THERAPEUTIC ADVANCES in
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Original Research

Real-life therapeutic effects of beclomethasone dipropionate/formoterol fumarate/glycopyrronium combined triple therapy in patients with chronic obstructive pulmonary disease

Corrado Pelaia, Giada Procopio, Fioramante Lello Rotundo, Maria Rosaria Deodato, Anna Ferrante Bannera, Francesco Giuseppe Tropea, Anna Cancelliere, Alessandro Vatrella and Girolamo Pelaia

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Abstract

Background: The small airway disease has been recognized as a central feature of chronic obstructive pulmonary disease (COPD). Triple fixed combination beclomethasone dipropionate/formoterol fumarate/glycopyrronium (BDP/FF/G) is provided as a pressurized single-dose inhaler based on an extra-fine formulation, which has been approved for patients with COPD experiencing frequent disease exacerbations.

Methods: The aim of our real-life single-center observational study was to investigate, in 22 patients with COPD, the effects of BDP/FF/G on lung function, respiratory symptoms, health status, and exacerbation rate. Several clinical and lung functional parameters were evaluated at baseline and after 12 months of treatment with combined inhaled triple therapy.

Results: With respect to baseline, after 12 months of treatment with BDP/FF/G, significant changes were recorded with regard to forced expiratory flow at 75% of forced vital capacity (FVC) ($p < 0.01$), forced expiratory flow at 50% of FVC ($p < 0.01$), forced expiratory flow at 25% of FVC ($p < 0.05$), and forced mid-expiratory flow between 25% and 75% of FVC ($p < 0.01$). Moreover, we observed reductions of total resistance ($p < 0.01$), effective resistance ($p < 0.01$), and effective specific resistance ($p < 0.01$). In the same period, residual volume diminished ($p < 0.01$) and forced expiratory volume in 1 s increased ($p < 0.01$). Moreover, in a subgroup of 16 patients, an enhancement of diffusion lung capacity ($p < 0.01$) was also detected. These functional results were paralleled by concomitant clinical effects, as evidenced by the improvements of modified British Medical Research Council (mMRC) dyspnea scale ($p < 0.001$), COPD Assessment Test (CAT) score ($p < 0.0001$), and COPD exacerbations ($p < 0.0001$).

Conclusion: In conclusion, the valuable findings of our observational study consist in the corroboration in a real-life context of the therapeutic effects evidenced by randomized controlled trials with regard to the use of the triple inhaled BDP/FF/G therapy in patients with COPD.

Keywords: airway resistance, COPD, exacerbations, small airway disease, triple inhaled therapy

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Correspondence to:
Corrado Pelaia
Department of Health Sciences, Campus Universitario 'S. Venuta', University 'Magna Græcia' of Catanzaro, Viale Europa – Località Germaneto, 88100 Catanzaro, Italy.
pelaia.corrado@gmail.com

Giada Procopio
Fioramante Lello Rotundo
Maria Rosaria Deodato
Anna Ferrante Bannera
Francesco Giuseppe Tropea
Anna Cancelliere
Girolamo Pelaia
Department of Health Sciences, Campus Universitario 'S. Venuta', University 'Magna Græcia' of Catanzaro, Catanzaro, Italy

Alessandro Vatrella
Department of Medicine, Surgery and Dentistry, University of Salerno, Fisciano, Italy

Introduction

The importance of peripheral airways in the pathophysiology and clinical manifestations of chronic obstructive pulmonary disease (COPD) makes them a key target of long-term pharmacological approaches.[1,2] It is well known that patients with COPD benefit from inhaled therapies which can relieve symptoms, reduce exacerbations and hospitalizations,[3,4] as well as increase airway caliber,[5] decrease lung hyperinflation,[6] and also improve exercise tolerance and overall quality of life. In clinical practice, inhaled triple therapy is widely prescribed as an intensive pharmacologic care for patients with COPD, who are symptomatic and continue to experience exacerbations despite maintenance treatment including one or two separate inhalers.

