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ORIGINAL RESEARCH

Managing Small Airways Dysfunction in COPD Patients in Real Life Under Fixed Triple Combination of Beclomethasone/Formoterol/Glycopyrronium: The MASCOT Real World Evidence Study

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Introduction: The efficacy of the fixed extrafine combination of beclomethasone/formoterol/glycopyrronium (BDP/FF/G 87/5/9 μg) has been evaluated in randomized controlled trials of patients with chronic obstructive pulmonary disease (COPD). However, only few data exist on its effectiveness on small airways dysfunction (SAD).

Methods: The MASCOT (MAnaging Small airways dysfunction in COPD patients in real life on the fixed Triple combination of BDP/FF/G 87/5/9 μg pMDI) prospective observational study evaluated the effectiveness of this combination on SAD in a period of 4 weeks, after direct switch from long-acting β_2-agonists (LABA) and long-acting muscarinic antagonists (LAMA) in COPD patients with SAD (forced expiratory flow at 25–75% of the vital capacity, FEF25-75% <60% predicted). The primary endpoint was improvement in R5-19 in oscillometry; secondary endpoints included other oscillometry parameters, lung function and health status (COPD assessment test-CAT, Saint-George's Respiratory Questionnaire-SGRQ).

Results: Between May 2022 and July 2023 we recruited 93 COPD patients (mean age 68.5 years, 82% men) with forced expiratory volume in 1 second (FEV_1, mean ± SD) 1.53 ± 0.47L (53.4 ± 14.5% predicted) and small airways dysfunction (FEF25-75% predicted 27.7 ± 15.4%). We observed statistically significant improvement in R5-19 between baseline (V1) and follow-up (V2) visits [median (IQR) V2 0.70 (0.41–1.10) vs V1 0.90 (0.60–1.83); mean change (95% CI) −0.49, −0.66 to −0.33 cmH_2O/L/sec, $p < 0.0001$). There were improvements in multiple parameters, including FEF25-75% (3.43, 1.20% to 5.66%, $p = 0.0005$), FEV_1 (0.142, 0.078 to 0.205 L, $p < 0.0001$) and RV/TLC (−6.09, −9.61% to −2,56% predicted, $p < 0.0001$), as well as improvement in CAT score −4.09 (−5.09 to −3.08) και SGRQ total score (−8.75, −11.58 to −5.93 points, $p < 0.0001$).

Conclusion: Extrafine triple therapy improved SAD and spirometric parameters, leading to improvement in health status at 4 weeks. These results need to be confirmed in longer studies.

Keywords: small airways, oscillometry, COPD, triple therapy

Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogenous progressive disease which affects the airways and/or the lung parenchyma, leading to impaired lung function and chronic respiratory symptoms.[1] COPD is a major cause of morbidity and mortality worldwide, affecting more than 300 million people globally, being the third cause of death in

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2019.[2] Increasing disease awareness and ongoing research aims to improve prevention and develop evidence-based treatment strategies.[3,4] Dual bronchodilation with a long-acting β_2-agonist (LABA) plus a long-acting muscarinic antagonist (LAMA) is considered the basis of pharmacological management of COPD and comprises the preferred initial approach by GOLD recommendations.[3] LABA/LAMA combinations increase lung function, reduce symptoms, improve quality of life and lower future exacerbation risk.[5] Nevertheless, a significant proportion of COPD patients will benefit additionally from triple therapy that includes inhaled corticosteroids (ICS).[6] Fixed triple combinations (LABA/LAMA/ICS) in a single device have been shown to reduce exacerbations and COPD related hospitalizations, improve lung function and quality of life compared to dual bronchodilation (LABA/LAMA).[7–9]

