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Real-Life Clinical and Functional Effects of Fluticasone Furoate/Umeclidinium/Vilanterol-Combined Triple Therapy in Patients with Chronic Obstructive Pulmonary Disease

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Keywords
Chronic obstructive pulmonary disease · Triple inhaled therapy · Exacerbations · Airflow limitation · Lung hyperinflation

Abstract
Background: Triple therapy consisting of a drug association including an inhaled corticosteroid, a long-acting muscarinic receptor antagonist and a long-acting β_2-adrenergic agonist, delivered via a single device, can be a valuable treatment for chronic obstructive pulmonary disease (COPD) patients experiencing frequent disease exacerbations. ***Objectives:*** The aim of this real-life, single-center, observational study was to evaluate, in 44 COPD patients with recurrent exacerbations, the effects of the triple inhaled therapy combining fluticasone furoate, umeclidinium, and vilanterol (FF/UMEC/VI). ***Methods:*** Within such a therapeutic context, several clinical and lung functional parameters were considered at baseline and after 24 weeks of treatment with combined inhaled triple therapy. ***Results:*** With respect to baseline, after 24 weeks of treatment with FF/UMEC/VI, significant changes were recorded with regard to Modified British Medical Research Council ($p < 0.0001$) and COPD Assessment Test ($p < 0.0001$) scores, COPD exacerbations ($p < 0.001$), forced expiratory volume in the first second ($p < 0.001$), residual volume ($p < 0.01$), forced mid-expiratory flow between 25 and 75% of FVC ($p < 0.0001$), inspiratory capacity ($p < 0.01$), forced vital capacity ($p < 0.05$), and peak expiratory flow ($p < 0.0001$). Moreover, in a subgroup of 28 patients, a significant increase of diffusion lung capacity ($p < 0.01$) was also detected. ***Conclusions:*** In conclusion, our real-life results suggest that triple inhaled therapy with FF/UMEC/VI, when given to COPD patients with frequent exacerbations, is able to positively impact on dyspnea and global health status as well as to significantly decrease COPD exacerbations and improve airflow limitation and lung hyperinflation.

Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable condition which represents one of the most important health problems of

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industrialized world. The global prevalence of COPD has been estimated at up to 13% [1], but it is progressively increasing due to smoking habit and air pollution. Indeed, COPD is already the third cause of death worldwide [2].

According to Global Initiative for Obstructive Lung Disease (GOLD) [3], COPD treatment is helpful in alleviating symptoms, preventing exacerbations and slowing down lung function decline. In addition to smoking cessation which plays a crucial preventive role, inhaled therapy can relieve symptoms as well as decrease exacerbations and hospitalizations [4, 5], increase airway caliber [6], and reduce lung hyperinflation [7]. Taken together, these favorable outcomes can contribute to improve exercise tolerance and overall quality of life. Inhaled medications are able to reach quickly and directly the internal lumen of the airways, thus allowing to use relatively low drug dosages, associated with optimization of therapeutic actions and minimization of side effects [8].

Many studies carried out in patients with severe COPD have shown that triple therapy, consisting of an inhaled corticosteroid (ICS) plus a long-acting muscarinic receptor antagonist (LAMA) and a long-acting β_2-adrenergic agonist (LABA), is more effective than dual bronchodilation with regard to both reduction of annual exacerbation rate and improvement in lung function [9–19]. However, until a couple of years ago, triple inhaled therapy was delivered via several devices, used more than once daily [20, 21]. Recently, combined inhaled therapies containing an ICS, a LABA, and a LAMA in the same device have been developed. These inhalers offer many advantages, also in regard to treatment adherence. Combined triple therapies assembled in a single inhaler include fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI), beclomethasone dipropionate/glycopyrronium/formoterol (BDP/G/F), and budesonide/glycopyrronium/formoterol (B/G/F). The simultaneous delivery to the airways of 3 drugs with different mechanisms of action can optimize their positive interactions.