Many studies in patients with severe COPD have shown that triple therapy, consisting of an inhaled corticosteroid (ICS) plus a long-acting β_2-adrenergic agonist (LABA) and a long-acting muscarinic receptor antagonist (LAMA), is more effective than double bronchodilation in order to lower annual exacerbation rate and improve lung function.[7–17] However, until a few years ago, triple inhalation therapy was delivered through several devices, used more than once a day.[18,19] More recently, combined inhaled treatments have been developed that contain an ICS, a LABA, and a LAMA in one device. These inhalers offer many advantages, even when it comes to treatment adherence. Triple combination therapies, assembled in a single inhaler, include beclomethasone dipropionate/formoterol fumarate/glycopyrronium (BDP/FF/G), fluticasone furoate/umeclidinium/vilanterol (FLF/UMEC/VI), and budesonide/glycopyrronium/formoterol (B/G/F). Indeed, simultaneous administration of these three drugs with different mechanisms of action can optimize their positive interactions in the airways. The triple fixed combination BDP/FF/G is provided as a pressurized single-dose inhaler (pMDI) based on an extra-fine formulation, which has been approved for maintenance treatment of adult patients with moderate-to-severe COPD, inadequately controlled by either ICS/LABA or LABA/LAMA associations. BDP/FF/G was developed through a clinical program consisting of 18 studies enrolling more than 8000 patients. Three large phase III trials, namely TRILOGY,[20] TRINITY,[21] and TRIBUTE,[22] demonstrated that in patients with COPD who have a history of previous exacerbations, this triple fixed combination is superior to ICS/LABA, LABA/LAMA, or LAMA alone in terms of improvement of lung function and prevention of COPD exacerbations. In these studies, the BDP/FF/G combination also induced a significant and consistent amelioration of quality of life, as assessed by the Saint George Respiratory Questionnaire (SGRQ). In particular, BDP/FF/G is an extra-fine formulation with a median aerodynamic diameter (MMAD) $<2\,\mu m$,[23] designed to reach both large bronchi and small bronchioles, the latter defined as peripheral airways $<2\,mm$ in diameter.[24] In fact, small airway dysfunction (SAD) plays a pivotal role in the pathogenesis of COPD, thus being considered as a functional hallmark of this disease. In patients with COPD, inflammation is predominantly localized in the small airways, and common inhaled therapies (bronchodilators and ICS) may not achieve a good deposition in the peripheral airways.[25] Progression of airflow limitation in COPD is concomitant with the presence of inflammatory cells (mainly polymorphonuclear granulocytes, macrophages, and lymphocytes) and with the thickening of small airway wall.[26] In patients with severe COPD, small airway obstruction is correlated with early death.[27] Therefore, the extra-fine formulation of BDP/FF/G combination can potentially treat small airway impairment and improve disease outcomes. Indeed, a high performance of currently available extra-fine formulations can significantly contribute to effectively target the main site of COPD development and progression.

The heterogeneity of airflow limitation, especially with regard to the increase in peripheral resistance, significantly contributes to the circadian variability of respiratory symptoms. BDP/FF/G is administered twice a day, thus guaranteeing bronchodilation over 24 h and counteracting the impact of morning and night symptoms. Another key requirement to achieve COPD treatment goals is adherence to inhaled therapies. Unsatisfactory adherence to inhaled drugs is very common in patients with COPD, especially when multiple devices are utilized.[28] The use of a single inhaler device, which contains the pharmacological agents responsible for both bronchodilation and anti-inflammatory action, can greatly facilitate adherence to inhaled therapy, thus contributing to improve clinical outcomes.

The effects of the fixed combination BDP/FF/G on patient quality of life, adherence, and clinical outcomes have not been fully evaluated in a real-life COPD population. Indeed, current scientific literature lacks real-world experiences related to the use of BDP/FF/G by patients with COPD. Therefore, the aim of our real-life single-center observational study was to investigate, in patients with COPD, the effects of BDP/FF/G triple inhaled therapy on respiratory symptoms, health status, lung function, and exacerbation rate.

