Clinical Effectiveness And Safety Of Glycopyrronium In Chronic Obstructive Pulmonary Disease And Asthma Copd Overlap: Acos Study

Prabhudesai PP , Singh BP, Bhattacharya PS, Katiyar S, Korukonda K

Sr. Consultant Pulmonologist, Om clinic and Lilavati Hospital and Research Centre, Mumbai, India – 400050
aumclinic@gmail.com

Sr. Consultant Pulmonologist and Chest specialist,
Midland Healthcare and Research Centre, Lucknow, India – 226006
bps2159@yahoo.com

Sr. Consultant Pulmonologist, Institute of Pulmocare & Research, DG-8, Action Area – I,
New Town, Kolkata, India – 700156.
parthachest@yahoo.com

Sr. Consultant Pulmonologist and Chest specialist, Chest Care Centre, 112/369A, 112/371, Dayal Rd, Khalasi Line,
Swaroop Nagar, Kanpur, Uttar Pradesh, India – 208002.
skkatiyar_in@yahoo.com

General Manager, Medical Services, Glenmark Pharmaceuticals Ltd,
Mumbai, India – 400099
krishnaprasad1971@hotmail.com

Abstract: Introduction: The burden of Asthma-COPD Overlap (ACO) Syndrome is evolving especially in light of growing burden for nonsmoking risk factors in India. Glycopyrronium add on therapy offers quick and complimentary bronchodilation and anti-inflammatory actions in poorly controlled COPD or ACO. **Material and Methods:** A prospective, observational, case control, drug utilization study was conducted at four centers during Jan' to Dec' 18 for COPD and ACO cases defined as per GOLD and Roundtable ATS recommendations respectively were enrolled in 1:1 ratio at four centers after IRB approval, written informed consent and Clinical trial registry of India registration (CTRI/2017/09/009845). A study sample size (n=160) was based on assessment of primary endpoint for a pre-bronchodilator FEV1 difference of 50% between the two groups of ACO and COPD receiving Glycopyrronium add on therapy compared to baseline values at 12 weeks with a dropout rate of 25% **Results:** 128 COPD (n=64) and ACO (n=64) cases with at least one prior exacerbation were randomized to Glycopyrronium (50 mcg, once a day) 'add-on' with FORM6/BUD200 mcg, twice a day for 12 weeks. Baseline demographics, Male/Female (119/09); Age 59.9±11.1y; Wt 59.1±13.7kg; FEV1 49.9%±15.8; Exacerbation ≥2/y, [82(64%)]; CAT (19.4±8.3); Smoker (90, 70.3%), Non-smoker (38, 29.7%). prebronchodilator FEV1 improvement difference between COPD and ACO groups met the pre-defined difference of ≥50% improvement at 12 weeks as 6.4±12.4% (127.1±248 ml, $p<0.03$). Post-hoc analyses for COPD and ACO Smoker frequent exacerbators showed prebronchodilator FEV1 (change) 123.2±356.4 ml ($p<0.0001$) and 320.9±335.3 ml ($p<0.0001$) respectively. In COPD and ACO non-smoker frequent exacerbators pre-dose FEV1 (change) of 216.2±354.9 ml ($p=0.001$) and 402.3±406.1 ml ($p=0.02$) was observed respectively. Intent to treat analyses showed TEAEs (7, 4.3%) of mild to moderate intensity with none requiring any treatment withdrawal. **Conclusion:** Glycopyrronium 50 mcg 'add-on' therapy offers incremental bronchodilation that is meaningfully clinically significant (MCID) in poorly controlled symptomatic Severe COPD and ACO.

Keywords: Asthma COPD Overlap, Chronic obstructive pulmonary disease, frequent exacerbator, Glycopyrronium, Non-smoker.