Small airways dysfunction (SAD) represents a fundamental pathophysiologic element of COPD.[10–12] Evidence of SAD has been shown in all COPD stages, especially in more advanced disease, while SAD presence has been related to symptom severity,[13] and increased risk of frequent exacerbations.[14] SAD may be difficult to assess and many methods have been developed, with different availability, complexity and reproducibility.[15] FOT is a novel, easy technique evaluating proximal and distal airway function without performing a forced expiratory maneuver. This has a particular utility in children, the elderly, and in patients with severe respiratory disease or specific contraindications.[16] Extrafine inhaled formulations have shown significant benefits on lung function measurements and increased lung deposition in peripheral airways in model studies in silico.[17] The TRILOGY,[8] TRINITY,[18] and TRIBUTE[19] studies have provided evidence of superiority of extrafine triple therapy via pressurized metered-dose inhaler (pMDI) versus LABA/ICS and LABA/LAMA in the reduction of exacerbations and improvement in lung function in patients with COPD; however, these studies did not focus on the efficacy of triple therapy on small airways dysfunction. Small clinical studies in COPD patients and smoking asthmatics have shown that ICS/LABA extra-fine formulations can improve small airway dysfunction, assessed by oscillometry and lung function parameters.[20,21] A number of real world evidence studies have been conducted with the extrafine combination of BDP/FF/G;[22–26] however, there is no data available on the early effectiveness of an extrafine fixed triple therapy on parameters evaluating small airways dysfunction in COPD patients in a real-life setting.

The MASCOT observational study was designed to investigate the effectiveness of the extrafine fixed triple combination of beclomethasone dipropionate, formoterol fumarate, and glycopyrronium on parameters evaluating small airways dysfunction parameters in COPD patients, after a switch to this treatment from dual therapy with LABA/LAMA.

Materials and Methods

Study Design and Setting

The MAnaging Small airway dysfunction in COPD patients in real life under fixed Triple combination of BDP/FF/G 87μg/5μg/9μg, Trimbow pMDI treatment) MASCOT study was a multicenter, non-interventional, prospective 4-week study of 2 visits in patients with COPD, that aimed to evaluate the early effectiveness of the extrafine fixed triple BDP/FF/G on small airways dysfunction, after a direct switch to this treatment from dual therapy with LABA/LAMA. The study was performed at 4 tertiary referral centers for COPD in Greece between May 2022 and July 2023. The study was performed in accordance with the recommendations of the Declaration of Helsinki, the International Conference of Harmonisation - Good Clinical Practice (ICH-GCP) Guidelines, the EU-Directive 2001/20 and all national requirements, and was approved by the Institutional Review Board (IRB) of the University Hospital of Ioannina. Written informed consent was obtained from all participants prior to inclusion in the study.

The decision for administration of fixed dose triple therapy was based on the treating physicians' medical judgment, before any choice to include the patients to the study. The medication was delivered with or without spacer, again based on the treating physicians' judgment, 2 puffs b.i.d. Use of short-acting β-agonists (SABA) as reliever medication was allowed, except in the morning of the visits; no other COPD medication was allowed throughout the study.

The study consisted of 2 visits: Visit V1 (baseline, Day 0) where informed consent was obtained, and recording of patients' characteristics and evaluation of eligibility was performed. Subsequently, pulmonary function testing including evaluation of small airways dysfunction was performed and health status was assessed. Training on the appropriate use of

the pMDI (with or without spacer) was performed. Visit V2 (Follow-up, Day 28 ± 3): Follow-up after, treatment change, small airways dysfunction and health status assessment were performed.

Study Population

Eligible patients were outpatients ≥40 years-old with a diagnosis of COPD by a chest physician, with a ratio of post-bronchodilator forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) of less than 0.70, a post-bronchodilator FEV_1 <80% pred and Forced Expiratory Flow at 25–75% of FVC (FEF25-75%) <60%. Patients should have a history of at least 1 exacerbation in the previous year on LABA/LAMA via dry powder inhaler (DPI). All patients were symptomatic, as defined by a COPD Assessment Test (CAT) score ≥10, had blood eosinophil count ≥100 cells/μL and were able to be trained to use properly a pMDI inhaler (with or without spacer as per physician's judgment). The decision for the initiation of treatment with single inhaler triple therapy with BDP/FF/G was made by the treating physician prior to the inclusion of patients in the study.