Methods

In this real-life single-center study, 22 patients with COPD on treatment with the single inhaler therapy BDP/FF/G (87/5/9 μg) were evaluated at the Respiratory Unit of 'Magna Græcia' University Hospital of Catanzaro, Italy. COPD was diagnosed in accordance with Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations.[29] Lung function tests were carried out according to American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines[30] by Master Screen Pulmonary Function Testing System and Master Screen Body (Jaeger, Germany). All FEV_1 values reported in our study refer to post-bronchodilator assessments. No patient exhibited relevant airflow improvement after bronchodilator reversibility testing. Of course, the typical features of airflow limitation in COPD make it very difficult for these patients to reliably repeat and reproduce the spirometric maneuvers required to perform inspiratory forced vital capacity (FVC). Measurement of diffusion lung capacity for carbon monoxide (DLCO) was performed as established by ERS/ATS standards for single-breath carbon monoxide uptake in the lung, and its level was corrected for the 'anemia effect' taking into account the hemoglobin value. Therefore, diffusion lung capacity was evaluated as corrected single-breath DLCO (DLCOcSB).[31]

At baseline, all enrolled patients were regularly taking either ICS/LABA or LAMA/LABA combinations, but experienced frequent COPD exacerbations, persistent breathlessness, and exercise limitation. BDP/FF/G was prescribed according to current eligibility indications and was taken at the dosage of two inhalations every 12 h. Previously administered inhaled therapies, also including either short-acting β_2-adrenergic agonists (SABA) or LABA, were discontinued.

Forced expiratory flow at 75% of FVC (FEF_{75}), forced expiratory flow at 50% of FVC (FEF_{50}), forced expiratory flow at 25% of FVC (FEF_{25}), as well as forced mid-expiratory flow between 25% and 75% of FVC (FEF_{25-75}) were evaluated at baseline and after 12 months of treatment with BDP/FF/G. We also assessed the effects of BDP/FF/G in the same 1-year period on airway resistance, considering total resistance (R_{tot}), effective resistance (R_{eff}), and effective specific resistance (sR_{eff}). Moreover, total lung capacity (TLC), inspiratory capacity (IC), residual volume (RV), FVC, forced expiratory volume in 1 s (FEV_1), peak expiratory flow (PEF), and DLCOcSB were measured. In addition, modified British Medical Research Council (mMRC) questionnaire score, COPD Assessment Test (CAT) score, and the number of COPD exacerbations were recorded. All aspects of patient history were investigated by direct on-site surveys, performed at baseline and after 12 months, as well as by monthly telephone interviews. This approach allowed us to quite effectively verify both adherence and device technique. We also evaluated drug safety and tolerability through a monthly telephone call, investigating whether patients had experienced infections or any worsening of health condition.

Statistical analysis was performed using Prism Version 9.3.1 (GraphPad Software Inc., San Diego, CA, USA). Data were expressed as mean ± standard deviation (SD) if normally distributed, otherwise as median values with interquartile range (IQR). The Anderson–Darling test was applied to investigate whether data were normally distributed. Student's *t* test or Mann–Whitney *U* test were used to compare variables, when appropriate. A p value less than 0.05 was considered to be statistically significant.

This observational study satisfied the standards of Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki. Furthermore, informed consent was obtained from all patients. Our investigation was also conducted according to what stated by the local Ethical Committee of Calabria Region (Catanzaro, Italy; document no. 263 – 23 July 2020).

Table 1. Baseline patient characteristics.

Age, mean (± SD), years	65.82 (± 8.02)
Male gender, *N* (%)	18 (81.8)
Female gender, *N* (%)	4 (18.2)
Weight, mean (± SD), kg	70.91 (± 15.80)
Height, mean (± SD), cm	166.5 (± 5.26)
BMI, median (IQR), kg/m^2	23.50 (22.00–29.25)
FEV_1, mean (± SD), % predicted	43.91 (± 14.34)
FEV_1/FVC, mean (± SD), %	46.59 (± 11.71)
RV, mean (± SD), % predicted	168.2 (± 45.10)
FEF_{25-75}, median (IQR), % predicted	29.00 (15.75–35.75)
Smokers and ex-smokers, *N* (%)	22 (100)
On treatment with ICS/LABA, *N* (%)	13 (59.1)
On treatment with LAMA/LABA, *N* (%)	9 (40.9)
COPD exacerbations, mean (± SD), *N*	5.14 (± 1.35)

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

Results

A total of 22 patients (18 males and 4 females) were enrolled. They were characterized by a mean age of 65.82 ± 8.02 years and a median body mass index (BMI) of 23.50 (22.00–29.25) kg/m^2. Median baseline FEF_{25-75} was 29.00 (15.75–35.75)% of predicted value. Mean baseline RV and FEV_1 were 168.2% ± 45.10% of predicted value and 43.91% ± 14.34% of predicted value, respectively. Baseline characteristics of the recruited subjects are summarized in Table 1.