FF/UMEC/VI has been licensed in the European Union as a maintenance treatment in adult patients with moderate-to-severe COPD, who cannot be adequately controlled by either ICS/LABA or LAMA/LABA combinations. According to GOLD, triple therapy is currently recommended only as a step-up approach from LAMA/LABA or ICS/LABA treatments [3]. Furthermore, triple inhaled therapy might be an effective pharmacological strategy in several COPD phenotypes including frequent exacerbators, eosinophilic trait, and asthma/COPD overlap syndrome [22–24]. In patients with symptomatic COPD and a history of exacerbations, the IMPACT (Informing the Pathway of COPD Treatment) trial has recently evaluated the relevant benefits and risks of 3 therapeutic regimens including FF/VI, UMEC/VI, and FF/UMEC/VI [25]. The results of the IMPACT trial showed that, when compared to FF/VI or UMEC/VI, the once-daily fixed combination FF/UMEC/VI further lowered the number of hospitalizations and the annual rate of moderate to severe COPD exacerbations, induced a better improvement in lung function and health-related quality of life, and especially decreased all-cause mortality. This latter result was corroborated by a recent post hoc analysis of the IMPACT study [26]. Furthermore, lower risks of COPD exacerbations and death from any cause were detected by the ETHOS (Efficacy and Safety of Triple Therapy in Obstructive Lung Disease) trial with regard to the use of B/G/F triple therapy, when compared to dual treatments consisting of either B/F ICS/LABA combination or G/F LAMA/LABA association [27].

However, scientific literature currently lacks real-world experiences referring to the use of FF/UMEC/VI by COPD patients. Therefore, within this context the aim of our present real-life, single-center, observational study has been to investigate, in COPD patients, the effects of the triple therapy consisting of once-daily FF/UMEC/VI fixed-dose combination on respiratory symptoms, global health status, lung function, and exacerbation rate.

Patients and Methods

Study Design and End points

This was a real-life, single-center study that included patients suffering from COPD, treated with the single inhaler therapy FF/UMEC/VI (92/55/22 mcg). These subjects were evaluated at the Respiratory Unit of "Magna Græcia" University Hospital of Catanzaro, Italy, from March 2019 to March 2020. COPD diagnosis was made according to GOLD recommendations [3]. Before beginning FF/UMEC/VI therapy, and after 24 weeks of treatment, lung function tests were performed according to ATS/ERS guidelines [28] by Master Screen Pulmonary Function Testing System and Master Screen Body (Jaeger, Hannover, Germany). Measurement of diffusion lung capacity for carbon monoxide (DLCO) was made according to ERS/ATS standards for single-breath carbon monoxide uptake in the lung, and its value was corrected for the "anemia effect" by considering hemoglobin level. Thus, diffusion lung capacity was expressed as corrected single-breath DLCO (DLCOcSB) [29]. FF/UMEC/VI was prescribed according to current eligibility indications. It was administered at the dosage of 1 inhalation every 24 h; therefore, all previous inhaled therapies were interrupted.

The main aims of this observational study were to assess in COPD patients, within the context of a real-life setting, the effects on clinical and functional parameters of the combined triple in-

haled therapy consisting of FF/UMEC/VI. Modified British Medical Research Council (mMRC) questionnaire, COPD Assessment Test (CAT), forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), residual volume (RV), forced mid-expiratory flow between 25 and 75% of FVC ($FEF_{25–75}$), total lung capacity (TLC), inspiratory capacity (IC), and peak expiratory flow (PEF) were assessed at baseline and after 24 weeks of treatment with FF/UMEC/VI. In most patients, DLCO was also measured. In addition, the number of COPD exacerbations was recorded at baseline (exacerbations occurred within the previous 6 months) and 24 weeks after the beginning of fixed triple therapy. Moreover, we evaluated drug safety and tolerability through a monthly telephone call, asking if patients had experienced infections, headache, cough, and gastrointestinal disorders and also requesting to indicate if any worsening of health status had occurred.

