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RESEARCH ARTICLE

A POST-APPROVAL, OBSERVATIONAL STUDY TO ASSESS CLINICAL IMPACT OF GLYCOPYRRONIUM IN HIGH RISK COPD WITH FREQUENT EXACERBATIONS: POST HOC ANALYSES

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Abstract

Background: Exacerbations remain a distinct clinical challenge in Chronic obstructive pulmonary disease (COPD) with consequent use of ICS in real-world practice of India. LAMA add-on therapy has been well highlighted by UPLIFT, TRIBUTE & KRONOS studies. Glycopyrronium add on therapy offers quick control of morning symptoms for likely improved patient adherence rates in COPD

Objectives: To assess the clinical impact and use of Glycopyrronium add-on therapy in outpatient settings, real world observational study was planned

Methods and Material: National, post-approval, observational, drug utilization, concurrent analyses was carried out at 128 centers during Sept '17 with institutional Ethics & CTRI registration. Post-hoc analyses was carried out by Quick Calcs GraphPad Prism ver. 7 software with $p<0.05$ considered as statistically significant

Results: The per protocol analyses for 1117 consecutive Glycpyrronium & ICS/LABA combination cases was conducted for patients with baseline demographics included Male/Female (76%/24%); mean Age 59.5y; FEV_1 (1.46 L/min, 48.9±16%), FEV_1/FVC (58.7±13.3%); Reversibility (13.7±16.2%), Exacerbation (≥1/y; 1117, 100%; ≥2/y, 389,35%), CAT (22±10). At 12 weeks, the overall group (1117) and frequent exacerbators (389) showed prebronchodilator FEV_1& CAT score change of 21% && 5.1 respectively ($p<0.0001$) at 12 wks. Post-hoc analyses for frequent exacerbators' (≥2/y, BDR ≤10%, n=152) showed clinically significant change in prebronchodilator FEV_1& CAT score of 22.8% & 5.4 respectively ($p<0.0001$) respectively showing positive test of interaction. Similarly the prebronchodilator FEV_1 improvement for Frequent exacerbators' with Reversibility (≥2/y, BDR ≥12%, n=156) was documented as 35% ($p<0.0001$). TEAEs included dry mouth (42, 3.8%), constipation (4,0.4%), exacerbation (2,0.2%) that were managed with symptomatic therapy

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Conclusion: Glycopyrronium 'Add–on' strategy to ICS/LABA for High risk symptomatic or exacerbator phenotype of COPD offers bronchodilation that is clinically significant
CTRI: Clinical Trial Registry of India (Registration) - CTRI/2018/04/012944.

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Introduction:-

COPD is a chronic inflammatory condition of the small airways thatisthe leading cause of morbidity and mortality across the globe especially amongst the non-communicable diseases. It is often associated with specific comorbidities including CVD leads to further increase in healthcare utilization and costs related to readmission and referral. Despite the availability of several pharmacological therapies including long-acting bronchodilators as LAMAs, the patient pool of COPD cases has exponentially grown with the current number estimated at 55.7 million in India (Dandona, 2018).

Glycopyrronium is a new generation 'ULTRA' LAMA that offers meaningful clinically significant persistent bronchodilation to control the Daily Morning symptoms within few minutes of inhalation. The treatment emergent improvement in Dynamic hyperinflation and exercise tolerance goes a long way in improving patient compliance and adherence that is so vital in COPD or other associated phenotypes including ACO, Bronchitis & Emphysematous hyperinflation.

The updated GOLD (2019) guidelines recommend the role of LAMA in High risk GOLD C category cases. In the randomized, controlled clinical trial of POET-COPD (Vogelmeier, 2011), Tiotropium monotherapy has shown clinically superior risk reduction when compared with Salmeterol in High risk cases of Severe COPD with prior history of exacerbations. The UPLIFT (Tashkin, 2008) study on other hand outlined the long-term impact on mortality and disease course with LAMA for Stable Severe cases of COPD while ~60% of the patients continued with background ICS+/-LABA

In real-world settings, most of the patients are symptomatic with history of at least one exacerbation in the last year. The complimentary anti-inflammatory action against neutrophils or macrophages with selective muscarinic antagonists or Glycopyrronium offers translational action in Severe or Highrisk COPD cases (Shen, 2014). The results of the Tiotropium monotherapy randomized trials (Vogelmeier, 2011;Tashkin, 2008) conducted in Severe COPD cases can be confounded by the lack of clear outcomes for patients with Frequent exacerbations and/or bronchodilator reversibility observed especially in UPLIFT (Tashkin, 2008) trial