After 12 months of treatment with BDP/FF/G, FEF_{75} increased from 1.79 ± 1.17 L/s to 2.23 ± 1.41 L/s ($p < 0.01$), FEF_{50} enhanced from 0.74 ± 0.53 L/s to 0.93 ± 0.61 L/s ($p < 0.01$), and FEF_{25} changed from 0.25 ± 0.10 L/s to 0.33 ± 0.20 L/s ($p < 0.05$) (Figure 1). These results were associated with a concomitant improvement of FEF_{25-75}, which in comparison with baseline value of 0.58 ± 0.31 L/s increased to 0.74 ± 0.42 L/s ($p < 0.01$) (Figure 1).

With regard to the effects of BDP/FF/G on airway resistance, 1 year after the first inhalation of BDP/FF/G, the mean value of R_{tot} reduced from 0.66 ± 0.29 kPa s/L to 0.53 ± 0.27 kPa s/L ($p < 0.01$), R_{eff} diminished from 0.59 ± 0.26 kPa s to 0.48 ± 0.24 kPa s ($p < 0.01$), and sR_{eff} decreased from 2.89 ± 1.52 kPa s to 2.42 ± 1.58 kPa s ($p < 0.01$) (Figure 2).

BDP/FF/G had a relevant effect on lung hyperinflation; indeed, during the study period, RV changed from 3.91 ± 1.09 L to 3.48 ± 1.10 L ($p < 0.01$) (Figure 3). RV reduction was paralleled by a concomitant improvement of FEV_1, which in comparison to the baseline value of 1.16 ± 0.43 L enhanced to 1.36 ± 0.56 L ($p < 0.01$) (Figure 3). IC increased from 1.78 ± 0.69 L to 1.99 ± 0.72 L ($p < 0.05$) (Figure 3). However, during the 1-year follow-up period, we did not detect statistically significant changes in the mean values of TLC (6.26 ± 1.24 L *versus* 6.23 ± 1.32 L, $p = 0.84$), FVC (2.11 ± 0.64 L *versus* 2.28 ± 0.65 L, $p = 0.06$), and PEF (3.68 ± 1.38 L/s *versus* 4.06 ± 1.81 L/s, $p = 0.08$) (Figure 3).

In 16 out of 22 patients, DLCOcSB was also measured at baseline and 1 year after the beginning of BDP/FF/G treatment. We found that DLCOcSB enhanced from 3.55 ± 1.46 mmol/min/kPa to 4.01 ± 1.78 mmol/min/kPa ($p < 0.01$) (Figure 4).

The functional impact of triple combined inhaled therapy was associated with considerable clinical effects on COPD symptoms and health status. Indeed, after 12 months of treatment with BDP/FF/G, mMRC dyspnea scale and CAT score consistently improved from 3.14 ± 0.71 to 2.13 ± 1.24 ($p < 0.001$) and from 25.45 ± 8.34 to 17.27 ± 8.21 ($p < 0.0001$), respectively (Figure 5). Moreover, the number

