Effectiveness of ICS/LABA and LAMA/LABA in COPD due to biomass

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LAMA/LABA and ICS/LABA are equally effective in improving exacerbations, quality of life, inspiratory capacity and respiratory symptoms in COPD due to biomass in comparison with COPD due to cigarette smoking https://bit.ly/3KgTJg1

Cite this article as: Ramírez-Venegas A, Montiel-Lopez F, Robles-Hernández RE, *et al*. Effectiveness of ICS/LABA and LAMA/LABA in COPD due to biomass. *ERJ Open Res* 2024; 10: 00154-2024 [DOI: 10.1183/23120541.00154-2024].

Received: 16 Feb 2024
Accepted: 11 May 2024

Abstract

Background COPD due to biomass exposure (COPD-B) is highly prevalent in low- and middle-income countries, and there are no clinical trials designed to evaluate the effectiveness of the treatments currently recommended for patients with COPD due to cigarette smoking (COPD-C). The purpose of the study was to compare the efficacy of fluticasone furoate/vilanterol (FF/V) 100/25 µg and umeclidinium/vilanterol (UMEC/VI) 62.5/25 µg on the rate of exacerbations, the time to first exacerbation, on dyspnoea, health-related quality of life (HRQL), forced expiratory volume in 1 s (FEV_1) and inspiratory capacity (IC) during a period of 6 months in patients with COPD-B and COPD-C, at a third level referral centre in Mexico City.

Methods A pilot, single-centre, open-label, parallel-group study included 132 patients with a history of at least two exacerbations. They were randomised to receive one of four treatment groups: 33 COPD-B patients received FF/VI 100/25 µg, 31 COPD-B patients received UMEC/VI 62.5/25 µg, 34 COPD-C patients received FF/V and 34 COPD-C patients received UMEC/VI.

Results There were no differences in exacerbation rates between patients receiving FF/VI or UMEC/VI in either the COPD-B (0.07 (95% CI 0.03–0.13), 0.06 (95% CI 0.03–0.12)) or COPD-C group (0.06 (95% CI 0.04–0.11), 0.08 (95% CI 0.05–0.13)), nor in the time of first exacerbation, nor FEV_1 and IC. All groups showed improvement in dyspnoea and HRQL, independently of medication used.

Conclusions Among patients with COPD-B and COPD-C with a history of exacerbation, FF/VI was equally effective as UMEC/VI in preventing exacerbations and improving dyspnoea and HRQL.

Background

COPD encompasses a diverse group of disorders resulting from different risk factors that lead to heterogeneous clinical courses [1–3]. COPD in never-smokers may be associated with domestic exposure to biomass smoke (COPD-B) and, according to the World Health Organization, represents a third of all cases of COPD with a prevalence of ∼2% in the general population [4]. The clinical course of COPD-B patients differs from that of COPD patients secondary to cigarette smoking (COPD-C) [2]. COPD-B patients are more likely to be female, with mild or moderate obstruction, more chronic bronchitis symptoms, more exacerbations, worse quality of life and more gas exchange abnormalities (hypoxaemia or

hypercapnia) than COPD-C [5, 6]. Some reports regarding the inflammatory profile in patients with COPD-B show inflammatory markers compatible with a sustained-type eosinophil-derived inflammatory response [7–10]. This could explain why more asthma-COPD characteristics are in a higher proportion in COPD-B than in COPD-C [10–13]. The predominance of airway inflammation with Type-2 eosinophil signature in the COPD-B patients suggests the potential benefit of inhaled corticosteroids (ICS) [14] in this population [15, 16].

Although COPD-B is a well-known entity, no controlled clinical trials have evaluated the effectiveness of the inhaled ICS/long-acting β_2-agonist (LABA) compared to the long-acting muscarinic antagonist (LAMA)/LABA treatment. We conducted a pilot study to compare the effectiveness of fluticasone furoate/vilanterol (FF/VI) 100/25 µg and umeclidinium/vilanterol (UMEC/VI) 62.5/25 µg on the rate of exacerbations, the time of the first exacerbation, on dyspnoea, health-related quality of life (HRQL), forced expiratory volume in 1 s (FEV_1) and inspiratory capacity (IC) during 6 months in patients with COPD-B and COPD-C. The study also explores whether either of the treatments is more beneficial for patients with COPD and traits compatible with asthma (COPD-A).

Methods

Study subjects

The study was conducted from August 2017 to July 2020 at the COPD Clinic of the Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas (INER) in Mexico City, a referral centre for respiratory diseases treating mainly uninsured low-income patients. COPD diagnosis was made following the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 guidelines. Patients had to be between 40 and 80 years old with FEV_1/forced vital capacity (FVC) <0.7 and a FEV_1 >30% of predicted. They had to have a history of at least two moderate exacerbations, defined as worsening of respiratory symptoms requiring oral corticosteroids and/or oral antibiotics but without hospitalisation, or one severe exacerbation, defined as worsening respiratory symptoms that required hospitalisation (>24 h), in the last year [14] and be free of exacerbations 4 weeks before inclusion. The patients with COPD-B had to have cooked with biomass stoves with a cumulative exposure of >100 hours-years (years of cooking with biomass stove times mean average daily hours exposed) [17]. In contrast, COPD-C had a cumulative exposure of >10 pack-years (mean average cigarettes/day smoked times years of smoking/20 cigarettes per pack). All patients had to be able to attend all study visits and perform pulmonary function tests satisfactorily.