Patient Characteristics

Older than 18 years patients with COPD were enrolled. Although the recruited subjects were regularly treated with either LAMA/LABA or ICS/LABA combinations, they reported persistent breathlessness and/or exercise limitation complicated by frequent COPD exacerbations. Forty-four patients (34 males and 10 females) were included. The mean (±standard deviation [SD]) age of enrolled population was 67.20 ± 8.086 years, and the median (interquartile range [IQR]) BMI was 26.00 (25.00–30.00) kg/m^2. Mean (±SD) baseline FEV_1 and RV were 48.55 (±13.62) % of predicted value and 151.2 (±48.15) % of predicted value, respectively. Median (IQR) baseline $FEF_{25–75}$ was 31.50 (18.50–43.00) %. Baseline patient characteristics are summarized in Table 1.

Statistical Analysis

Statistical analysis was performed using Prism version 8.2.1 (GraphPad Software Inc., San Diego, CA, USA). Normally distributed data were expressed as mean ± SD, otherwise as median values with IQR. Parametric and nonparametric tests were chosen on the basis of data normality. The Anderson-Darling test and Kolmogorov-Smirnov test were applied to assess if data were normally distributed. Student's *t* test or Mann-Whitney U test were used to compare variables, when appropriate. A *p* value lower than <0.05 was considered to be statistically significant.

Table 1. Baseline patient characteristics

Age, mean (±SD), years	67.2 (±8.09)
Male gender, *N* (%)	34 (77.3)
Female gender, *N* (%)	10 (22.7)
Weight, mean (±SD), kg	77.6 (±15.9)
Height, mean (±SD), cm	167.5 (±8.37)
BMI, median (IQR), kg/m^2	26 (25–30)
FEV_1, mean (±SD), % predicted	48.5 (±13.6)
FEV_1/FVC, mean (±SD), %	58.7 (±11.1)
RV, mean (±SD), % predicted	151.2 (±48.1)
$FEF_{25–75}$, median (IQR), % predicted	31.5 (18.5–43.0)
Smokers and ex-smokers, *N* (%)	44 (100)
On treatment with ICS/LABA, *N* (%)	23 (52.3)
On treatment with LAMA/LABA, *N* (%)	21 (47.7)

SD, standard deviation; IQR, interquartile range; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; RV, residual volume; $FEF_{25–75}$, forced mid-expiratory flow between 25 and 75% of FVC; ICS, inhaled corticosteroid; LABA, long-acting β_2-adrenergic agonist; LAMA, long-acting muscarinic receptor antagonist.

Table 2. Summary of effectiveness outcomes

	Before FF/UMEC/VI	FF/UMEC/VI (6 months)	*p* value
mMRC dyspnea scale, median (IQR)	3 (3–4)	2 (1–3)	**<0.0001**
CAT score, mean (±SD)	23.30 (±9.289)	14.15 (±9.578)	**<0.0001**
FEV_1, mean (±SD), L	1.369 (±0.4543)	1.540 (±0.4924)	**<0.001**
RV, median (IQR), L	3.245 (2.658–4.138)	3.175 (2.470–3.873)	**<0.01**
$FEF_{25–75}$, median (IQR), L/s	0.6450 (0.3775–1.005)	0.7750 (0.5250–1.070)	**<0.0001**
TLC, mean (±SD), L	6.289 (±1.557)	6.203 (±1.511)	0.4932
IC, mean (±SD), L	1.907 (±0.6841)	2.114 (±0.6427)	**<0.01**
FVC, mean (±SD), L	2.323 (±0.6552)	2.475 (±0.6580)	**<0.05**
PEF, mean (±SD), L/s	4.125 (±1.346)	4.823 (±1.639)	**<0.0001**
DLCOcSB, mean (±SD), mmol/min/kPa	4.808 (±1.365)	5.224 (±1.466)	**<0.01**
COPD exacerbations, mean (±SD), *N*	4.815 (±2.185)	2.344 (±2.252)	**<0.001**

SD, standard deviation; IQR, interquartile range; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; mMRC, Modified British Medical Research Council; CAT, COPD Assessment Test; FEV_1, forced expiratory volume in the first second; RV, residual volume; FVC, forced vital capacity; $FEF_{25–75}$, forced mid-expiratory flow between 25 and 75% of FVC; TLC, total lung capacity; IC, inspiratory capacity; PEF; peak expiratory flow; DLCOcSB, corrected single-breath diffusion lung capacity for carbon monoxide; COPD, chronic obstructive pulmonary disease. Bold entries, referring to *p* values, emphasize the statistical significance of the detected differences.