Key exclusion criteria were: (1) a moderate or severe COPD exacerbation (ie receiving systemic corticosteroids and/or antibiotics or need for hospitalization) in the 4 weeks prior to the screening visit; (2) asthma or other respiratory disease (eg, bronchiectasis, cystic fibrosis, interstitial lung disease or any other clinically or functionally significant lung disorder); (3) long-term oxygen therapy at home; (4) pregnancy/lactation or planned pregnancy; (5) history of hypersensitivity or contraindications to any of the components of the study drug; (6) participation in interventional study within 4 weeks prior to enrolment; or (7) refusal or inability to provide informed consent.

Assessments

The evaluation of lung function and small airways dysfunction was performed in the baseline and the follow-up visit, in the morning, with the following methods:

1. Forced Oscillometry Technique (FOT, Resmon PRO Full V3), measuring peripheral resistance (difference between resistance at 5Hz and 19Hz, R5-19), frequency resonance (Fres), area of reactance (AX), and reactance (X5).
2. Simple spirometry, including mid-expiratory flows at 75%, 50% and 25% of FVC (MEF75%, MEF50% and MEF25%, respectively) and FEF25-75%.
3. Static lung volumes by body plethysmography, including total lung capacity (TLC), residual volume (RV), and functional residual capacity (FRC).
4. Ventilation heterogeneity via single breath and multiple breath nitrogen washout (in a subgroup of patients, n = 22), including N2 Delta and lung clearance index (LCI).

The symptoms and health status of patients was evaluated with validated questionnaires: COPD assessment test (CAT)[27] and Saint George's Respiratory Questionnaire (SGRQ)[28,29] at each visit.

Endpoints

The primary endpoint of the study was improvement in small airways function at 4 weeks after treatment change, assessed by R5-19. Secondary endpoints included changes in other small airways dysfunction parameters, including impulse oscillometry parameters (Frs, AX and X5), spirometry parameters (FEF25-75%, FEV_1, FVC, FEV_1/FVC, MEF75%/50%/25%), improvement in static lung volumes (RV/TLC, RV, FRC), and improvement in ventilation heterogeneity (N2 Delta and LCI) at 4 weeks. Finally, we evaluated the change in symptoms and health status as a change in CAT (minimal clinically important difference, MCID 2 points)[30] and SGRQ (MCID 4 points).[29]

Statistical Analysis

Categorical data are presented as n, %; numerical data are presented as mean ± SD or medial (interquartile range) if normally or non-normally distributed, respectively. The calculation of the sample size was based on the primary parameter of the study R5-19 and more specifically on the change in R5-19 between baseline and after 4 weeks of treatment. Based on previous reports,[21] the sample size was estimated at 90 for a 0.07 change in R5-19, with SD 0.12,

using a 95% confidence interval (C.I.) and a precision of 0.025 (approximately the 1/3 of the change of R5-19=0.07/3). The change of R5-19 (the primary endpoint) and secondary endpoints at 4 weeks was calculated as the mean with 95% confidence intervals (CI). Comparisons between baseline Visit and Visit 2 were assessed by Mann–Whitney *U*-tests and correlations were evaluated with Spearman's rank correlation coefficient. Analyses were performed with GraphPad Prism version 10.0.0 for Mac, GraphPad Software, Boston, Massachusetts USA, www.graphpad.com). A p value of ≤0.05 was considered as statistically significant.

Results

Demographics and Baseline Characteristics

We recruited 93 patients with COPD. The demographic and spirometric characteristics at enrollment are presented in Table 1. Most of them were men, with a mean age 68.5 years, and 77% were current smokers. Patients had a mean FEV_1 of 1.53 L (53% predicted) and a history of 1.52 moderate and 0.41 severe exacerbations in the previous year; 75 patients (80.1%) of patients presented at least 1 moderate exacerbation and 38 patients (40.1%) presented at least 1 severe exacerbation.