The institutional ethical committee board reviewed and approved the protocol. The trial was registered at clinicaltrials.gov (NCT05342558). All patients provided a written informed consent form (ICF). This study was conducted following the tenets of the Declaration of Helsinki.

Study design and methods

A pilot, single-centre, randomised, open-label, parallel-group clinical trial was designed so that COPD-B and COPD-C patients received FF/VI 100/25 µg or UMEC/VI 62.5/25 µg once daily for 6 months.

Before the screening process, tables of random numbers were used for sequences for treatment assignment. After signing the ICF, during the screening/randomisation visit, baseline assessments were performed on patients with COPD-B or COPD-C as follows: dyspnoea measurement (modified Medical Research Council scale (mMRC)), HRQL measurements (COPD assessment test (CAT), Saint George's Respiratory Questionnaire (SGRQ)) [18–20]. After these tests, pre-bronchodilator spirometry, IC, diffusion capacity of carbon monoxide (D_{LCO}), 6-min walking test (6MWT) and post-bronchodilator spirometry measurements were made. If patients were not naïve to treatment, a washout period from LAMA and LABA of 7 days and ICS of 21 days was instructed, where only short-acting β_2-agonist was used until the randomisation visit. Patients were randomly assigned with medication in a 1:1 ratio, according to the sequence, to receive either FF/VI (100/25 µg) or UMEC/VI (62.5/25 µg) once daily for 6 months (figure 1). Although it was an open-label study, to prevent biases and be able to introduce blindness in the drug administration, technicians who performed clinical questionnaires and pulmonary function tests (PFTs), and attending physicians were unaware of the assigned treatment. Open-label salbutamol (100 µg) was provided as rescue medication.

Adherence was measured by counting the doses dispensed from the devices returned during the follow-up visits. High adherence was defined when at least 80% of the daily doses were inhaled during each period. In the same visits, questionnaires and PFTs were performed except D_{LCO}, which was only measured at baseline. The presence of exacerbations between visits, adverse events (AEs), changes in concomitant medication and the use of health resources were evaluated remotely in the 2nd and 4th months. A follow-up phone call visit was made 1 month after the end of treatment to corroborate adherence, AEs or exacerbations.

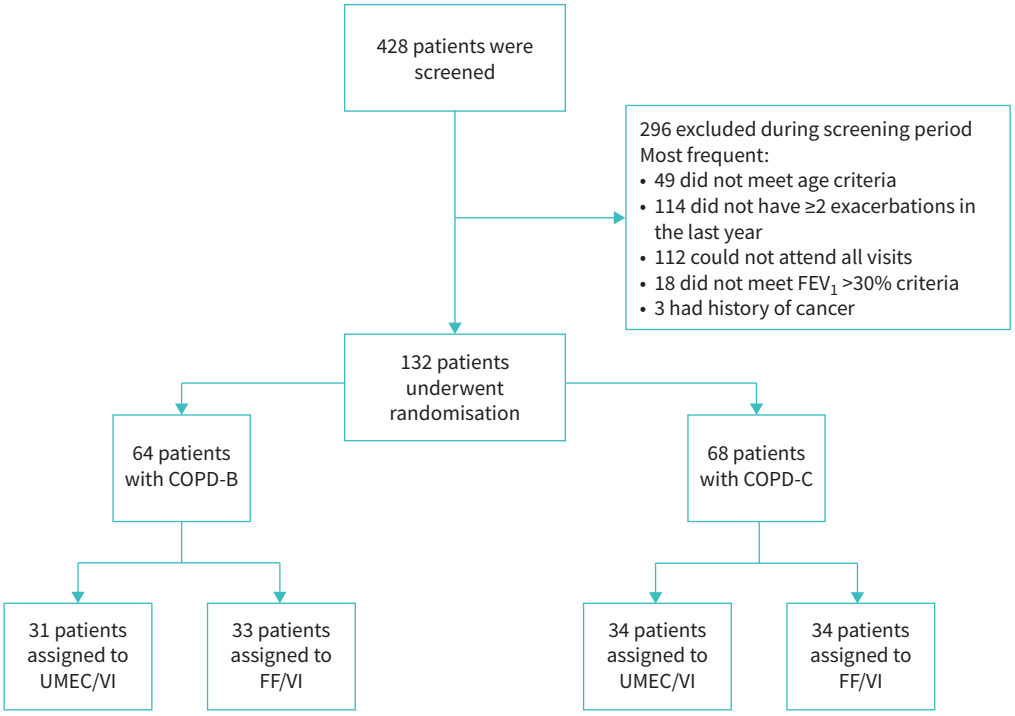

FIGURE 1 Consort diagram. COPD-B: COPD associated to biomass exposure; COPD-C: COPD associated to cigarette smoking; UMEC/VI: umeclidinium/vilanterol 62.5/25 µg; FF/VI: fluticasone furoate/vilanterol 100/25 µg.

Procedures

The spirometry procedure was done following the American Thoracic Society (ATS)/European Respiratory Society (ERS) statements [21] and using Mexican standard reference equations [22], similar to the Third National Health and Nutrition Examination Survey values for Mexican-Americans [23]. Bronchodilator responsiveness was calculated according to the ATS/ERS guidelines 2005 [21] and 2019 [24]. The D_{LCO} procedure followed the 2017 ATS/ERS criteria [25]. 6MWT procedure was done following ATS/ERS criteria [26].