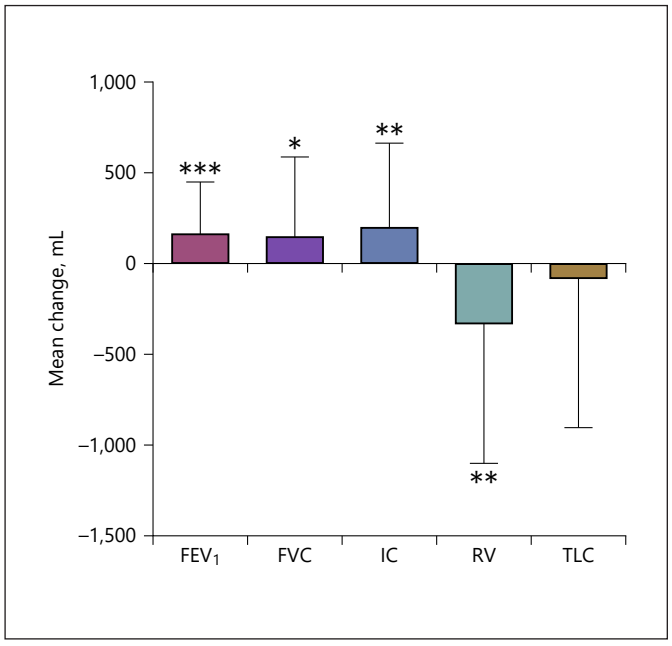

Fig. 1. Mean changes of FEV_1, FVC, IC, RV, and TLC after 24 weeks of combined triple inhaled therapy (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$). FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; IC, inspiratory capacity; TLC, total lung capacity; RV, residual volume.

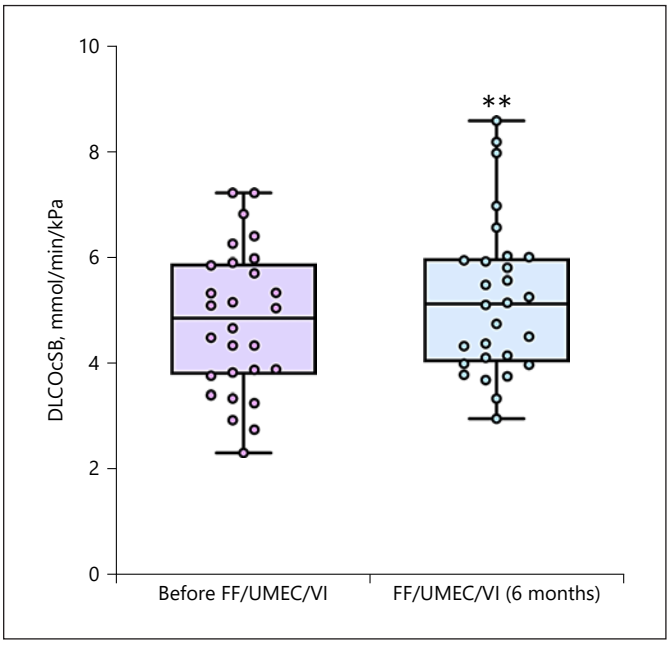

Fig. 2. Effect of FF/UMEC/VI on DLCOcSB. In regard to the 28 patients who satisfactorily performed DLCOcSB, test values significantly increased after 24 weeks of combined triple inhaled therapy (**$p < 0.01$). FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; DLCOcSB, corrected single-breath diffusion lung capacity for carbon monoxide.

Results

The main clinical and functional findings are summarized in Table 2. After 24 weeks of treatment with FF/UMEC/VI combined therapy, the score of mMRC dyspnea scale significantly improved from a baseline value of 3 (3–4) to 2 (1–3) ($p < 0.0001$). Furthermore, this important clinical result was confirmed by a significant reduction of CAT score, whose value dropped from 23.30 ± 9.289 to 14.15 ± 9.578 ($p < 0.0001$).