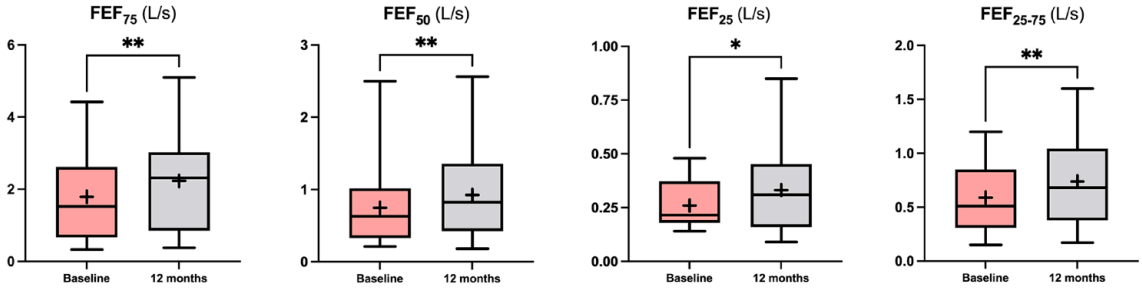

Figure 1. Effects of 12-month treatment with BDP/FF/G on FEF_{75}, FEF_{50}, FEF_{25}, and FEF_{25-75}.
The '+' symbol is plotted at the mean. The line in the middle of the box indicates the median value; the box extends from the 25th to 75th percentile. Whiskers express the highest and the lowest values.
BDP/FF/G, beclomethasone dipropionate/formoterol fumarate/glycopyrronium; FEF_{25}, forced expiratory flow at 25% of forced vital capacity; FEF_{25-75}, forced mid-expiratory flow between 25% and 75% of forced vital capacity; FEF_{50}, forced expiratory flow at 50% of forced vital capacity; FEF_{75}, forced expiratory flow at 75% of forced vital capacity.
*$p < 0.05$.
**$p < 0.01$.

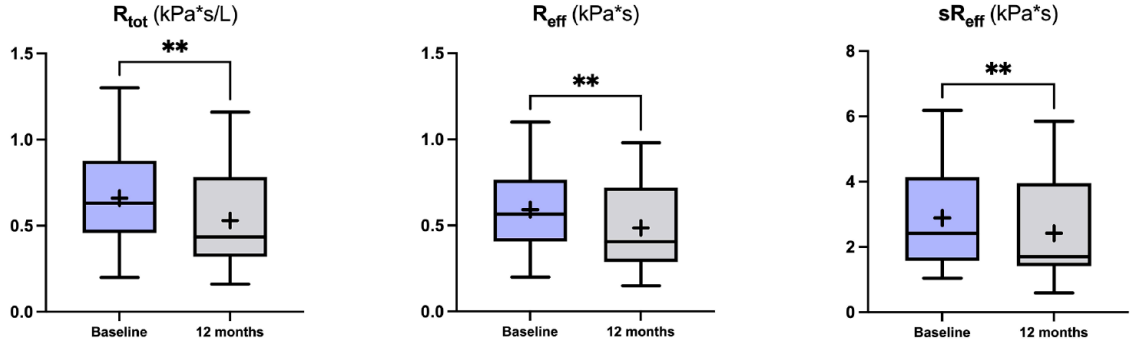

Figure 2. Effects of 12-month treatment with BDP/FF/G on R_{tot}, R_{eff}, and sR_{eff}.
The '+' symbol is plotted at the mean. The line in the middle of the box indicates the median value; the box extends from the 25th to 75th percentile. Whiskers express the highest and the lowest values.
BDP/FF/G, beclomethasone dipropionate/formoterol fumarate/glycopyrronium; R_{eff}, effective resistance; R_{tot}, total resistance; sR_{eff}, effective specific resistance.
**$p < 0.01$.