Outcomes

The primary outcome was the moderate–severe exacerbation rate over the study period, which was measured during the 1st, 3rd and 6th months of clinical visits with the symptom diary as the presence of AEs, changes in concomitant medication, use of health resources and treatment adherence.

Other outcomes evaluated were the time to first COPD exacerbation, dyspnoea (mMRC scale), health status related to quality of life (SGRQ, CAT) and lung function (FEV_1, FVC, IC). All outcomes were evaluated at the 1st and 3rd month clinical visit in the 6 month treatment period. Also, a minimal clinically significant difference (MCID) [27] for FEV_1, IC, SGRQ, CAT and dyspnoea was calculated after 6 months of treatment [27, 28].

To investigate the benefits in the outcomes with both treatments in the COPD-A group, we analysed the proportion of patients with traits compatible with asthma by using the definition of COPD–asthma overlap (history of asthma before 40 years of age, or the presence of high reversibility ⩾400 mL and ⩾15% of FEV_1 in the post-bronchodilator test and serum levels of eosinophils ⩾300 cells·mm^{-3}) [29].

Adverse events

AEs were registered in patients' diaries and by the physician during each visit. An AE was defined as any new symptom unrelated to COPD or COPD exacerbation after the randomisation visit. AEs are reported in the supplementary material.

Statistical analysis

This study used descriptive statistics to summarise qualitative variables, presenting frequencies and percentages. The normality of continuous variables was assessed using the Shapiro–Wilk test. Normally

distributed continuous variables were expressed as mean and standard deviations, while non-normally distributed variables were reported as medians with interquartile ranges. A comparative analysis among different study groups (COPD-B+UMEC/VI, COPD-B+FF/VI, COPD-C+UMEC/VI and COPD-C+FF/VI) was conducted using the Chi-squared test for qualitative variables and either ANOVA or Kruskal–Wallis tests for continuous variables.

All efficacy analyses were based on intention to treatment data. Exacerbation rates were analysed using a generalised linear mixed negative binomial model for each group, with the treatment variable serving as a covariate. This model accounted for moderate and severe exacerbations during the 24 weeks. Factors such as treatment, type of exposure (biomass or cigarette smoke), baseline smoking, current biomass use and severity of airflow limitation were considered in the model.

Exacerbation rates were analysed within subgroups using the same negative binomial mixed linear model. This model incorporated the diagnosis of COPD-A, COPD exposure group, age and sex as fixed effects. Each model included interaction variables between the subgroup of interest and treatment as covariates.

Kaplan–Meier method and the Cox regression model were used in each group to analyse the time to first exacerbation displayed in supplementary figure S2. Both models included age, sex, treatment and post-bronchodilator FEV_1 % predicted covariates. The statistical analyses were carried out using Stata v.14.0 and R software.

Results

As shown in figure 1, 428 patients underwent the screening visit. We enrolled 132 patients (65 COPD-B and 67 COPD-C) from September 2017 until March 2020. Study recruitment ended early because of the COVID-19 pandemic. In the COPD-B group, 31 patients received UMEC/VI, and 33 received FF/VI. In the COPD-C group, 34 received UMEC/VI, and 34 received FF/V.

The demographic and clinical characteristics of the patients are shown in table 1. More COPD-B subjects were female and shorter than the COPD-C subjects. The COPD-B group contained more patients with diabetes and arterial hypertension than the COPD-C group. The proportion of patients with an eosinophil count $\geqslant$300 cells·mm^{-3} was similar in all four groups (~23%, p=0.934). The history of exacerbations in the previous year and clinical assessment (mMRC, SGRQ, CAT measurements) were similar in the four arms. Treatment adherence was high and similar in all four groups.

Baseline PFTs did not show differences between groups (table 2). However, according to the GOLD stage classification, more COPD-B patients were at GOLD I stage than COPD-C patients. In the 6MWD test, COPD-B patients walked less than COPD-C patients; however, when expressed by the percentage of predicted distance, the result was similar for both groups.

Supplementary table S1 shows the proportion of patients in COPD-B and COPD-C groups who presented criteria for COPD-A. A similar prevalence of COPD-A was found in both groups (COPD-B 45% *versus* COPD-C 32%, p=0.242). The traits associated with COPD-A are described in table 3. Patients with COPD-C overlap presented a better bronchodilator response than patients with COPD-B overlap. The total eosinophil count was higher in the COPD-B and COPD-C overlap groups compared to patients without overlap. The rest of the biomarkers did not present differences between groups.

Primary efficacy analyses

The exacerbations rate per 6 months (observation period) for COPD-B with FF/VI was 0.07 (95% CI 0.03–0.13), and with UMEC/VI was 0.06 (95% CI 0.03–0.12). The exacerbations rate for COPD-C with FF/VI was 0.06 (95% CI 0.04–0.11), and for UMEC/VI was 0.08 (95% CI 0.05–0.13). There were no differences in the rate ratio for exacerbations between patients who received FF/VI or UMEC/VI neither in the COPD-B nor the COPD-C group (supplementary figure S1). There was also no difference between time to first exacerbation in either COPD group, whether they had received FF/VI or UMEC/VI (supplementary figure S2). No difference in the exacerbation rates was also found if models were adjusted by the COPD-A characteristics or eosinophils counts (neither $\geqslant$300 nor $\geqslant$100 cells·mm^{-3}) (figure 2). There was no difference in the rest of the outcomes in patients with COPD-A.