Table 1 Demographics and Baseline Characteristics of Study Participants (n = 93)

Parameter	Value
Age (years)	68.5 ± 8.2
Sex	
Male (n, %)	76 (81.7%)
Female (n, %)	17 (17.3%)
BMI (kg/m^2)	27.1 ± 5.1
Smoking habit	
Current smokers	72 (77.4%)
Ex-smokers	21 (22.6%)
Pack-years	57.2 ± 26.7
COPD duration (years)	6.9 ± 4.9
Exacerbations in the previous year	
Moderate	1.52 ± 0.87
Severe	0.41 ± 0.51
Spirometric parameters	
FEV_1, L	1.53 ± 0.47
FEV_1% predicted	53.4 ± 14.5
FVC, L	2.82 ± 0.68
FVC, % predicted	74.4 ± 13.9
FEV_1/FVC ratio	0.54 ± 0.11
FEF25-75%, % predicted	27.7 ± 15.4

(*Continued*)

Table 1 (Continued).

Parameter	Value
CAT score	16.1 ± 11.1
SGRQ total score	34.9 ± 19.4

Note: Categorical data are presented as n, %; numerical data are presented as mean ± SD or medial (interquartile range) if normally or non-normally distributed, respectively.
Abbreviations: FEF25-75%, forced expiratory flow at 25–75% of FVC; FEV_1, forced expiratory volume in 1 sec, CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; SGRQ, Saint George's Respiratory Questionnaire.

Changes in R5-19 at 4 weeks (Primary Endpoint)

The primary endpoint was met as the R5-19 oscillometry parameter was significantly improved between the baseline (V1) and the follow-up (V2), with a mean change (95% CI) −0.49 (−0.66 to −0.33) cmH_2O / L/s ($p < 0.0001$) (Table 2 and Figure 1A).

Changes in Other Oscillometry and Pulmonary Function Parameters at 4 weeks

Changes in other oscillometry and pulmonary function parameters are shown in Table 2. Specifically, we observed significant improvements (mean changes) in AX −7.58 cmH_2O/L ($p < 0.0001$, Figure 1B) and X5 −0.99 cmH_2O/L/s ($p < 0.0001$, Figure 1C). Moreover, there were statistically significant changes in spirometry at 4 weeks compared to baseline, including a mean improvement in FEF25-75% of 3.43% predicted ($p = 0.0005$, Figure 2A), a mean improvement in FEV_1 of 0.14 L ($p < 0.0001$, Figure 2B), and a mean improvement in FVC of 0.19 L ($p < 0.0001$, Figure 2C). We also observed improvements in static

Table 2 Changes in Study Parameters Between the Baseline (V1) and Follow-up (V2) Visits

Parameter	Visit 1 Median (IQR)	Visit 2 Median (IQR)	Δ (95% CI)	p value
R5-19, cmH_2O/L/s	0.90 (0.60, 1.83)	0.70 (0.41, 1.10)	−0.49 (−0.66, −0.33)	<0.001
Fres, Hz	20.0 (12.1, 29.2)	17.10 (10.10, 21.50)	−3.45 (−5.31, −1.59)	<0.0001
AX, cmH_2O/L	15.40 (7.60, 58.70)	11.0 (6.60, 15.20)	−7.58 (−10.36, −4.80)	<0.0001
X5, cmH_20/L/s	3.30 (1.70, 9.80)	1.70 (1.30, 7.10)	−0.98 (−1.43, −0.53)	<0.0001
RV/TLC, %	63.0 (49.0–110.0)	56.0 (46.0–106).0	−6.1 (−9.61, −2.56)	<0.0001
RV, % predicted	112.0 (90.0,135.0)	106.0 (92.0,125.0)	−10.31 (−18.01, −2.61)	0.0014
FRC, % predicted	107.0 (90.0,120.0)	98.0 (89.0, 115,0)	102.6 (98.27, 106.9)	0.043
N2 Delta	555.0 (447.0, 964.0)	563.0 (397.0, 633.0)	−150.8 (−294.2, −7.44)	0.093
LCI	8.8 (6.9, 9.6)	7.2 (6.5, 8.1)	−0.85 (−1.55, −0.14)	0.143
FEV_1, L	1.55 (1.13, 1.85)	1.69 (1.37, 1.94)	0.14 (0.07, 0.20)	<0.0001
FEV_1, % predicted	54.0 (42.0, 66.0)	59.0 (49.0, 69.5)	5.16 (2.89, 7.43)	<0.0001
FVC, L	2.73 (2.43, 3.26)	3.0(2.58, 3.39)	0.19 (0.11, 0.27)	<0.0001
FEV_1/FVC	0.54 (0.43, 0.65)	0.56 (0.45, 0.64)	0.01 (−0.002, 0.03)	0.0002