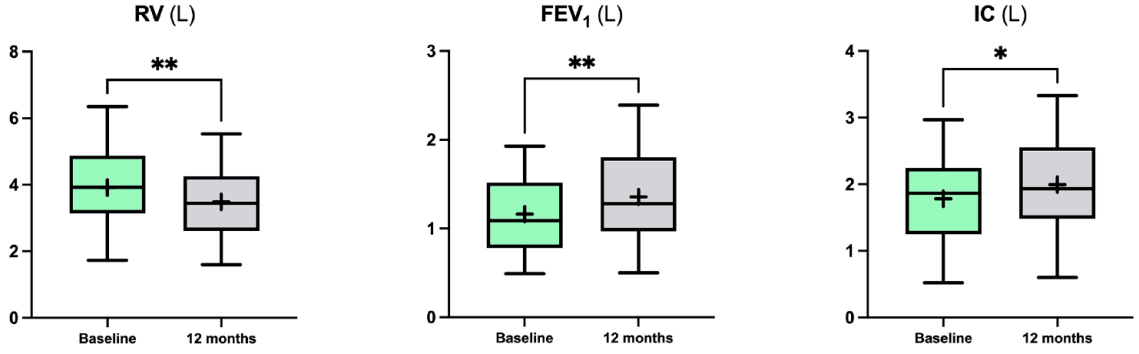

Figure 3. Effects of 12-month treatment with BDP/FF/G on RV, FEV_1, and IC.
The '+' symbol is plotted at the mean. The line in the middle of the box indicates the median value; the box extends from the 25th to 75th percentile. Whiskers express the highest and the lowest values.
BDP/FF/G, beclomethasone dipropionate/formoterol fumarate/glycopyrronium; FEV_1, forced expiratory volume in 1 s; IC, inspiratory capacity; RV, residual volume.
*$p < 0.05$.
**$p < 0.01$.

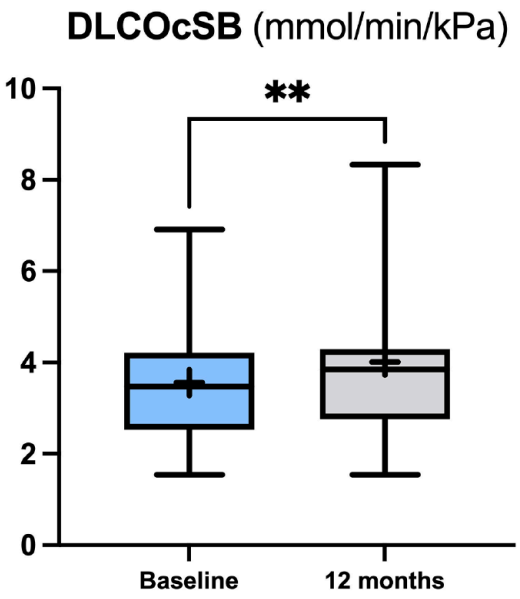

Figure 4. Effect of 12-month treatment with BDP/FF/G on DLCOcSB.
The '+' symbol is plotted at the mean. The line in the middle of the box indicates the median value; the box extends from the 25th to 75th percentile. Whiskers express the highest and the lowest values.
BDP/FF/G, beclomethasone dipropionate/formoterol fumarate/glycopyrronium; DLCOcSB, corrected single-breath diffusion lung capacity for carbon monoxide.
$^{**}p < 0.01$.

of COPD exacerbations experienced in the previous year significantly decreased from 5.14 ± 1.35 to 3.31 ± 1.49 ($p < 0.0001$) (Figure 5).

Discussion

In this real-life experience, the triple inhaled therapy, consisting of a device delivering BDP/FF/G twice a day, significantly decreased respiratory symptoms and exacerbation rate, as well as improved lung function. In particular, our results show that the aforementioned triple therapy remarkably increased FEV_1, FEF_{25-75}, FVC, IC, and PEF, and also reduced RV. In a subset of patients, this combined inhaled treatment also improved DLCOcSB. With regard to such extensive effects on several functional parameters, a plausible explanation can rely on the effective therapeutic action exerted by BDP/FF/G extra-fine formulation on peripheral airways. Indeed, this is the lung district where the pathologic process underlying COPD develops and progresses. Such considerations are very important, given the crucial role played by SAD in both clinical and functional manifestations of COPD.[1,32]