Other efficacy end-points

Table 4 shows the changes in lung function, symptoms and HRQL after 6 months of treatment. Only the COPD-B group had a significant increase in IC when they inhaled UMEC/VI (1.5±0.6, 1.7±0.5, p=0.026)

TABLE 1 Demographic and clinical characteristics of COPD associated with biomass exposure (COPD-B) *versus* COPD associated with cigarette smoking (COPD-C) and treatment groups

Variable	COPD-B+UMEC/VI	COPD-B+FF/VI	COPD-C+UMEC/VI	COPD-C+FF/VI	p-value
Patients n	31	33	34	34	
Demographic characteristics					
Age years, mean±SD	72±8	70±9	68±6	69±8	0.225
Female, n (%)	28 (90)	28 (85)	13 (38)	10 (29)	<0.001
Somatometry, mean±SD					
Height m	1.49±0.07	1.47±0.07	1.64±0.11	1.63±0.08	0.004
BMI kg·m^{-2}	27±5	29±6	28±7	26±4	0.084
Biomass and tobacco exposure					
Tobacco smoke index pack-years, median (IQR)			50 (42)	42 (30)	0.116
Biomass smoke index hours-years, median (IQR)	285 (208)	318 (363)			0.783
Current exposure to biomass, n (%)	4 (13)	6 (18)			0.599
Comorbidities, n (%)					
Diabetes mellitus	10 (32)	10 (30)	7 (21)	3 (9)	0.089
Systemic arterial hypertension	17 (55)	18 (55)	8 (24)	16 (47)	0.032
OSAS	0 (0)	4 (12)	4 (12)	4 (12)	0.256
Asthma	5 (16)	5 (15)	3 (9)	4 (12)	0.806
Use of ICS at the screening, n (%)	9 (29)	2 (6)	11 (32)	6 (18)	0.038
Eosinophils ⩾300 cells·mm^{-3}, n (%)	8 (27)	7 (21)	8 (25)	6 (21)	0.934
History of exacerbations in the previous year, n (%)					
⩾2 moderate	25 (81)	30 (91)	30 (88)	30 (88)	0.647
⩾1 severe	7 (23)	4 (12)	6 (18)	6 (18)	0.748
Health-related quality of life, mean±SD					
SGRQ total score	46±18	47±18	40±19	39±18	0.994
CAT score	17±8	17±7	15±9	14±7	0.134
Dyspnoea score					
mMRC score, mean±SD	2±0.9	1.8±0.9	1.9±1.1	1.6±0.9	0.431
BDI score, median (IQR)	6 (4)	6 (3)	6 (4)	6 (2)	0.481

For continuous variables, an ANOVA or Kruskal–Wallis test was used depending on its normality; for categorical variables, Chi-squared was used. UMEC/VI: umeclidinium/vilanterol 62.5/25 µg; FF/VI: fluticasone furoate/vilanterol 100/25 µg; BMI: body mass index; IQR: interquartile range; OSAS: obstructive sleep apnoea syndrome; ICS: inhaled corticosteroids; SGRQ: St George's Respiratory Questionnaire; CAT: COPD Assessment Test; mMRC: modified Medical Research Council; BDI: baseline dyspnoea index.

and in FEV_1 if they inhaled FF/VI (1.4±0.5, 1.5±0.5, p=0.026). Significant improvement in CAT and SGRQ total scores was found for all groups at the end of treatment and during the follow-up (figure 3 and supplementary tables S4–5).

There was a significant impact on the MCID results in the CAT score and SGRQ assessment for all groups, with a trend to be higher for FF/VI in the COPD-B group than in COPD-C (figure 4).

The mean adherence of all patients was 97±12% with no difference between the four groups (p=0.396).

Safety and AE profile

The incidence of AEs was similar across both treatments (supplementary table S6). One death was reported in the FF/VI group and was unrelated to the study. The most common AEs reported were headaches (11%). The use of medical care resources during the treatment period was more frequent in the UMEC/VI group (UMEC/VI 13% *versus* FF/VI 5%, p=0.026). There was no difference in the incidence of pneumonia in the two groups: 2.2% for all patients (UMEC/VI 3.07% *versus* FF/VI 1.5%, p=0.98).

Discussion

To our knowledge, this study is the first controlled clinical trial evaluating the efficacy of treatment with ICS/LABA (fluticasone furoate/vilanterol) *versus* LAMA/LABA (umeclidinium/vilanterol) on exacerbations, dyspnoea and HRQL in patients with COPD-B compared with COPD-C. Over 6 months of treatment, there were no differences in exacerbation rates and time to first exacerbation between patients who received FF/VI or UMEC/VI in the biomass or the tobacco COPD group. All groups showed improved quality of life and dyspnoea questionnaires independent of the cause of COPD or medication used.