A more satisfactory control of COPD symptoms and the better health status were associated with a significant improvement of lung function. Mean changes in FEV_1, FVC, IC, RV, and TLC are illustrated in Figure 1. In particular, 6 months after the beginning of triple inhaled therapy, FEV_1 increased from a baseline value of 1.369 ± 0.4543 L to 1.540 ± 0.4924 L ($p < 0.001$). In addition, FF/UMEC/VI triple therapy exerted a significant effect on lung hyperinflation caused by persistent airway obstruction. In fact, RV median value decreased from 3.245 (2.658–4.138) L to 3.175 (2.470–3.873) L ($p < 0.01$) at the 24th week. The effect of FF/UMEC/VI on lung hyperinflation was concomitant with a significant increase of small airway caliber. Indeed, after 6 months of triple therapy, $FEF_{25–75}$ median value improved from baseline 0.6450 (0.3775–1.005) L/s to 0.7750 (0.5250–1.070) L/s ($p < 0.0001$). After 24 weeks, TLC decreased from 6.289 ± 1.557 L to 6.203 ± 1.511 L, but this reduction was not statistically significant ($p = 0.4932$). Mean IC value significantly increased, with respect to baseline, from 1.907 ± 0.6481 L to 2.114 ± 0.6427 L after 6 months ($p < 0.01$). Moreover, when compared to the baseline value of 2.323 ± 0.6552 L, FVC enhanced to 2.475 ± 0.6580 L at the 24th week ($p < 0.05$). After 6 months of treatment, PEF improved from a baseline measurement of 4.125 ± 1.346 L/s to 4.823 ± 1.639 L/s ($p < 0.0001$).

In 28 out of 44 patients, DLCOcSB was also measured at baseline and 6 months after the beginning of combined triple therapy. The remaining 16 patients were not able to collaborate enough, in order to perform a good quality DLCO test. We observed a significant increase of DLCOcSB value from 4.808 ± 1.365 mmol/min/kPa to 5.224 ± 1.466 mmol/min/kPa ($p < 0.01$) (Fig. 2). When compared to the 6-month period preceding the enrollment, the mean number of COPD exacerbations per patient decreased from 4.815 ± 2.185 to 2.344 ± 2.252 ($p <$

0.001); this latter result was recorded 6 months after starting treatment with FF/UMEC/VI.

With regard to the adverse events possibly caused by FF/UMEC/VI inhaled therapy, only 1 patient referred constipation and gastrointestinal symptoms that induced him to interrupt triple therapy assumption after 6 months. No patient experienced pneumonia or other airway infections.

Discussion

In this real-life experience, once-daily single-inhaler triple therapy with FF/UMEC/VI induced relevant changes related to improvement of dyspnea and health status, reduction of moderate to severe COPD exacerbations rate, and better lung function. In particular, our findings show that the above triple therapy significantly increased FEV_1, $FEF_{25–75}$, FVC, IC, and PEF as well as decreased RV. Moreover, in a subgroup of patients, this inhaled treatment also enhanced DLCO. Despite the obvious limitation due to the relatively small number of recruitable patients in a single-center study, our observational investigation suggests that in a real-life context, the positive effects of FF/UMEC/VI on lung function could be even greater than those reported by the IMPACT trial.

It is well known that most trials evaluating in COPD patients the efficacy of "open triple" therapies versus either dual or single inhaled treatments, not only reported beneficial modifications of lung function but also showed significant improvements in health status, rescue medication use, and risk of exacerbations, associated with a good drug safety and tolerability profile [10–15, 30–34]. Furthermore, different ICS/LAMA/LABA combinations in a single inhaler have been studied, including BDP/G/F and FF/UMEC/VI.