1. INTRODUCTION

The clinical burden of obstructive airway diseases including bronchial asthma and COPD continues to be large with greater contribution to morbidity and mortality compared to any other non-communicable infectious or respiratory condition in India. As part of the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) [1], the prevalence of major chronic respiratory diseases and the deaths and disability-adjusted life-years (DALYs) caused by them for India was estimated as to 55·3 and 37.9 million cases of COPD or Br. asthma respectively. However the high prevalence of both has always evolved causing some patients to present both entities concomitantly as ACO. Notwithstanding the plethora of definitions that have built in ambiguity on the diagnosis if not management of ACO, the GINA/GOLD document leads the front with a checklist of overlapping characteristics before spirometry assessment and confirmation for any obstructive airway diseases or ACO. The Spanish Society of Pneumology and Thoracic Surgery (SEPAR) and the Roundtable Groups (ATS) have endorsed case definitions based on major and minor criteria based on spirometry assessments [2]. Prevalence estimates of ACOS in the general population ranged from 1.8% to 2.7% with the former estimate based on spirometry criteria and the later estimate based on self-reporting of a physician diagnosis. Among populations of patients with clinical asthma, the estimated prevalence of concurrent COPD ranged from 16% to 61% and among those with clinical COPD, the prevalence of current asthma ranged from 5% to 55% again fueling the concept on a distinct yet relevant phenotype of obstructive airway disease that may often be missed as an early diagnosis in real world outpatient settings [3] The clinical implications of undiagnosed or undertreated ACO can be huge due to this group having more symptoms, worse quality of life, and greater risk of exacerbations than patients with COPD often requiring maintenance therapy with ICS. The

role of LAMA in combination with ICS/LABA has been well endorsed by GINA & GOLD guidelines for management of ACO or GOLD D category as Step care approach. In addition the GOLD guidelines (2019) recommend escalation of therapy to triple drug combination (LAMA/LABA/ICS) especially in symptomatic or exacerbator phenotype that have been suboptimally controlled by background or prior LAMA/LABA or ICS/LABA therapy especially in GOLD C and D categories. The role of ICS is suggested for peripheral eosinophilia or eos ≥300 or ≥100 □L with two moderate or one severe exacerbation in the last year. The clinical phenotypes of symptomatic COPD as Severe or frequent exacerbator has been well highlighted in the TRILOGY [5] and TRIBUTE [6] trials on the triple drug combination. LAMAs offer complimentary anti-inflammatory effects involving interleukin-1β and tumor necrosis factor alpha (TNF-α) following exposure to triggers or cigarette smoke that may be relevant in the management of ACO or COPD with frequent exacerbations as studied by Shen [7]. However there is limited clinical evidence on the clinical role and impact of LAMAs including Tiotropium on the above definitions of ACO or COPD phenotypes as highlighted in SEPAR and Roundtable ATS recommendations [2]. The classical definitions revolve around demonstration of significant bronchodilator reversibility with background history or biological markers for eosinophilic phenotype in COPD cases. These cases are therefore more likely to be responsive to Glycopyrronium since it offers slow dissociation from M3 receptors for Trough FEV1 improvements that are clinically meaningful (MCID) To further understand the differential impact of Glycopyrronium add-on therapy on COPD & related phenotypes including ACO management in 'Real world' clinic settings, a prospective observational clinical study was planned.