International guidelines (GOLD, 2019) have suggested the triple drug combination of ICS/LABA/LAMA as therapeutic strategy in these cases to offer comprehensive reduction in symptoms while preventing further exacerbations especially in patients with Frequent exacerbators and Sr. eosinophils >300 c/mm. In this line the triple drug combination studies of IMPACT (Lipson, 2018) and TRIBUTE (Papi, 2018) studies have successively shown significantly greater reduction in symptoms and exacerbation rate when utilized as initial-line or as sequential therapy for obstructive airway disease patients with COPD or Asthma. However ACO remains a distinct clinical entity with overlapping symptoms and characteristics of either Br. asthma or COPD (GINA 2018). The prevalence of ACO in the general population ranges between 1.6% and 4.5%, in COPD patients (Barrecheguren, 2015) between 12.1% and 55.2%, and in patients with asthma, between13.3% and 61% (Kauppi, 2011). GesEPOC-GEMA consensus document defines ACO as the presence of persistent airflow limitation in a smoker or former smoker who presents characteristics of asthma. This definition requires the concomitant presence of 3 basic elements ie. persistent airflow limitation over time, essential to confirm the presence of permanent obstruction that does not change spontaneously or after treatment; accumulated history of smoking (current or past) as a principal risk factor; typical characteristics of asthma, including clinical, biological and functional manifestations (Plaza, 2017).

There is however little evidence to highlight the omnipresence of ACO in India with relevant therapeutic strategy of utilizing LAMA in combination with ICS/LABA. To further explore the clinical outcome of LAMA in High risk COPD with prior exacerbations, a case cohort analyses as Glycopyrronium in cOpd phenotypes, A drug utilization surveilLance (GOAAL) study in outpatient settings of India was planned

Methods:-

This post-approval, observational, drug utilization, concurrent analysis—GOAAL study (Clinical Trial Registry of India CTRI/2018/04/012944)—of Glycopyrronium 'add on' therapy were performed in patients with High risk COPD after obtaining approval from the local ethics committee, with registration in the Clinical Trial Registry of India. Consecutive patient records from the last three weeks receiving Glycopyrronium 'add-on' therapy were collated from 128 outpatient centers that utilized the CAT score for assessing symptom control in spirometrically assessed COPD cases across India were accessed in September 2017. The concurrent analyses involved follow up of these cases for for 12 weeks with the study conducted as per the principles of International Conference of Harmonization for Good clinical practice and Declaration of Helsinki while ensuring confidentiality of patient identifiers during transcription of records before analyses

The inclusion criteria included COPD pts with GOLD B/C status who were Symptomatic with ≥1 moderate-to severe exacerbation in last six months that required antibiotics or short course oral corticosteroids, COPD diagnoses with $FEV_1/FVC<0.7$ with FVC<80%. The consecutive records were assessed for follow-up visits at 4 and 12 weeks. Per protocol analyses was conducted for patient records with at least one follow up visit for analyses of primary endpoints involving pre-bronchodilator FEV_1 and CAT score improvement at 12^{th}wk. Safety variables were assessed as treatment emergent adverse event rate at 12 weeks with Karch and Lasagna scale used to risk assess the intensity of adverse events as Mild, moderate or severe. Cases were identified as pure COPD or asthma copd overlap (ACO) on the basis of bronchodilator reversibility of ≤10 % and ≥12% FEV_1 improvement following short-acting bronchodilator or Salbutamol inhalation of 400 mcg respectively

Any AE that is associated with death, inpatient hospitalization (in case the study was being conducted on out-patients), prolongation of hospitalization (in case the study was being conducted on in-patients), persistent or significant disability or incapacity, a congenital anomaly or birth defect, or is otherwise life threatening was classified as SAEs. In case of any of these Serious Adverse Events, appropriate notification records on notification to National Coordination Centre, PvPI (CDSCO) utilizing Suspected Adverse Drug Reaction Reporting form on pvpi.ipcindia@gmail.com were also assessed for analyses

Descriptive statistical analyses was planned for the epidemiological variables with the primary endpoints on prebronchodilator FEV_1 and CAT score improvement were conducted by Student's T test. Statistical analyses was carried out by Quick Calcs Graphpad Prism ver. 7 software with $p<0.05$ considered as statistically significant

The clinical study was registered on Clinical Trial Registry of India as CTRI/2018/04/012944

Results:-

The per protocol analyses for 1117 completed cases receiving Glycopyrronium add-on therapy for twelve weeks was carried out from 128 centres across India. One sixty three cases were lost to follow up after baseline visit in this concurrent analyses and excluded form the analyses. Baseline demographics included Male/Female (76%/24%); mean Age 59.5y; FEV_1 (1.46 L, 48.9±16%), FEV_1/FVC (58.7±13.3%); Reversibility (13.7±16.2%), Exacerbation (≥1/y; 728, 65%; ≥2/y, 389, 35%), CAT (22±10), respectively.