TABLE 2 Baseline pulmonary function tests for COPD associated with biomass exposure (COPD-B) and COPD associated with cigarette smoking (COPD-C) groups and by treatment

Variable	COPD-B+UMEC/VI	COPD-B+FF/VI	COPD-C+UMEC/VI	COPD-C+FF/VI	p-value
Patients, n	31	33	34	34	
Lung function, mean±SD					
FEV_1 % pred post-BD[#]	58±20	60±17	65±24	69±21	0.279
FVC % pred post-BD[#]	80±16	82±13	84±19	86±16	0.254
FEV_1/FVC post-BD L	0.596±0.12	0.635±0.15	0.511±0.10	0.507±0.12	0.084
D_{LCO} % pred[#]	86±24	89±20	67±27	70±22	0.424
IC % pred	119±33	130±35	111±25	121±41	0.062
GOLD spirometric airflow limitation, n (%)					
Stage I	10 (32)	12 (36)	3 (9)	3 (9)	0.010
Stage II	11(35)	18 (55)	18 (53)	16 (47)	
Stage III	10 (32)	3 (9)	11 (32)	14 (41)	
Stage IV	0 (0)	0 (0)	2 (6)	1 (3)	
6MWD m, median (IQR)	360 (143)	360 (166)	403 (115)	472 (113)	<0.001
6MWD % pred, mean±SD	74±17	67±21	73±18	85±18	0.700

For continuous variables, an ANOVA or Kruskal–Wallis test was used depending on its normality; for categorical variables, Chi-squared was used. UMEC/VI: umeclidinium/vilanterol 62.5/25 µg; FF/VI: fluticasone furoate/vilanterol 100/25 µg; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; BD: bronchodilator; D_{LCO}: diffusion capacity of the lung for carbon monoxide; IC: inspiratory capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; 6MWD: 6-min walking distance; IQR: interquartile range. [#]: predicted values calculated for Latino population.

In this study, only 39% of patients on either medication had exacerbations during the study period, with the exacerbation being similar for all medication groups. The low number of exacerbations may be related to the relatively short observation time. Indeed, most large studies have considered at least 1 year of observation to evaluate enough events to detect significant differences [30, 31]. Also, the sample size in each arm may have needed to be higher. We knew in advance that we would not be able to carry out a study with so many subjects over 1 year. In fact, no association was found in the exacerbation rates when analysing low (100-299 cells·mm^3) and high (⩾300 cells·mm^{-3}) eosinophil count; this could be explained by the small sample size.

By design, we decided to perform a pilot trial to evaluate whether these medications were differentially effective in other outcomes typically evaluated in COPD-C trials. Both therapies were effective because of the significant improvement observed in mMRC, SGRQ and CAT scores in both COPD groups. Within the objectives of the international guidelines, the control of symptoms and improvement in HRQL are part of the primary objectives in treating COPD [14, 32]. These outcomes, which have shown improvement with the different LAMA/LABA and ICS/LABA in COPD-C [33, 34], had not been evaluated with these therapies in COPD-B. Other studies have shown that quality of life is worse in COPD-B than in COPD-C [6, 7, 35, 36], also when adjusted by age and FEV_1 [6]. Our results show that either LAMA/LABA or

TABLE 3 Asthma–COPD overlap characteristics by exposure groups

Variable	COPD-B+overlap	COPD-B+no overlap	COPD-C+overlap	COPD-C+no overlap	p-value
Patients, n	27	37	22	46	
Eosinophils count, median (IQR)	406 (421)[#]	122 (134)	242 (263)[#,+]	133 (148)	0.007
Previous asthma diagnosis, n (%)	14 (67)	0 (0)	17 (85)	5 (12)	<0.001
IgE UI·mL^{-1}, median (IQR)	56 (88)	25 (88)	39 (31)	36 (41)	0.14
FEV_1 response mL, mean±SD[§]	147±197	98.2±110	269±184[¶,f]	92±151	<0.001
FVC response mL, mean±SD[§]	158±220	95±135[##]	408±318[¶¶,++]	140±160	<0.001
FEV_1 change (%), mean±SD[§]	15±20	9±10	25±17[§§]	7±12	<0.001
FVC change (%), mean±SD[§]	10±19	6±8	18±14[ff,###]	6±6	<0.001

For continuous variables, an ANOVA or Kruskal–Wallis test was used depending on its normality; for categorical variables, Chi-squared was used. COPD-B: COPD associated with biomass exposure; COPD-C: COPD associated with cigarette smoking; IQR: interquartile range; IgE: immunoglobulin E; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. *Post hoc* test: [#]: p<0.05 *versus* COPD-C+no overlap; [¶]: p<0.05 *versus* COPD-B+no overlap; [+]: p<0.05 *versus* COPD-C+overlap; [§]: predicted values calculated for Latino population; [f]: p<0.05 *versus* COPD-B+no overlap; [##]: <0.05 *versus* COPD-C+no overlap; [¶¶]: p<0.05 *versus* COPD-C+no overlap; [++]: p<0.05 *versus* COPD-B+no overlap; [§§]: p<0.05 *versus* COPD-C+no overlap; [ff]: p<0.05 *versus* COPD-C+no overlap; [###]: p<0.05 *versus* COPD-C+no overlap.