BDP/G/F has been developed as an extra-fine formulation in pressurized metered-dose inhaler which delivers 87/5/9 mcg of BDP/G/F, according to a twice daily dosage schedule. This triple therapy is indicated for maintenance treatment in adult patients with moderate-to-severe COPD, who are not adequately controlled by ICS/LABA combinations. In particular, the TRINITY trial demonstrated that the single inhaler BDP/G/F combination was more effective than tiotropium alone with regard to the effects on both pre-dose FEV_1 and annual rate of moderate to severe exacerbations [18]. In addition, the TRILOGY study comparatively evaluated inhaled treatments with either BDP/G/F or BDP/F, thus showing significant advantages of triple therapy in terms of Transition Dyspnea Index (TDI) focal score and prolongation of the time to first clinically important deterioration as defined by the following changes: decrease ≥100 mL from baseline FEV_1; increase ≥4 units from baseline SGRQ total score, deterioration ≥1 unit from baseline occurrence of moderate/severe COPD exacerbation, or death [16]. Moreover, in the subgroup of TRILOGY patients classified as GOLD group B (CAT score >10 and 1 exacerbation in the previous year, not leading to hospitalization or emergency room admission), BDP/G/F reduced the rate of moderate/severe exacerbations in comparison to BDP/F [35]. These results were consistent with those observed in the TRINITY study, which showed that BDP/G/F delayed clinically important deterioration with respect to tiotropium, and reduced the rate of moderate/severe exacerbations in GOLD group B patients [16, 35]. Finally, the TRIBUTE trial demonstrated a more favorable benefit/risk ratio granted by BDP/G/F, when compared with the dual bronchodilator combination indacaterol/glycopyrronium [36]. In particular, triple therapy elicited a greater reduction of moderate to severe exacerbation rate, without increasing the risk of pneumonia events.

FF/UMEC/VI has been developed as a multidose dry-powder inhaler formulation, delivered through the ELLIPTA device. Each inhalation provides a fixed dosage of 92/55/22 mcg of FF/UMEC/VI at a recommended schedule of 1 administration per day. In European Union, this triple therapy is indicated as a maintenance treatment in adult patients with moderate-to-severe COPD who are not adequately controlled by dual therapies consisting of either LAMA/LABA or ICS/LABA fixed combinations [37]. In regard to the clinical development of FF/UMEC/VI, 2 main randomized studies have been carried out. The FULFILL study compared FF/UMEC/VI with budesonide/formoterol combination for 24 weeks in patients with severe airflow limitation, but no relevant risk of exacerbations, as well as in subjects with moderate airflow limitation and high risk of exacerbations [19]. The authors of this trial reported better effects of the triple combination on FEV_1 and health status. A subsequent study phase extended up to 52 weeks was carried out in a subgroup of about 24% patients, who experienced a greater reduction of exacerbation rate with FF/UMEC/VI, when compared to budesonide/formoterol. In the IMPACT study, FF/UMEC/VI was compared to FF/VI and UMEC/VI, all delivered via the ELLIPTA device [25]. This study showed a higher reduction of exacerbation rate provided by triple therapy with respect to the 2 dual treatments as well as greater benefits on FEV_1 and health status. In addition, a

recent post hoc analysis of the IMPACT trial has also shown that regimens containing FF (FF/UMEC/VI and FF/VI) significantly lowered all-cause mortality with respect to UMEC/VI [26]. Such key findings about the decreases in COPD exacerbations and all-cause mortality have been recently confirmed by the ETHOS study, which demonstrated that the triple fixed combination B/G/F was superior to G/F dual bronchodilation as well as to B/F association [27]. Therefore, the results of IMPACT and ETHOS trials suggest that the relevant benefits experienced by COPD patients undergoing triple inhaled treatments, with regard to significant reductions of exacerbation and death risks, depend on a potential "pharmacological class effect" rather than on drug compositions of triple therapies.

