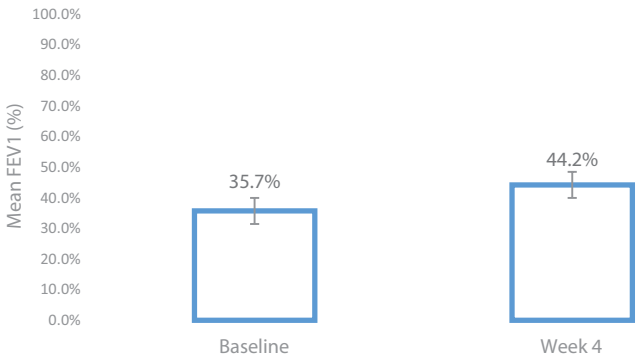

Figure 4: Mean FEV_1 in Severe COPD group at four weeks (P* < 0.0001 vs. baseline)**

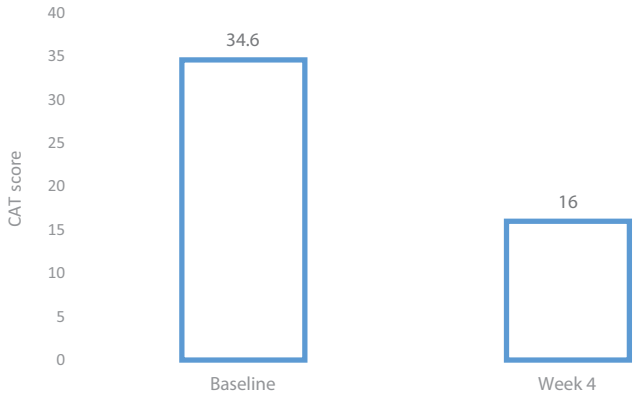

Figure 5: Mean CAT score for Severe COPD group at four weeks (P* < 0.0001vs. baseline)**

The study met the primary endpoint of non-inferiority for intergroup differences between moderate and severe COPD for FEV_1 improvement and 30-day rescue medication for any exacerbation requiring rescue medication.

This is the first study to demonstrate the 30-day readmission or exacerbation rate in high-risk COPD cases with moderate or severe exacerbation for patients receiving nebulized LAMA/LABA or glycopyrronium 25 mcg and arformoterol 15 mcg, one inhalation twice a day as maintenance delivered by VMN. Small volume nebulizers including VMNs offer compact, convenient, portable, noiseless device option for likely improved patient compliance and adherence with simple tidal breathing that is vital especially in the patients hospitalized due to severe exacerbation who demonstrate low PIFR in the post-discharge phase. Several studies have highlighted the stability and feasibility of dry powder inhaler inhalation in patients with PIFR of 90 L/min, however, in a prospective, observational study by Sharma,[9] most of the cases demonstrated much lower values of 71 ± 22.12 L/min in the post-discharge phase following an acute exacerbation.

The complexity and dexterity of inhalation therapy with pressurized metered-dose inhaler (pMDI) involving patient hand mouth coordination, lack of priming, breath-holding or emptying of respiratory airways before inhalation often precludes the high rate of inhalation errors as demonstrated by Cho-Reyes[11] that is often relevant despite the availability and use of spacers. Even the use of SMI requires an accurate priming and breathing technique with longer inhalation and holding period as compared to conventional pMDIs. In general, patients that commit errors during inhalation therapy hiring, tend to be older, more debilitated and to have greater severity of disease due to multiple comorbidities including cardiac risk factors of hypertension and/or CVD as demonstrated in the current study. In elderly patients, unintentional nonadherence to inhalation therapy often comes from cognitive impairment, hearing or visual loss, and other physical disabilities, such as arthritis and tremors resulting in poor coordination, which significantly affect their ability to understand and follow the suggested treatment. In this line, the recent introduction and availability of new generation advanced nebulizers including VMNs have resulted in patients and their caregivers to be increasingly satisfied with nebulized drug delivery, in terms of symptom relief, ease to use, and improved quality of life.[12]

European Research Society Guidelines[13] recommend the use of nebulization strategy in obstructive airway disease patients with severe airflow limitation (acute exacerbation), frequent users of rescue medications and patients unable to use or coordinate or carry spacers along with pMDIs that may be of clinical relevance especially in patients with Severe asthma or ACO who are more prone to exacerbations. GOLD[6] also recommends nebulizers to be used in specific populations, such as patients with inspiratory flow rates as low as 30 L/s or patients with poor hand-eye coordination while advocating the clinical role and use of LAMA/LABA in such cases requiring ED visit or hospitalization. The current study is first in its kind to demonstrate the clinical feasibility and practicality of LAMA/LABA involving glycopyrronium and arformoterol admixture in real-time before nebulization through a hand-held device for patients in post-discharge phase following hospitalization or ED visit for AECOPD.

In the current study, there was a lone case (1, 2.04%) that reported exertional symptoms of dyspnea that were resolved with physician-administered strategy of home nebulization with nebulized glycopyrronium and arformoterol given as four dosages in a day for a week. The patient subsequently completed the follow-up visit with no use of any additional dosages in the 2nd, 3rd, and 4th week, respectively. The safety analyses reported compares favorably with the clinical trials

reported by Ferguson[10] and Hanania.[14] In a 1-year long-term study on nebulized glycopyrronium 50 mcg BID administered for high-risk COPD with cardiac risk factors (n = 1087), the clinical impact and safety of LAMA mono- and combination therapy with LABAs (42%) were assessed. The TEAEs reported were comparable to placebo arm with persistent symptoms or dyspnea reported in 4.5% (27/620 cases). Similarly, Hanania[14] reported dyspnea of 6.5% (35/541 cases) with formoterol nebulization administered as 20 mcg twice a day inhalation for moderate to severe COPD in a multicentric, randomized, and controlled clinical trial involving 1071 cases.

CONCLUSION

Severe exacerbation represents an important milestone in COPD topography, often associated with declining lung function, increased exacerbation, and mortality rate due to systemic inflammation and comorbidities that warrants the use of cardio – "safe" bronchodilators including glycopyrronium and arformoterol.

Nebulized glycopyrronium and arformoterol with VMN offers bronchodilation as demonstrated by improvement in FEV_1 and reduction in CAT score that is clinically significant in moderate or severe COPD cases with successful use of the drugs as "Rescue Medication" for likely translational impact on patient compliance, adherence, and quality of life.

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DISCLOSURES

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