(*Continued*)

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Table 2 (Continued).

Parameter	Visit 1 Median (IQR)	Visit 2 Median (IQR)	Δ (95% CI)	p value
MEF75%, % predicted	32.0 (16.0, 47.0)	36.0 (20.0, 48.0)	2.69 (−0.003, 5.38)	<0.0001
MEF50%, % predicted	28.0 (16.0, 42.0)	31.0 (18.0, 45.0)	3.79 (1.30, 6.28)	0.0003
MEF25%, % predicted	29.0 (17.0, 55.0)	29.0 (21.0, 51.0)	0.63 (−1.62, 2.89)	0.066
FEF25-75%, % predicted	28.0 (15.0, 39.0)	30.0 (17.5, 44.0)	3.43 (1.2, 5.66)	0.0005
CAT score	14.0 (11.0, 19.0)	10.0 (7.50, 13.50)	−4.08 (−5.09, −3.08)	<0.0001
SGRQ total score	31.03 (17.43, 50.44)	19.28 (14.47, 34.64)	−8.75 (−11.58, −5.93)	<0.0001

Abbreviations: AX, area of reactance; FEF25-75%, forced expiratory flow at 25–75% of FVC; FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; Fres, frequency resonance; MEF, mid-expiratory flow; LCI, lung clearance index; R5-19 (difference between resistance at 5Hz and 19Hz); SGRQ, Saint George's Respiratory Questionnaire; X5, reactance.

lung volumes, including a mean improvement in RV/TLC% of −6.1% ($p < 0.0001$, Figure 2D). Ventilation heterogeneity evaluated via multiple breath nitrogen washout (N2 Delta and LCI) did not exhibit significant change between visits in a small subgroup of patients (n = 22).

Change in CAT Score and SGRQ Total Score Between V1 and V2

Both CAT and SGRQ scores significantly improved after treatment with BDP/FF/GB by −4.09 (−5.09 to −3.08) points ($p < 0.0001$) and −8.75 (−11.58 to −5.93) points ($p < 0.0001$), respectively (Table 2, Figure 3A and B). At visit 2, 73 patients (78%) reached the MCID of 2 points for CAT, while 39 patients (42%) reached the MCID of 4 points for SGRQ.

Correlations of Improvements in R5-19 and Health Status with Functional Parameters

Correlations between changes in R5-19 (ΔR5-19) and changes in functional parameters are presented in Table 3. The improvement in R5-19 exhibited a strong correlation with the improvement in AX (r = 0.85), and modest correlations with the improvement in FEF25-75% predicted (r=−0.45) and FEV1 (r=−0.41). It also presented correlations with changes in RV/TLC, FEV_1/FVC and other oscillometry parameters.