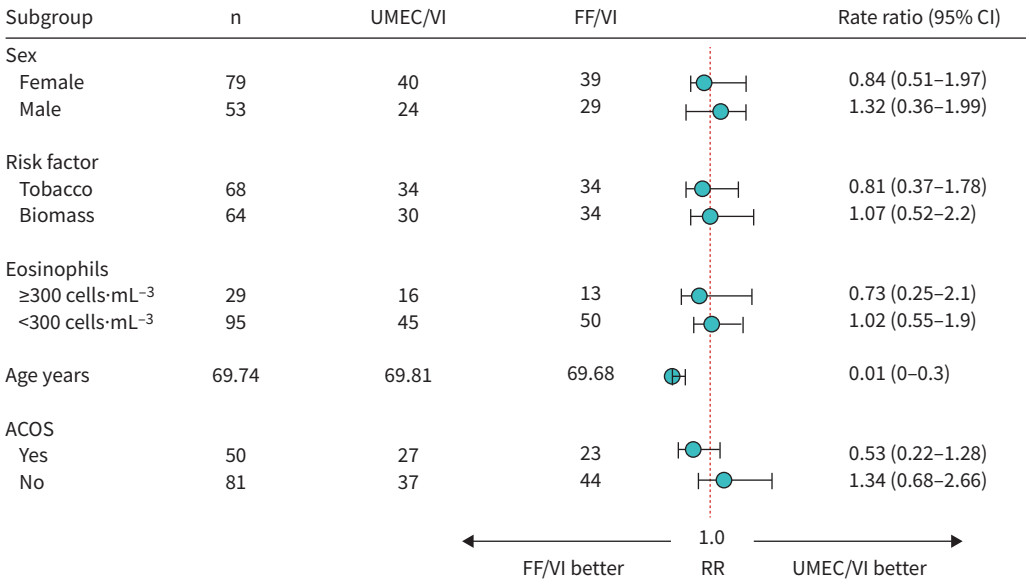

FIGURE 2 Effect of treatment with umeclidinium/vilanterol 62.5/25 µg (UMEC/VI) *versus* fluticasone furoate/vilanterol 100/25 µg (FF/VI) on the exacerbation rate per 6 months stratified by tobacco and biomass risk and other variables. ACOS: asthma–COPD overlap syndrome; RR: risk rate.

ICS/LABA are effective medications for improving HRQL and dyspnoea in these patients. Furthermore, the significant proportion of patients achieving an MCID improvement in the CAT and SGRQ scores supports the value of both drugs (FF/VI and UMEC/VI) in treating COPD-B. It is worth highlighting how FF/VI was more effective in improving symptoms and quality of life outcomes, while UMEC/VI was more effective in enhancing dyspnoea and IC outcomes. Previously, we demonstrated how indacaterol or tiotropium improves hyperinflation in COPD-B [37]. These women present hyperinflation with a modest decrease in the FEV_1. Notably, the COPD-B population, which has a much higher baseline FEV_1 than COPD-C, substantially improves their quality of life and respiratory symptoms. In this sense, by

TABLE 4 Changes in dyspnoea, health-related quality of life, and lung function in COPD associated with biomass exposure (COPD-B) and COPD associated with cigarette smoking (COPD-C) patients after 6 months of umeclidinium/vilanterol 62.5/25 µg (UMEC/VI) or fluticasone furoate/vilanterol 100/25 µg (FF/VI) treatment

Variable	COPD-B+UMEC/VI		COPD-B+FF/VI		COPD-C+UMEC/VI		COPD-C+FF/VI	
	Mean±SD	p-value	Mean±SD	p-value	Mean±SD	p-value	Mean±SD	p-value
Patients n	31		33		34		34	
Symptoms and quality of life								
Baseline mMRC	2.2±0.8	0.024	1.7±0.9	0.100	1.9±1.1	0.013	1.5±0.9	0.029
6-month mMRC	1.7±1.1		1.5±0.9		1.5±1.2		1.3±0.7	
Baseline CAT	18±8	0.008	18±6	<0.001	15±9	<0.001	14±7	0.002
6-month CAT	12±8		11±8		11±7		9±8	
Baseline SGRQ	45±18	0.002	45±19	<0.001	39±19	0.008	38±19	<0.001
6-month SGRQ	34±19		30±19		33±17		27±18	
Lung function								
Baseline FEV_1 L	1.21±0.5	0.231	1.36±0.5	0.026	1.42±0.5	0.242	1.69±0.6	0.584
6-month FEV_1 L	1.25±0.5		1.45±0.5		1.46±0.5		1.68±0.7	
Baseline FVC L	2.23±0.8	0.355	2.38±0.7	0.112	2.29±0.7	0.389	2.67±1	0.671
6-month FVC L	2.30±0.8		2.46±0.8		2.31±0.6		2.63±1.1	
Baseline IC L	1.5±0.6	0.026	1.7±0.5	0.737	2.1±0.7	0.241	2.08±0.7	0.217
6-month IC L	1.7±0.5		1.6±0.4		2.1±0.6		2.2±0.6	

mMRC: modified Medical Research Council scale; CAT: COPD Assessment Test; SGRQ: St George's Respiratory Questionnaire; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; IC: inspiratory capacity. t-tests were used to evaluate the change in respiratory function between groups.