Table 1:- Baseline demographics of High risk COPD cases (n=1117).

Parameters	Characteristics	N	Mean (%)
Per protocol analyses	Total	1117	100%
Gender	Male	849	76.0%
	Female	268	24.0%
	Age	1117	59.5 ±11.2y
	Weight	1117	60.6 ±12.4kg
Lung function assessment	FEV_1	1117	48.9 ±16%
	FEV_1/FVC	1117	58.7 ±13.3%
	CAT	1117	22 ±10
Current/Ex. Smoker	Cigarette smoke	726	12.5 pack/yrs
Non smoker	Biomass fuel exposure	155	6.3 exposure.yrs
	Occupational exposure	236	4.4 exposure.yrs

Reversibility		1117	13.7 ±16.2%
Sr. Eosinophil		435	3.7 ±2%
History of Exacerbations	≥1/yrs	1117	100%
	≥ 2/yrs	389	35%
COPD Drug History	LAMA+LABA	138	12.4%
	Xanthine	127	11.4%
	Steriods (OCS)	12	1.1%
	SABA/SAMA	126	11.3%
Comorbidities	Hypertension	487	43.6%
	CVD	88	7.9%
	Type 2 D	270	24.2%
	Atopy	115	10.3%
	Others	33	3%

COPD defined as spirometrically assessed cases with $FEV_1/FVC<0.7$, $FEV_1<80\%$ and smoking index of ten pack years on Glycopyrronium 50 mcg 'add-on' therapy were collated and followed up for 12 weeks during this concurrent study. Clinical records with follow-up data for at least 12 weeks were deemed as treatment completers for the perprotocol analyses. The mean exposure rate to cigarette smoke, biomass fuel and occupational hazard was documented as 12.5 pack, 6.3 exposure & 4.4 exposure years respectively

Efficacy variables:

High risk COPD*:*

High risk cases with prior history of atleast 1 exacerbation in the last year and high symptom status (CAT ≥10) were analysed. The overall group (n=1117) showed pre- bronchodilator FEV_1 & CAT score change of 21% and 5.1 respectively ($p<0.0001$) at 12weeks.

COPD frequent exacerbator with and without reversibility:

Post-hoc analyses for COPD with frequent exacerbations ((≥2/y, BDR ≤10%, n=152) showed clinically significant change in FEV_1 & CAT score of 14% (210.9 ml) and 4.8 respectively ($p<0.0001$) respectively. Similarly the prebronchodilator FEV1 improvement for Frequent exacerbators' with Reversibility (≥2/y, BDR ≥12%, n=156) was documented as 35% (523 ml) and 5.4 ($p<0.0001$) (Fig 1 and 2)

Asthma COPD overlap due to non-smoking risk factors:

Prebronchodilator FEV_1 (%) showed significant improvement in ACO sub-group/s with ACO-Bio-mass exposure (49) and ACO-Occupational exposure (39) were observed as 18% ($p<0.03$) & 26% ($p<0.0001$) respectively

The mean change in CAT score was clinically significant ($p<0.0001$) for High risk COPD, ACO with frequent exacerbation, ACO-Smoker, ACO-Biomassexposure, ACO-Occupational exposure groups at 12weeks

Safety analyses:

TEAEs included Dry mouth (42, 3.8%), Headache (5, 0.4%), Constipation (4,0.4%) of mild to moderate intensity with exacerbation in 2 (0.2%) cases that were managed with symptomatic therapy (Fig 3). There were no other adverse events or SAEs that warranted referral for hospitalization or treatment withdrawal

Discussion:-

This real-world, observational, cross-sectional, concurrent study highlights the clinical impact and utilization of Glycopyrronium in High risk COPD cases. LAMA add on therapy to ICS/LABA is usually recommended for GOLD D cases or as sequential therapy for uncontrolled, progressive cases on LAMA/LABA combination. In this line, this is the first Indian study to demonstrate the clinical benefit of Glycopyrronium 'add on' therapy in High risk COPD cases predominantly with frequent exacerbations, similar to the trials of TRILOGY (Singh, 2016) and TRIBUTE (Papi, 2018) that involved patients with severe exacerbation or as sequential therapy following progression due to dual drug or LAMA/LABA combination use.