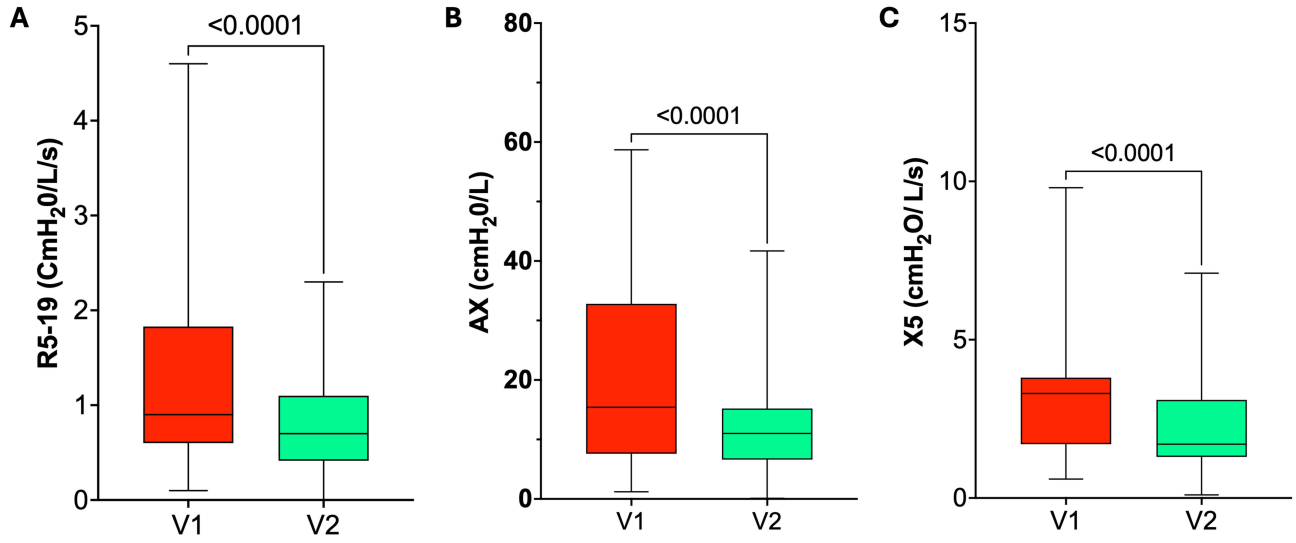

Figure 1 Change between visits in forced oscillometry measures: (**A**) R5-19, (**B**) AX and (**C**) X5.
Abbreviations: R5-19, difference between resistance at 5Hz and 19Hz; AX, area of reactance; X5, reactance.