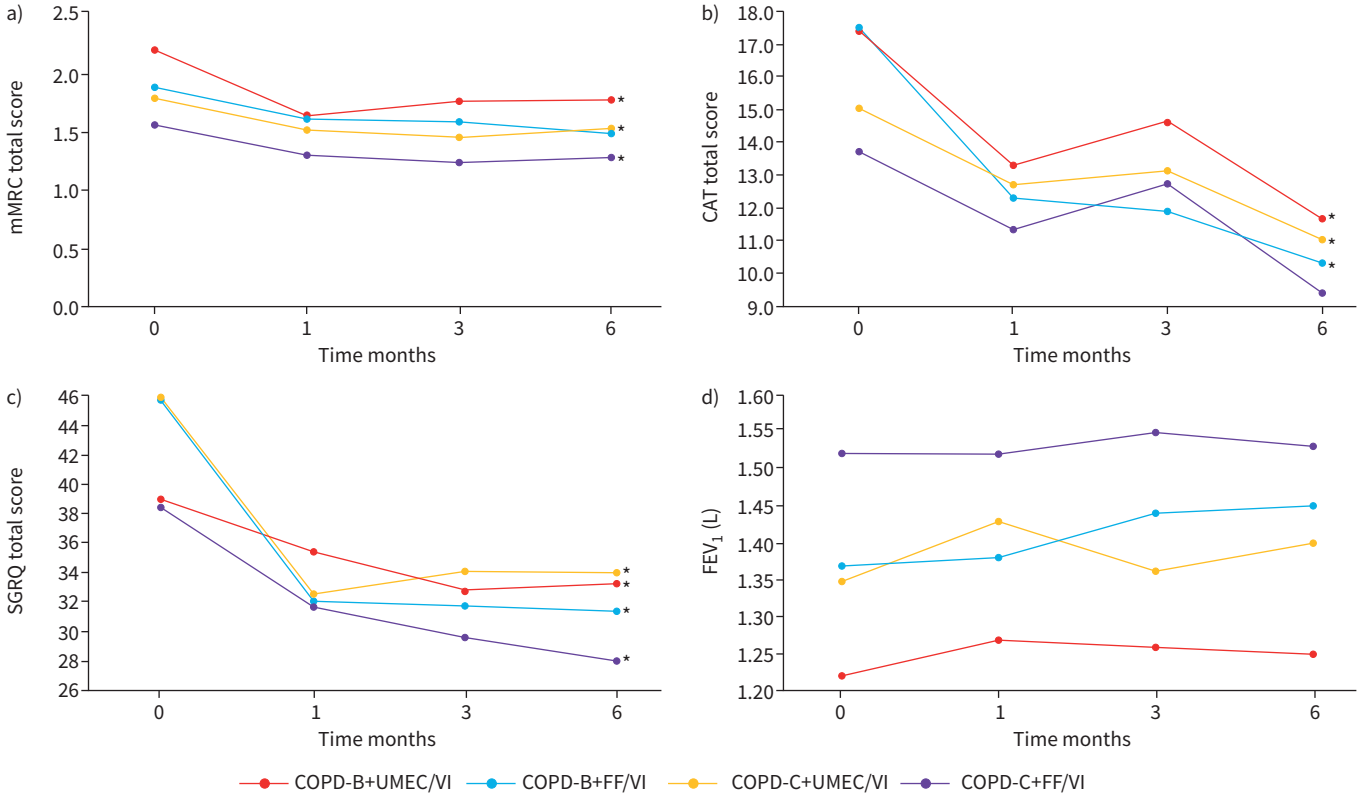

FIGURE 3 Predictive margins of time at 1, 3 and 6 months by exposure and treatment groups. a) A significant decrease over 6 months was observed in modified Medical Research Council (mMRC) total score in COPD associated to biomass exposure (COPD-B)+umeclidinium/vilanterol 62.5/25 µg (UMEC/VI) (p<0.009), COPD associated to cigarette smoking (COPD-C)+UMEC/VI (p=0.027) and COPD-C+fluticasone furoate/vilanterol 100/25µg (FF/VI) (p=0.043). b) A significant decrease over 6 months was observed in COPD Assessment Test (CAT) total score in COPD-B+UMEC/VI (p<0.001), COPD-B+FF/VI (p<0.001) and COPD-C+UMEC/VI (p<0.001) after 6 months of treatment. c) A significant improvement over 6 months was observed in St George's Respiratory Questionnaire (SGRQ) total in COPD-B+UMEC/VI (p<001), COPD-B+FF/VI (p<0.001), COPD-C+UMEC/VI (p=0.008) and COPD-C+FF/VI (p=0.006). d) No significant improvement in forced expiratory volume in 1 s (FEV_1) (L) was observed in any group. *: p<0.05.

demonstrating that both LAMA/LABA and ICS/LABA are effective medications in this population, patients with COPD-B could also benefit from triple therapy (LAMA/LABA/ICS) if they met the criteria established by international guidelines. In our study, 23% of the patients with COPD-B met the criteria to receive triple therapy [14].

The findings related to the asthma–COPD overlap in both groups deserve some comments. Some published data suggest that this phenotype may be as prevalent and more severe in low and middle-income countries, which are experiencing the simultaneous burdens of household air pollution exposure and high rates of urbanisation and sprawl [10]. Although studies are scarce, COPD-B has been reported with more features of COPD-A [1, 38], more predominance of biomarkers compatible with a Th2 inflammatory profile [7–10, 35] and greater bronchial hyperreactivity [10, 39] than COPD-C. That is why adding ICS to LABA or LAMA should be a good strategy for testing COPD-B.

In our study, using accepted criteria to define asthma–COPD overlap, there was no significant difference in prevalence between groups. The same was true for the response to bronchodilators using the old and current criteria [40] (supplementary table S1). Likewise, the number of eosinophils was very similar between COPD-B and COPD-C where <30% of both groups had ⩾300 cells·mm^{-3} of eosinophils. Regardless of the cause of COPD, for patients who presented COPD-A phenotype, treatment with LABA/LAMA or ICS/LABA was equally effective in reducing exacerbations, improving quality of life and dyspnoea.