2. MATERIAL AND METHODS

A post-approval, observational, prospective, open label, case control, multicentric study of Glycopyrronium 'add on' therapy was performed in patients with COPD and ACO after obtaining approval from the institutional ethics committee or review board, and registration in the Clinical Trial Registry of India (CTRI/2017/09/009845) at four centers of Mumbai, Lucknow, Kanpur and Kolkata in India. Patients with diagnosis of COPD and ACO defined by GINA/GOLD and ATS roundtable recommendations were assigned in 1:1 ratio to receive Glycopyrronium plus Formoterol/Budesonide combination DPI. The study analyses was conducted as per the principles of International Conference of Harmonization for Good clinical practice and Declaration of Helsinki after approval on study documents from Institutional Review Board and written informed consent before study initiation. The patient identifiers and confidentiality was ensured with the study conducted as per Declaration of Helsinki and ICH GCP guidelinesThe inclusion criteria included COPD and ACO cases, patients who have had no exacerbation within last 4 weeks of screening and enrollment. Smoking or Nonsmoker COPD was defined as cases with age ≥40 years, symptomatic (CAT ≥10) with ≥1 exacerbation in the last year, post-bronchodilator FEV1/FVC ratio <0.70, and FEV1 <80% of predicted normal at screening visit; ≥10 pack years of smoking or biomass/household chullah/occupational dust exposure for ≥10 years. ACO was defined as cases with Persistent airflow limitation (post-bronchodilator FEV1/FVC <0.70; At least 10 pack-years of tobacco smoking or equivalent indoor or outdoor air pollution exposure (e.g., biomass); post-bronchodilator response improvement in FEV1 of >12% with 200 ml increase and elevated eosinophil or known allergy or atopy status were included in the study The exclusion criteria History of hypersensitivity to drugs contains anticholinergics, beta-adrenergic, lactose; Diagnosis of asthma; Patients vaccinated with live attenuated vaccines within 2 weeks prior to screening visit or during run-in period; Patients who had COPD exacerbation or lower respiratory tract infections that required antibiotic, oral or parenteral corticosteroid treatment within 4 weeks prior to screening visit or during run-in period; Patients who have a history of myocardial infarction, heart failure, acute ischemic coronary disease or severe cardiac arrhythmia requiring treatment within last 6 weeks; Patients with concomitant pulmonary disease, e.g., pulmonary tuberculosis (unless confirmed by imaging to be no longer active) or clinically significant bronchiectasis, sarcoidosis and interstitial lung disorder; Patients who use oxygen therapy; Patients with active liver disease or hepatic dysfunction (AST and/or ALT >3 x ULN) or Patients with nephrotic syndrome or renal insufficiency (sr. creatinine >1.5 mg/dl); Women who are pregnant or nursing; Known symptomatic prostatic hypertrophy requiring drug therapy or operation; Patients with narrow-angle glaucoma requiring drug therapy; Patients receiving oral xanthine's including theophylline, acebrophylline, deriphyllineThe study formulations were prescribed as Glycopyrronium 50 mcg administered as single dose (Morning) with Formoterol 6/Budesonide 200 mcg dry powder inhalation (given Morning & Evening) and the patients followed up at four and twelve weeks in either of the groups of COPD and ACO Per protocol analyses was conducted for patient records with at least one follow up visit for analyses of primary endpoints involving predose FEV1, CAT score and Treatment emergent adverse events (TEAEs) at 12th week. Safety variables as MedDRA coded events were analyzed for treatment emergent- and/or serious adverse events. Any AE that is associated with death, hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or is otherwise life threatening were classified as SAEs. At every visit, treatment compliance to the therapy was assessed by the inhalation capsule (DPI) count Statistical considerations: Treatment completers for per protocol set (PPS) were identified as patients who completed the study with no other major protocol deviations. Study sample size was based on assessment of primary endpoint for a pre-bronchodilator FEV1 difference of 50% between the two groups of ACO and COPD receiving Glycopyrronium add on therapy compared to baseline values at 12 wks. Based on this expected difference in effect size between the two arms and dropout rate involving 25%, a sample size of 160 pts would be required assuming 80% power to detect a difference in means between two groups with a two-sided alpha of 5%. Statistical analyses for primary & post hoc analyses involving categorical and numerical data was carried out by the Fisher exact test and Student t test, using QuickCalcs GraphPad Prism (version 7.05; San Diego, CA), with two-tailed P values <.05 considered statistically significant. Descriptive statistics were used for assessment of treatment-emergent adverse events at 8 weeks.

3. RESULTS

One hundred seventy-six patients were screened for the intent-to-treat population (n=160) that were assigned to COPD (n=80) and related phenotype i.e. ACO (n=80). The patients were followed up at 4th and 12th week for symptom and spirometry lung function assessment respectively. Thirty-one cases were lost to follow-up after baseline visit with a lone case excluded from analyses due to protocol deviation (Fig 1).