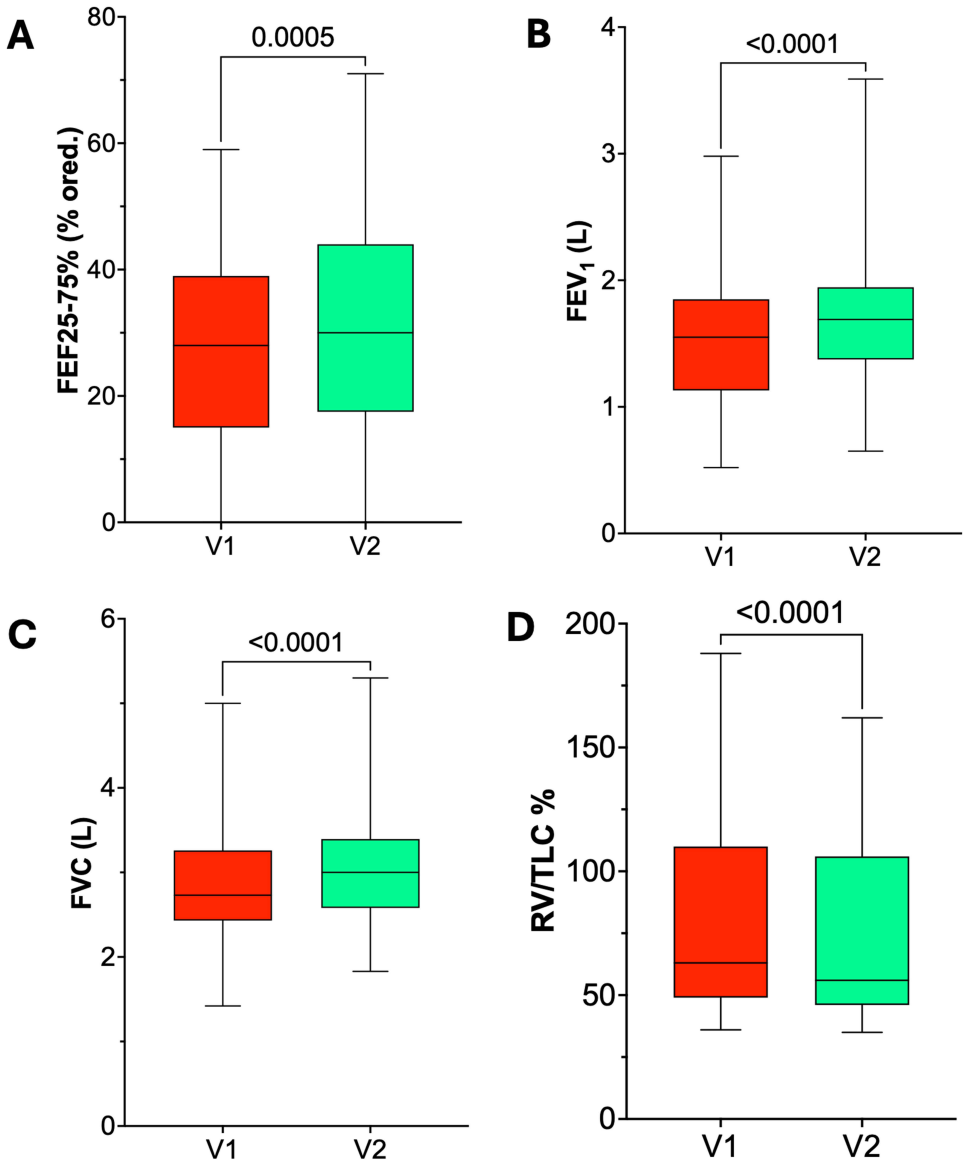

Figure 2 Change between visits in pulmonary function testing measures: (**A**) FEF25-75%, (**B**) FEV_1, (**C**) FVC, and (**D**) RV/TLC.
Abbreviations: FEF25-75%, mid-expiratory flow at 25–75%; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity.

Correlations between CAT and SGRQ changes and functional parameters are presented in Table 4. The change in CAT score correlated with improvement in R5-19 (r = 0.40), and in other oscillometry parameters, except X5, as well as with change in FEV_1 (r = −0.39), and in FEF25-75%. Improvement in SGRQ presented only a weak correlation with the change in R5-19 (r = 0.21), while there were no correlations with other SAD parameters.

Discussion

In the MASCOT study we observed significant improvements in small airways function and health status at 4 weeks after the direct switch to the extrafine fixed triple combination of BDP/FF/GB in patients symptomatic and/or exacerbating on a LABA/LAMA DPI. The study met its primary endpoint showing an improvement in the R5-19 oscillometry parameter, as well as in other indices of SAD, including FEF25-75% and RV/TLC, and additional oscillometry parameters. These improvements were accompanied by clinically relevant improvements in FEV_1 and patients' symptoms and quality of life.