The mean prebronchodilator FEV_1 improvement of 315, 210.9 and 523 ml in these High risk COPD cases (≥1 exacerbation/yr), COPD with frequent exacerbation (≥2 exacerbation/yr)& ACO with frequent exacerbations at the

end of twelve weeks therapy demonstrates the clinical impact of the add-on therapy in providing bronchodilation or Trough FEV_1 that is meaningfully clinically important difference of >100 ml thereby further substantiating the role of Glycopyrronium as a Ultra LAMA that is useful for Severe or very severe COPD cases. Real world evidence on the role and delivery of Tiotropium as add-on or fixed dose combination with ICS/LABA through a single dry powder inhaler device or as add-on therapy is limited. In a real world study to assess the effectiveness of a triple drug combination in Severe COPD, the results with Tiotropium/Formoterol/Ciclesonide dry powder inhaler resulted in prebronchodilator FEV1 improvement of 200 ml ($p<0.0001$) for Smoker COPD patients with infrequent exacerbations (Deb, 2016)

The study reported the results for twelve weeks Glycopyrronium add on therapy to ICS/LABA before rationalizing the review of ICS use in frequent exacerbators or Asthma COPD overlap cases. Asthma COPD overlap or COPD cases with BDR (>15%,400ml) and related exacerbations have often remained a clinical challenge with GesEPOC-GEMA (Plaza, 2017) recommendations on a likely diagnosis of overlap syndrome. The complexity of the diagnoses was further commented by GINA for likely BDR (>12%, 200 ml) along with other risk factors to be considered as Asthma-COPDoverlap. Post-hoc analyses for this ACO subgroup with or without frequent exacerbations was further evaluated in this study. The mean prebronchodilator FEV_1 and CAT score improvement in ACO subgroups were clinically significant including the test of interaction for clinical impact assessment as compared to the High risk COPD or overall group results. The exposure including Smoking or Nonsmoking risk factors or Biomass and occupational hazards were documented in these cases for atleast five years as recommended by GINA for a diagnosis of ACO. The results of the study for this subgroup are till date the first of its kind for Glycopyrronium when used as mono-or combination therapy

The study results are limited by the cross-sectional, concurrent design that evaluated Glycopyrronium ‘addon’ therapy clinical records for Highrisk COPD. The lack of homogeneity in the ICS/LABA background or current co-therapy with Salmeterol/Fluticasone or Formoterol/Budesonide may have also confounded the overall results in terms of bronchodilation or Trough FEV_1 improvement. Nevertheless the results of this post-hoc analyses are significant and first in its kind in demonstrating the effects of LAMA or Glycopyrronium ‘add on’ therapy in Frequent exacerbator and ACO ie. COPD with Reversibility that can be further validated through randomized or case control clinical studies

Conclusion:-

LAMA remains the backbone of COPD management with their antisecretory and complimentary bronchodilatory actions. The current post-approval, observational, drug utilization, case cohort concurrent analyses highlights the clinical impact of Glycopyrronium 50 mcg dry powder inhaler as ‘add on’ therapy in High risk severe, symptomatic COPD cases with prior exacerbation. The post-hoc analyses in addition highlights the flexibility of Glycopyrronium 50 mcg dry powder inhaler as ‘add on’ strategy to ICS/LABA especially for COPD cases due to smoking or nonsmoking risk factors demonstrating reversibility in addition to frequent exacerbators

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Disclosures:
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Conflict of Interest:
None.