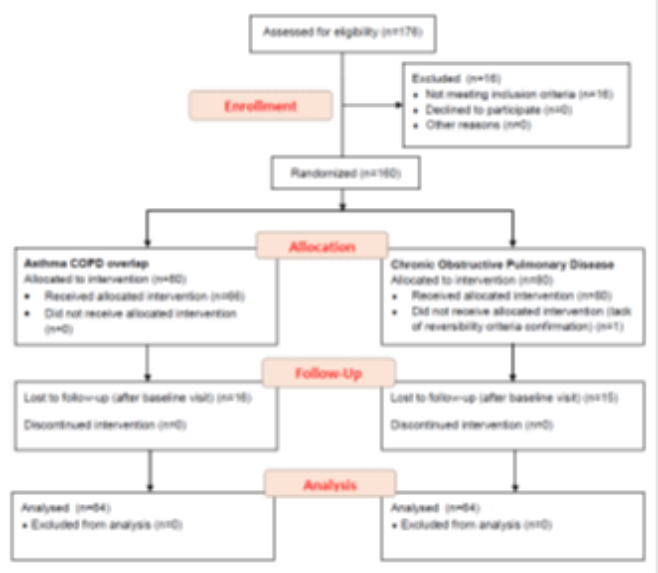

***Figure 1**: Patient disposition chart for COPD and ACO patients receiving Glycopyrronium*

Baseline demographics for 128 completed cases of COPD (n=64) and ACO (n=64) included Male/Female (119/09); Age 59.92±11.1 y; Wt. 59.1±13.7 kg; prebronchodilator FEV1 49.9%±15.8; Reversibility 15±12.5%; Exacerbation ≥2/y, [82(64%)]; <2/y, [46 (36%)]; CAT (19.4±8.3); Smoker (90, 70.3%), Nonsmoker (38, 29.7%) respectively. Smoker status was identified for patients with current or past exposure to tobacco for ≥10 pack years. Nonsmoker were identified for cases with exposure to biomass, household chullah or occupational dust exposure for ≥10 years (Table 1)

A. Efficacy variables

Pre-dose FEV1 and CAT score improvement were assessed by spirometry for COPD and ACO cases having history of at least one exacerbation in the last year at 4th and 12th week respectively. Exacerbation was defined as acute worsening of the symptoms with cough, sputum and dyspnea requiring oral anti-infectives, corticosteroids or hospitalization

***Table 1:** Baseline demographics for per protocol analyses (n=128)*

		N(%)
Cases	Per protocol analyses	128 (100%)
Age		59.92 ± 11.1 y
Sex	Male	119 (93%)
	Female	9 (7%)
Weight		59.12 ± 13.7
Symptoms	Wheeze	46 (36%)
	Chest Tightness	36 (28%)
	Breathlessness	100 (78%)
	Cough	108 (84)
Lung function	FEV1 (L)	1.3±0.5
	FEV1 (%)	49.9±15.8
	FEV1/FVC (%)	60.2± 9.2
	Reversibility (%)	15± 12.5
	CAT	19.4±8.3
	Sr. eosinophil (%)	4.6±14
Diagnosis	COPD	64 (50%)
	ACO	64 (50%)
Medical history	Hypertension	23 (18%)
	ASCVD	2 (2%)
	Type 2 Diabetes	9 (7%)
	Others	3 (2%)
COPD	Exacerbation h/o (<2/y)	27 (42%)
	Exacerbation h/o (≥2/y)	37 (58%)
	Smoker/Ex-smoker	45 (70.3%)
	Non-Smoker	19 (29.7%)
	Sr. eosinophil (%)	5.3±3.7%
ACO	Exacerbation h/o (<2/y)	19 (30%)
	Exacerbation h/o (≥2/y)	45 (70%)
	Smoker/Ex-smoker	45 (70.3%)
	Non-Smoker	19 (29.7%)
	Sr. eosinophil	4±14%
	Atopy history	28 (43.7%)
Pulmonary medications before study entry	SAMA &/or SABA	46 (36%)
	ICS/LABA	82 (64%)
	Xanthines	23 (18%)

1) COPD group:

In High risk COPD (n=64) group with baseline prebronchodilator FEV1 46.5±16%, Reversibility (7.9±18%), CAT score [21.3+/-8.5] there was significant change in Pre-dose FEV1 and CAT score as 7.9 %+/-17.9 (158.1±356.4 ml) ($p<0.0001$) and -5.8±8 ($p< 0.0001$) respectively

2) ACO group:

In ACO (n=64) with baseline prebronchodilator FEV1 52.8±15.8%, Reversibility (22.2±12.5%), CAT (17.6+/-5), Sr. eosinophil (4 ±3.5%), Atopy (28, 43.7%), there was significant change in Pre-dose FEV1 and CAT score as 13.9+/-17.6% (285.2±350.2 ml) ($p<0.0001$) and -5.8±7.8 ($p<0.0001$) respectively The intergroup difference for prebronchodilator FEV1 improvement between COPD and ACO groups met the pre-defined difference of ≥50% improvement at 12 weeks as 6.4±12.4% (127.1±248 ml, $p<0.03$) (Fig 2)

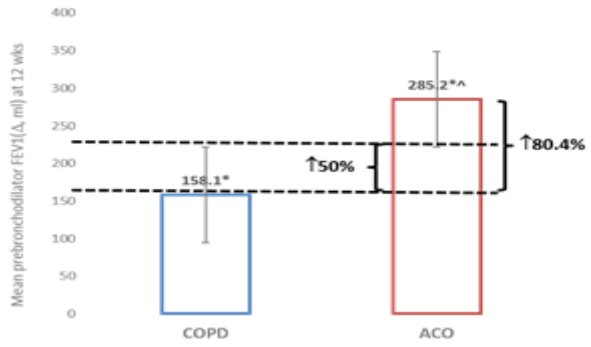

Fig 2: *Mean prebronchodilator FEV1 (Δ) at 12 weeks for High risk COPD and ACO groups on prior ICS/LABA or SABA therapy; *p<0.0001 vs baseline, ^p<0.03 vs COPD group*

3) Post hoc analyses:

COPD frequent exacerbator: Post-hoc analyses for COPD with frequent exacerbations (≥2/y, n=37) showed clinically significant change in FEV1 & CAT score of 123.2±356.4 ml & -5.2±8 respectively (p<0.0001) respectively. In the Nonsmoking COPD group (n=19), with frequent exacerbations (≥2/y) showed clinically significant change in FEV1 & CAT score of 216.2±354.9 ml (p=0.001) & -5.7±4.7 respectively (p=0.0003) respectively ACO frequent exacerbator: Post-hoc analyses for ACO cases with frequent exacerbations (≥2/y; n=45) showed clinically significant change in FEV1 & CAT score of 320.9±335.3 ml (p<.0001) & -5.8±7.8 (p<0.0001) respectively. In the Nonsmoking ACO group (n=19), clinically significant change in FEV1 & CAT score of 402.3±406.1 ml (p=0.02) & -6.9±4.6 (p<0.0001) respectively was observed Patient compliance was assessed by tele-monitoring and investigator at every follow-up visit and confirmed to be complete with more than of the 80% of the dosages estimated to be consumed by the patients

B. Safety variables:

Intent to treat analyses showed TEAEs (7, 4.3%) of mild to moderate intensity with none requiring any treatment withdrawal or modification (Fig 3)

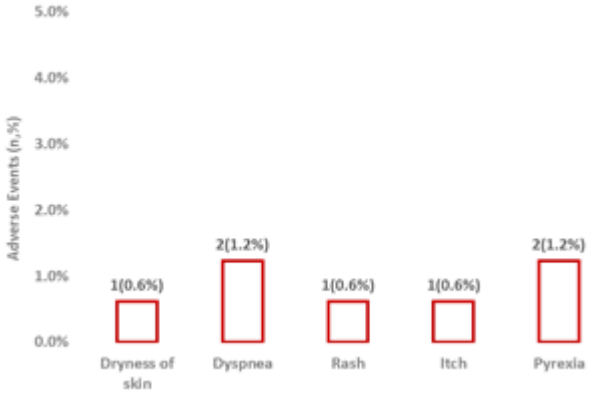

Fig 3: *Adverse events in the COPD and ACO groups receiving Glycopyrronium add on therapy at 12 weeks*