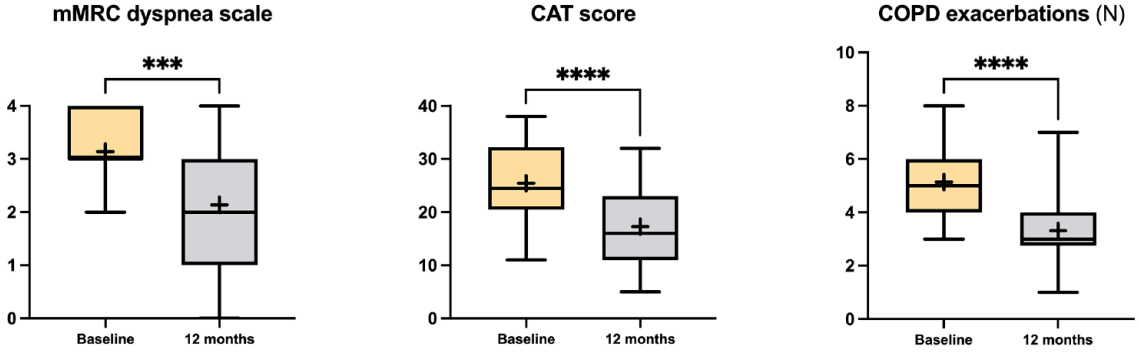

Figure 5. Effects of 12-month treatment with BDP/FF/G on mMRC dyspnea scale, CAT score, and COPD exacerbations. With regard to COPD exacerbations, baseline values refer to the number detected within 12 months before enrollment.
The '+' symbol is plotted at the mean. The line in the middle of the box indicates the median value; the box extends from the 25th to 75th percentile. Whiskers express the highest and the lowest values.
BDP/FF/G, beclomethasone dipropionate/formoterol fumarate/glycopyrronium; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; mMRC, modified British Medical Research Council.
$^{***}p < 0.001$.
$^{****}p < 0.0001$.

When compared with non-extra-fine preparations in patients with moderate-to-severe COPD, the extra-fine formulation of BDP/FF/G is characterized by a better intrapulmonary drug deposition, leading to a significant improvement in static lung volumes, associated with a reduced extra-thoracic drug accumulation.[33,34] This observation supports other findings, indicating that in patients with moderate-to-severe airflow limitation, exposure to relatively low doses of an extra-fine formulation of beclomethasone dipropionate prevented COPD exacerbations to the same extent of higher dosages of non-extra-fine fluticasone propionate.[35] Hence, the results of our real-life study probably depend on the homogeneous distribution of extra-fine BDP/FF/G along the entire respiratory tree from large to small airways. In this regard, we herein demonstrate in a real-world context that, with respect to previous treatments, extra-fine BDP/FF/G not only increased FEV_1, as already reported by randomized controlled trials (RCTs; TRINITY, TRILOGY, TRIBUTE), but also improved other relevant functional parameters. In particular, in our real-life experience, BDP/FF/G significantly reduced lung hyperinflation, as documented by the relevant RV decrease, associated with a specular IC increase. Such a lung deflation elicited by BDP/FF/G triple therapy is a likely consequence of the enhanced caliber of small airways, as suggested by our results referring to the significant FEF_{25-75} increment. In fact, the obstruction of peripheral airways is the main pathophysiologic determinant of defective expiratory flow and the subsequent intra-alveolar air trapping.[36] In comparison with FEF_{25-75}, oscillometry is a better method to assess small airway caliber; however, this technique is not often used in daily clinical practice. It is thus logical to speculate that the powerful anti-inflammatory action exerted at the bronchiolar level by extra-fine beclomethasone diproprionate can be strongly potentiated by the effective relaxation of small airway smooth muscle induced by the synergistic effects of extra-fine formoterol and glycopyrronium. Overall, such a combined pharmacologic activity can lead to a marked small airway enlargement, which facilitates expiratory airflow and decreases air trapping/lung hyperinflation. Because dyspnea and exercise intolerance experienced by COPD patients are strictly linked to lung hyperinflation, it can be argued that both mMRC and CAT score improvements detected in our study are dependent on pulmonary deflation elicited by BDP/FF/G. In a recent study carried out by Crisafulli *et al.*,[37] a strong relationship between SAD and CAT score was demonstrated, thereby reflecting SAD involvement in the health status of patients with COPD. CAT score can be reliably used in daily clinical practice to assess the impact of COPD symptoms on the risk of developing severe disease exacerbations. This makes it easier to match therapies and patients on the basis of their individual needs. In addition, lung hyperinflation is also implicated in the development of COPD exacerbations.[38] Indeed, when compared with the stable clinical stages of COPD, disease exacerbations are characterized by a further worsening of air trapping, due to escalation of bronchoconstriction and airway inflammation. Therefore, the improvement in lung hyperinflation manifested by our patients under treatment with BDP/FF/G can also contribute to prevent COPD exacerbations. Our findings show that the annual rate of COPD exacerbations significantly decreased, even if the absolute number remained quite high. However, differently from the period preceding the BDP/FF/G treatment, no exacerbation required hospitalization because of its severity.