Despite the convincing evidence regarding the effectiveness of triple inhaled therapies, emerging from recent randomized trials, current scientific literature includes only a very few real-life studies. In this regard, our present observational investigation suggests that when in a real-world setting common ICS/LABA or LAMA/LABA fixed combinations are replaced by FF/UMEC/VI, this triple therapy can induce FEV_1 increments which may even exceed those detected in randomized trials. More importantly, in addition to FEV_1 which was the only spirometric parameter reported by TRINITY, TRILOGY, TRIBUTE, FULFILL, IMPACT, and ETHOS trials, we also focused our attention on other functional measures evaluating small airway caliber and lung hyperinflation. The latter is the main pathophysiologic determinant of dyspnea and low exercise tolerance in COPD patients [38]. Therefore, we think that a deep evaluation of the clinically relevant effects of COPD treatments cannot ignore the potential lung deflating actions of inhaled drugs used in daily clinical practice. In this regard, it is noteworthy that our findings highlight a significant RV reduction produced by FF/UMEC/VI with respect to baseline. RV decrease was paralleled by a specular IC increase. Because we also showed a significant beneficial effect of FF/UMEC/VI on $FEF_{25–75}$, it is conceivable that improvement of airflow limitation at level of small airways may represent the predominant mechanism by which the above triple inhaled therapy deflated the lungs of our COPD patients. Indeed, the increase of small airway caliber resulting from the anti-inflammatory action of FF, combined with the bronchodilating effects of UMEC/VI, can critically improve airflow, thereby favoring a relevant decrease of air trapping and lung hyperinflation. Hence, it can be reasonably argued that the significant lung-deflating action exerted by FF/UMEC/VI, in comparison to baseline, likely explains the positive effects displayed by this triple therapy on both dyspnea and global health status, shown by our results referring to mMRC and CAT scores, which displayed similar improvements. Moreover, lung hyperinflation is also involved in the pathophysiology of COPD exacerbations [39, 40]. In fact, with respect to the relatively stable phases of COPD, during exacerbations lung hyperinflation further worsens because of moderate to severe increases in both airway inflammation and bronchoconstriction. Therefore, we can infer that our data regarding the good preventive effect of FF/UMEC/VI on COPD exacerbations are likely due to the powerful combined anti-inflammatory and bronchodilating actions of this triple therapy.

Moreover, it is quite interesting that we observed a significant increase of DLCO value induced by FF/UMEC/VI, though not all enrolled patients were able to perform correctly the DLCO test. To our knowledge, no other previous study has detected DLCO improvements elicited by inhaled triple therapies. A possible explanation of this unexpected finding could be attributed to the improvements in airflow limitation and lung hyperinflation. Indeed, such positive ventilatory effects might promote an enlargement of blood/gas exchange area, resulting in an increased diffusion lung capacity.

Taken together, our findings suggest that the use of FF/UMEC/VI in COPD treatment optimizes the interactions between LAMA and LABA as well as between ICS and LABA. Indeed, LAMA and LABA reciprocally potentiate their different bronchodilating mechanisms, consisting of the competitive antagonism exerted by LAMA on muscarinic cholinergic receptors, and the functional antagonism of airway smooth muscle contraction implemented by LABA via activation of the β_2-adrenergic receptor/adenylyl cyclase/cAMP/PKA transduction system [8, 41, 42]. The latter signaling pathway is also responsible for facilitation of nuclear translocation of the intracellular receptors of corticosteroids, which in turn stimulate the transcriptional activity of the β_2-adrenergic receptor gene [43].

In conclusion, the main strength of our observational study is the real-life COPD setting, within which we here show the effectiveness of FF/UMEC/VI with regard to both clinical and functional outcomes. Of course, similar to all real-world single-center studies, our present investigation also includes some limitations, mainly due to the relatively small number of enrolled patients, associated with the lack of randomization design and control arm (ICS/LABA and/or LAMA/LABA). A further limitation of this real-life experience refers to its relative short dura-

tion, which can interfere with our understanding of the real impact of triple therapy on study outcomes, especially with regard to exacerbation rate. Therefore, we plan to monitor the recruited patients for longer periods, thus extending our observations to more suitable and reliable time points.

Statement of Ethics

Such a single-center clinical and functional investigation met the standards of Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki. All recruited patients signed a written informed consent. This observational study was also performed according to what stated by the local Ethical Committee of Calabria Region (Catanzaro, Italy; document no. 263 – July 23, 2020).

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

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Author Contributions

All authors contributed to design and carry out the study protocol as well as to write the text and draw the figures.

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