The two cases of Dyspnea (1.2%) of mild to moderate intensity reported in the COPD group were managed symptomatically with no consequent sequelae observed

4. DISCUSSION

This post hoc analyses highlights for the first time the clinical utility of GLY 50 mcg add-on therapy to FF/BUD dry powder inhalation in High risk (symptomatic) or frequent exacerbators of COPD and ACO. LAMA in combination with ICS/LABA demonstrated significant improvement in prebronchodilator FEV1 and CAT score for symptomatic severe COPD cases. The results are comparable to findings of TRILOGY [5] and TRIBUTE [6] involving GLY/FF/Beclomethasone dry powder inhalation studies demonstrating Pre-dose FEV1 improvement that is meaningfully clinically significant (MCID) at the comparable endpoints of 12 weeks therapy while risk stratifying the patients for induction or maintenance therapy with ICS in the COPD cases High risk COPD: Step-up therapy for High risk COPD cases with background ICS/LABA or SAMA/SABA therapy for exacerbator phenotype remains a clinical challenge. In these patients on prior ICS/LABA with poor control or further exacerbations, however, triple drug combination is often considered as a feasible option [4,9]. In the 52-wk TRINITY trial conducted with extrafine Budesonide / Formoterol fumarate / Glycopyrronium (BUD100 / FF6/GLY12.5 mcg pMDI) as a three arm study, Tiotropium (TIO) add on to ICS/LABA showed predose FEV1 improvement of (~) 100 ml at twelve weeks when administered to High risk COPD with severe airflow obstruction (prebronchodilator FEV1, 36.7%) with history of at least one moderate to severe exacerbation in the last year despite background therapy with ICS/LABA or ICS/LAMA in 73% cases [10]. In the current study there was a clinically significant mean Pre-dose FEV1 improvement of 158.1±356.4 ml with Glycopyrronium 50 mcg DPI add-on therapy when administered for High risk or Severe COPD (FEV1 46.9±16 %) cases at the end of twelve weeks with background ICS/LABA therapy that may be explained by the slow dissociation of Ultra LAMA i.e. Glycopyrronium from M3 receptor for long-lasting and improved trough FEV1 levels

Frequent exacerbator phenotype: Step up therapy in case of an Exacerbator phenotype has been well highlighted by GOLD (4) especially for patients on prior therapy with ICS/LABA or LAMA. The guidelines recommend continued role of ICS for patients for patients with two moderate or one severe exacerbation in the last year while demonstrating peripheral eosinophil levels of ≥100 µL. In the current post-hoc analyses a mean pre-dose FEV1 improvement of 123.2±356.4 ml was observed for COPD cases with elevated peripheral eosinophil level (5.3±3.7%), frequent exacerbations and prior use of ICS/LABA (82, 64%) that withstood the test of interaction when compared with the overall group. The study results at twelve weeks showed predose FEV1 improvement from baseline that were meaningfully clinically significant (>100 ml) unlike TRIBUTE trial outcomes observed with BUD/FF/GLY combination (100/6/10 µg, two inhalations twice a day with pMDI) given for baseline poorly controlled High risk COPD cases [6].

Nonsmoking COPD: Worldwide, an estimated 17 to 38.8% COPD patients are non-smokers (11) based on GOLD spirometry assessment criteria with consequent DALYs related to ambient air pollution (33.6%), household pollution (25.8%), second-hand smoke (7.4%) and occupational exposure (16.5%) especially in India (1). However the definition for their obvious correlation with the severity risk assessment often remains a subject of debate. A working definition on this was first provided by Behera (1991) with exposure index (EI) calculated as the average number of hours spent on exposure or occupation daily multiplied by the number of years. A significant risk of chronic bronchitis was observed to be associated with a biomass exposure index of 60 by Mahesh [12]. The ATS definition however recommends at least 10 pack-years of tobacco smoking or equivalent indoor or outdoor air pollution exposure (e.g., biomass) as highlighted and included in the current study. The current study highlights the clinical complimentary impact of LAMA or Glycopyrronium add-on therapy showed pre-dose FEV1 of 216.2±354.9 ml ($p<0.0001$) amongst the High risk COPD) cases