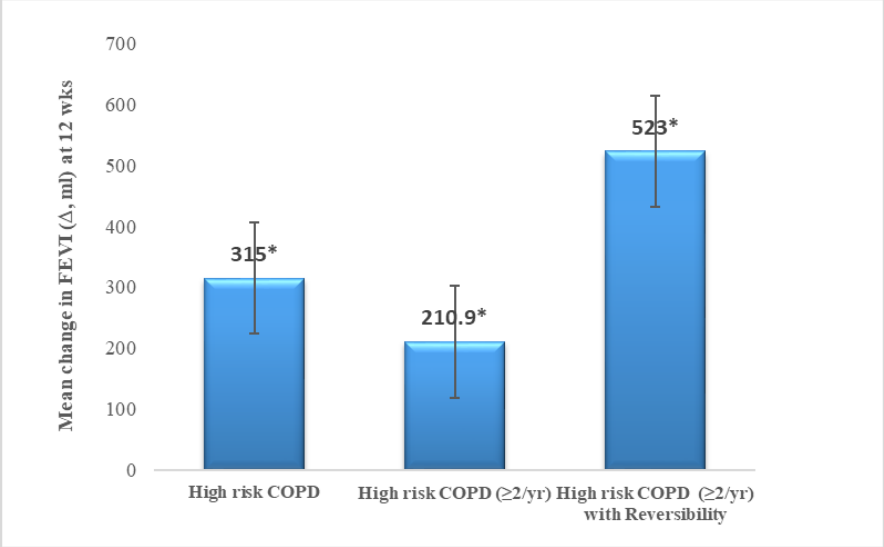

Fig 1:- Mean prebronchodilator FEV_1 change (ml) in High risk COPD, Frequent exacerbator, Frequent exacerbator with Reversibility at 12 wks; *p≤0.0001 vs. Baseline.

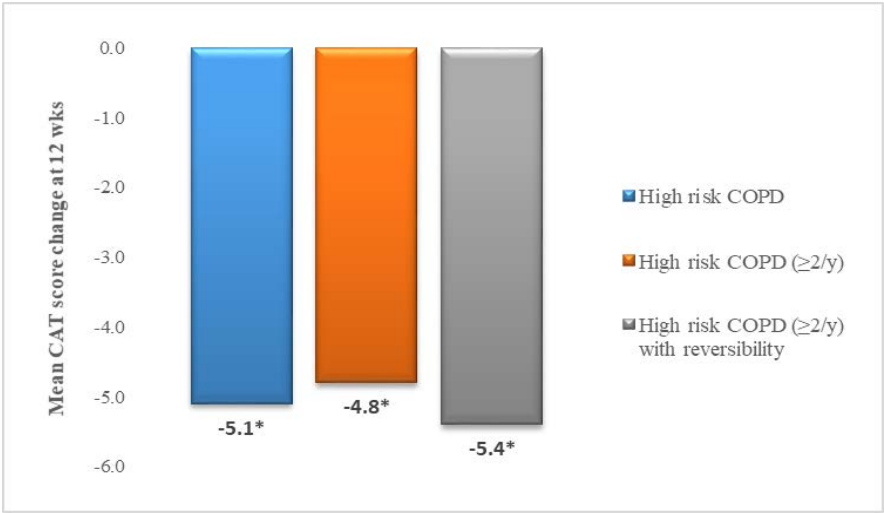

Fig 2: Mean CAT score change (Δ) in High risk COPD, Frequent exacerbator, Frequent exacerbator with Reversibility at 12 wks; *p<0.0001 versus baseline.

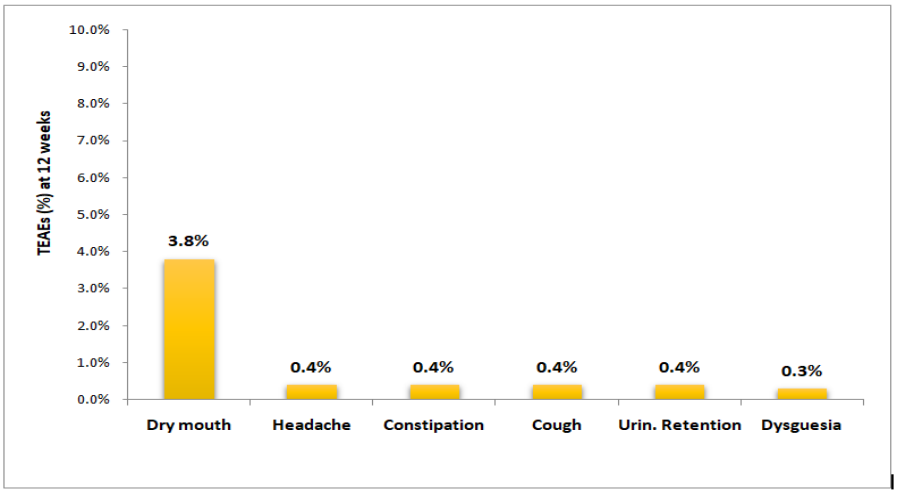

Fig 3:- Treatment emergent adverse events observed for the overall group (n=1117) at 12 wks.

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