In this study, adequate compliance with inhaled therapy was observed. The technic for the ellipta device, particularly, is easy to understand, and we believe this aids in good adherence to treatment. Also, the use

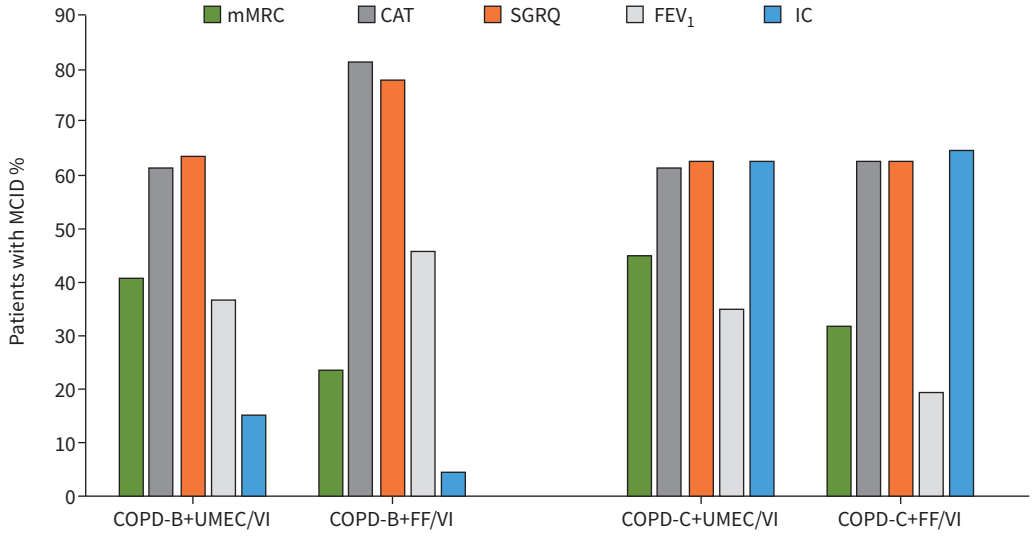

FIGURE 4 Minimal clinically important difference (MCID) in different values after 6-month treatment compared by COPD groups by treatment. Comparison made using Chi-squared test. Although, there were no differences between treatment arms ($p>0.05$), a higher proportion in the COPD associated to biomass exposure (COPD-B) +fluticasone furoate/vilanterol 100/25 µg (FF/VI) group showed a MCID in COPD Assessment Test (CAT) and St George's Respiratory Questionnaire (SGRQ) assessments. FEV_1: forced expiratory volume in 1 s; IC: inspiratory capacity.

of ICS/LABA did not contribute to a greater number of pneumonia cases when compared with LAMA/LABA in both COPD groups.

Strengths

It also measured patient-related outcomes, including dyspnoea, symptoms and quality of life. The positive response to these outcomes also indicates that the medications used effectively improve these outcomes.

Limitations

We also acknowledge that the study has some limitations. Indeed, the sample size was too small to detect differences in exacerbation rates. Therefore, we cannot conclude that there may have been differences between the therapies evaluated in patients with COPD-B and COPD-C if the study had included more patients. Also, the study was not blinded. However, the personnel who carried out the clinical questionnaires and PFTs and attending physicians were permanently blinded regarding the inhaler that the patients used. Finally, the follow-up time was short, which prevented from measuring more events (exacerbations) over a more extended period. However, the good response in patient-reported outcomes and lung function supports a significant benefit for the patients suffering from COPD independent of its cause.

Conclusions

In conclusion, in this pilot study, we found that among patients with COPD-B who had a history of exacerbations during the previous year, ICS/LABA was equally as effective as LAMA/LABA in preventing exacerbations and improving symptoms, dyspnoea and HRQL, with no detectable increase in AEs, especially pneumonia.

Provenance: Submitted article, peer reviewed.

Data availability: The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

This study is registered at www.clinicaltrials.gov with identifier number NCT05342558.

Ethics statement: The institutional ethical committee board reviewed and approved the protocol (C49-17). All patients provided a written informed consent form.

Authors contributions: A. Ramírez-Venegas contributed to the conception and design of the study, acquisition of data, analysis, interpretation of data, drafting the article, and revising it critically for important intellectual content. R.H. Sansores, R.J. Hernández-Zenteno and R. Pérez-Padilla contributed equally to the conception and design of the study, acquisition of data, analysis and interpretation of data, and revising the manuscript critically for important intellectual content. F. Montiel-Lopez, R.E. Robles-Hernández and M. Cassou-Martínez contributed equally to acquiring data, analysing and interpreting data, drafting the article, and revising it critically for important intellectual content. J.L. Pérez Lara-Albisua contributed to the conception and design of the study, and revising the manuscript critically for important intellectual content. B.R. Celli, C. González-González, M.E. Mayar-Maya, A.P. Hernández-Morales, R. Falfán-Valencia, I. Thirión-Romero and O. Pérez-Bautista contributed equally to analysing and interpreting data, and revising the manuscript critically for important intellectual content. All authors contributed equally to the final approval of the version to be submitted.

Conflict of interest: A. Ramírez-Venegas reports receiving personal fees from GlaxoSmithKline, AstraZeneca and Boehringer Ingelheim for speaking engagements. R.E. Robles-Hernández and R.J. Hernández-Zenteno report receiving personal fees from GlaxoSmithKline and AstraZeneca for speaking engagements. B.R. Celli reports receiving personal fees from GlaxoSmithKline, Boehringer Ingelheim, Novartis, Sanofi-Aventis and Menarini for consulting services. O. Pérez-Bautista reports receiving personal fees from Boehringer Ingelheim for speaking engagements. The remaining authors have no conflict of interest to report.

Support statement: The study was funded by the Chamber of Deputies of Mexico. Funding information for this article has been deposited with the Crossref Funder Registry.

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