Asthma-COPD overlap: Despite the considerable prevalence of ACO that has various representation in clinical practice including reactive or early bronchitis due to environmental risk factor exposure few randomized controlled trials have been performed. Using the GINA/GOLD stepwise approach, Lainez (14) identified an identical ACO prevalence of 11% from asthma and COPD cohorts. In the current study, ACO cohort was identified based on the ATS roundtable recommendations of three major and one minor criteria (2) involving age, smoke-/nonsmoking risk factors, bronchodilator reversibility (≥12%, 200 ml) (2,15). This is the first study to report the clinical impact of GINA/GOLD recommended triple drug regimen of LAMA/LABA/ICS involving Glycopyrronium while demonstrating a significant change in Pre-dose FEV1 of 320.9±335.3 ml ($p<0.0001$) and 402.3±406.1 ml ($p=0.02$) from baseline at 12 weeks for Frequent exacerbator and non-smoking ACO cases respectively. The two other reports on TIO 18mcg 'add-on' therapy benefits to ICS/LABA with pre-dose FEV1(Δ, 5%) and CAT score (Δ, 9.36) improvements were likely to be confounded by the poor delineation of ACO involving lone consideration of bronchodilator reversibility (BDR) as reported by Nazarenko [16] and Xu [17]

Safety analyses: Glycopyrronium 'add-on' therapy was well tolerated with negligible incidence of local or systemic effects due to inhaled corticosteroids. The daily symptoms were well controlled with Dyspnea in only two cases (1.2%) at the end of observation period involving twelve weeks following Glycopyrronium 50 mcg add-on to background ICS/LABA therapy The study results indicate towards the clinical effectiveness and safety of Glycopyrronium 'add on' therapy in the clinical phenotypes of COPD and ACO with frequent exacerbations and high symptom status following poor control with predominantly ICS/LABA based therapy. The results met the primary consideration for at least 50% greater improvement in pre-dose FEV1 observed with triple drug combination involving Glycopyrronium for ACO cases compared to COPD

Study limitations: The results are limited by a short observation period to assess the continued role of ICS for exacerbation risk reduction. Nevertheless the results are suggestive on the likely role and impact of Glycopyrronium 'add-on' to ICS/LABA therapy in carefully delineated cases of High risk COPD with frequent exacerbations or ACO as defined by GINA/GOLD or ATS roundtable recommendation to avoid the real world challenges of Type 2 diabetes, pneumonia or tuberculosis especially in India

5. CONCLUSION

Worldwide Asthma and COPD are making galloping strides towards morbidity and mortality due to increased prevalence or exposure to risk factors involving smoking, domiciliary or workplace exposure to second-hand/bio-mass smoke, air pollution, history of tuberculosis, chronic asthma, respiratory-tract infections during childhood, and poor socioeconomic status are likely contributors for the growing burden of chronic respiratory diseases for their management with bronchodilators. However both High risk COPD and ACO remain progressive, often characterized by frequent exacerbations and impaired QoL in such cases. Careful delineation of these cases by spirometry or Step-up therapy with an Ultra-LAMA often remains a prudent option for most of these High risk cases that are poorly controlled on SABA or ICS/LABAGlycopyrronium 'add-on' therapy offers quick, selective, persistent bronchodilation that is meaningfully clinically significant (MCID) with complimentary anti-inflammatory effects for likely therapeutic synergy in poorly controlled Severe COPD and ACO cases.

Disclosure

This clinical study was funded by Glenmark Pharmaceuticals Ltd, Mumbai, India

Conflict of Interest

None

ACKNOWLEDGEMENT

ACOS study investigators would acknowledge the support of Preeti Kumbhar, Rujuta Gadkari, Hanmant Barkate for editorial assistance and statistical analyses

REFERENCES

[1]. L. Dandona, "India State-Level Disease Burden Initiative CRD Collaborators*. The burden of chronic respiratory diseases and their heterogeneity across the states of India: the Global Burden of Disease Study 1990–2016," Lancet Global Health, 6, pp.e1363–74, 2018.