Moreover, we noticed that BDP/FF/G significantly ameliorated DLCOcSB, although some of our patients were not capable of correctly performing this important functional test. Such a relevant result of BDP/FF/G treatment could be explained by considering that bronchodilation and lung deflation improve the dynamics of pulmonary ventilation. Indeed, the consequent expansion of air surface might increase the blood/gas exchange area, thus enhancing the diffusion capacity of lungs. This finding further corroborates our previous observations referring to similar effects exerted by FLF/UMEC/VI inhaled triple therapy.[39]

Taken together, the results of this real-life investigation suggest that the utilization of BDP/FF/G in patients with COPD maximizes the positive pharmacologic interaction occurring between LABA and LAMA, as well as between LABA and ICS. In particular, LABA and LAMA exert complementary and synergistic bronchodilating actions, originating from the reciprocal potentiation of muscarinic receptor antagonism, implemented by LAMA, and cAMP-dependent functional antagonism of airway smooth muscle contraction,

induced by LABA.[40] The cAMP signaling pathway, activated by β_2-adrenergic receptor stimulation, also potentiates the migration from cytoplasm to the nucleus of the activated glucocorticoid receptor, thus enhancing the anti-inflammatory properties of corticosteroids. These latter drugs in turn enhance the transcriptional rate of the gene encoding the β_2-adrenergic receptor, whose density on target airway smooth muscle cells is thus up-regulated by corticosteroids.[41]

By analogy with all other real-life single-center investigations, our present study is also characterized by some unavoidable limitations, including the small size of patient population, and the absence of both a control arm and a randomization procedure. Moreover, peripheral blood eosinophil counts, which are very useful biomarkers for ICS prescription, were not available for most enrolled participants. Furthermore, because of the higher prevalence of COPD among men in Southern Italy, our study included a small number of female patients. Conversely, we think that the main strength of the present clinical investigation is the real-world setting, which also allowed us to periodically verify the satisfactory degree of patient adherence and device technique, frequently monitored before and during the study period. The latter features did not change between the beginning and the end of our observation.

In conclusion, the valuable findings of our real-life observational study consist in the corroboration, within the context of clinical practice, of the positive therapeutic effects evidenced by RCT with regard to the use of the triple inhaled BDP/FF/G therapy in patients with COPD. In particular, the beneficial actions exerted on small airways by extra-fine BDP/FF/G bettered airflow limitation, pulmonary hyperinflation, and lung diffusing capacity. These functional effects explain our results referring to remarkable improvements in clinical symptoms and COPD exacerbations.

Declarations

Ethics approval and consent to participate

This study was carried out in agreement to what decided by the local Ethical Committee of Calabria Region (Catanzaro, Italy; document no. 263 – 23 July 2020). Written informed consent to publish this paper has been obtained from all subjects involved in the study.

Consent for publication

Study participants provided their informed consent to publish the data collected during the investigation period.

Author contributions

Corrado Pelaia: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Validation; Visualization; Writing – original draft; Writing – review & editing.

Giada Procopio: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing – original draft.

Fioramante Lello Rotundo: Conceptualization; Data curation; Investigation; Validation; Visualization; Writing – original draft.

Maria Rosaria Deodato: Conceptualization; Data curation; Investigation; Methodology; Validation; Visualization.

Anna Ferrante Bannera: Conceptualization; Data curation; Investigation; Methodology; Validation; Visualization.

Francesco Giuseppe Tropea: Conceptuali_ zation; Data curation; Investigation; Methodology; Validation; Visualization.

Anna Cancelliere: Conceptualization; Data curation; Investigation; Methodology; Validation; Visualization.

Alessandro Vatrella: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Validation; Visualization; Writing – review & editing.

Girolamo Pelaia: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Validation; Visualization; Writing – review & editing.

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Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

The data presented in this study are available on request from the corresponding author.

ORCID iDs

Corrado Pelaia https://orcid.org/0000-0002-4236-7367

Giada Procopio https://orcid.org/0000-0001-5148-3610

Girolamo Pelaia https://orcid.org/0000-0001-9288-8913

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