[2]. D.D. Sin, M. Miravitlles, D.M. Mannino, et al, "What is asthma-COPD overlap syndrome? Towards a consensus definition from a round table discussion," Eur Respir J., 48, pp. 664-73, 2016.

[3]. V. Plaza, F. Álvarez, M. Calle, C. Casanova, B.G. Cosío, A. López-Viña, "Consensus on the Asthma–COPD Overlap (ACO) Between the Spanish COPD Guidelines (GesEPOC) and the Spanish Guidelines on the Management of Asthma (GEMA)," Arch Bronconeumol., 53(8), pp. 443–449, 2017.

[4]. Global initiative on Chronic obstructive lung disease, "Pocket Guide To COPD Diagnosis, Management, And Prevention. A Guide for Health Care Professionals. GOLD 2019 Report," Available: https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf. [Accessed: Jul. 28, 2019].

[5]. D. Singh, A. Papi, M. Corradi, et al, "Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial," Lancet, 388, pp. 963–73, 2016.

[6]. A. Papi, J. Vestbo, L. Fabbri L, et al, "Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial," Lancet, 391(10125), pp. 1076-1084, 2018.

[7]. L.L. Shen, Y.N. Liu, H.J. Shen, et al, "Inhalation of glycopyrronium inhibits cigarette smoke-induced acute lung inflammation in a murine model of COPD," Int. Immunopharmacol., 18(2), pp. 358-364, 2014.

[8]. J.A. Wedzicha, D. Banerji, K.R. Chapman, et al, "Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COP," N. Engl. J. Med., 374(23), pp. 2222-2234, 2016.

[9]. N. Baxter, K. Gruffydd-Jones, V. Mak, I. Small, "Primary care respiratory society. Evaluation of appropriateness of inhaled corticosteroid (ICS) therapy in COPD and guidance on ICS withdrawal," Available: https://www.pcrs-uk.org/resource/stepping-down-inhaled-corticosteroids-copd SteppingDownICS_FINAL5.pdf. [Accessed: Jan. 28, 2020]

[10]. J. Vestbo, A. Papi, M. Corradi, "Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial," Lancet, 389(10082), pp. 1919-1929, 2017.

[11]. G. Zeng, B. Sun, N. Zhong, "Non-smoking-related chronic obstructive pulmonary disease: a neglected entity?," Respirology, 17(6), pp. 908-912, 2012.

[12]. D. Behera, S.K. Jindal, "Respiratory symptoms in Indian women using domestic cooking fuels," Chest, 100(2), pp. 385-388, 1991.

[13]. P.A. Mahesh, B.S. Jayaraj, A.K. Prabhakar, S.K. Chaya, and R. Vijaysimha R, "Identification of a threshold for biomass exposure index for chronic bronchitis in rural women of Mysore district, Karnataka, India," Indian J. Med. Res. 137(1): 87–94, 2013.

[14]. S. Lainez, I. Court-Fortune, P. Vercherin, L. Falchero, T. Didi, "Clinical ACO phenotypes: Description of a heterogeneous entity," Respir. Med. Case Rep., 28, pp. 100929, 2019.

[15]. A.N. Aggarwal, R. Agarwal, S. Dhooria, et al, "Joint Indian Chest Society-National College of Chest Physicians (India) guidelines for spirometry," Lung India, 36(Suppl 1), pp. S1–S35, 2019.

[16]. K. Nazarenko, Y. Feschenko, L. Lashyna, "The effect of tiotropium bromide on lung function parameters in patients with asthma- COPD overlap syndrome," European Respiratory Journal, 48, pp. PA3372, 2016.

[17]. H. Xu, X. Lu, "Inhaled Glucocorticoid with or without Tiotropium Bromide for Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome," J. Coll. Physicians Surg. Pak., 29(3), pp. 249-252, 2019.