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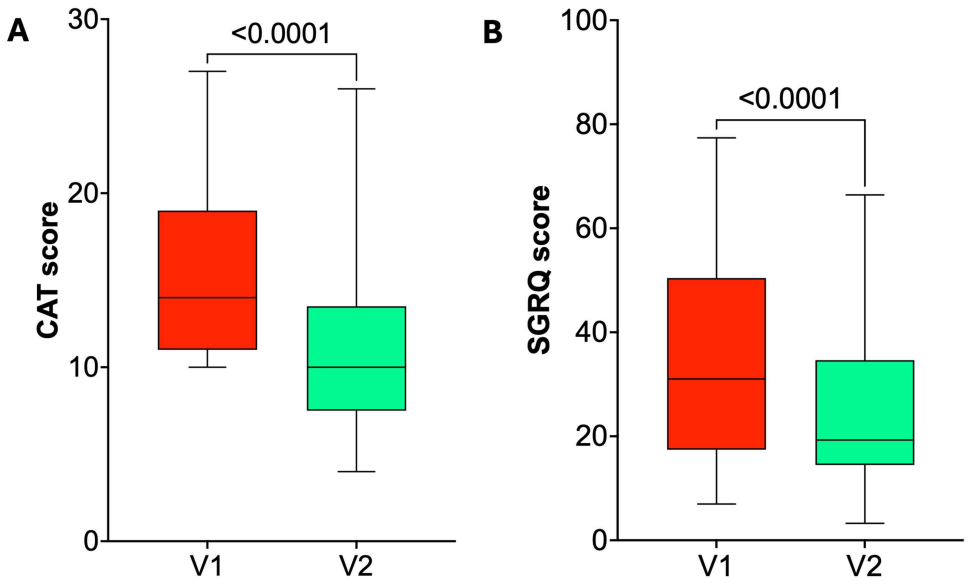

Figure 3 Change between visits in patients' health status as evaluated by (**A**) CAT score, and (**B**) SGRQ score.
Abbreviations: CAT, COPD assessment test; SGRQ, Saint George's Respiratory Questionnaire.

To our knowledge, MASCOT is the first real-life study using multiple modalities to evaluate the effectiveness of extrafine fixed triple therapy on small airways dysfunction. Small airways are highly affected in COPD, showing epithelial and subepithelial tissue thickening, reduced collagen density, mucus plugging and loss of alveolar attachments.[31] Being highly prevalent in more than three quarters of COPD patients, SAD occurrence increases with disease severity,[13] is associated with FEV_1 decline,[32] increased hyperinflation and worse health status.[13,33] Thus, prompt SAD detection and management may have preventative implications as well. Extrafine formulations have shown satisfactory access to small airways, compared to DPI formulations. Peripheral lung deposition of extrafine formulation of BDP/FF/GB in an in-silico study using functional respiratory imaging showed superiority compared with fluticasone furoate/vilanterol/umeclidinium in patients with moderate to very severe COPD, with ICS peripheral deposition being approximately three-fold greater than non extrafine particle.[34] In this study we showed that spirometry and plethysmography parameters were markedly improved within 4 weeks, while FOT was evaluated as the principal modality to assess SAD in COPD patients. No changes in ventilation heterogeneity were observed, but this may have been due to the small number of participants that these tests were performed (n = 22), as these were available in only one of the study centers. It has been recently proposed that it is important to distinguish between small airways disease and dysfunction, with the latter referring to a single functional property of a parameter, while small airways disease indicates that conditionally several functional components of airway destruction prove a specific pathophysiological phenotype of a clinically distinct disease, while small airways disease involves several functional components of airway destruction prove a specific pathophysiological phenotype of a clinically distinct disease.[35] For clarity, in the MASCOT study the term SAD represents small airways dysfunction, as we are evaluating multiple parameters that may be overlapping but are not necessarily present in all patients.

As a marker of small airways resistance, R5-19 exhibited great sensitivity in assessing the effect of extrafine triple therapy in SAD, and ΔR5-19 was associated with ΔFEF25-75% as the "gold standard" of SAD evaluation with spirometry, as well with AX, another measure of SAD. ΔR5-19 was also associated with symptomatic improvement of COPD patients, as assessed by the CAT and SGRQ scores. Limited previous reports have demonstrated that oscillometry has a role in COPD addressing functional evaluations and assessing possible treatment effects. In a cross-sectional analysis of the ECLIPSE study in COPD, impulse oscillometry was reproducible and indicative of disease severity by Global Initiative for Obstructive Lung Diseases (GOLD) stages.[36] A retrospective study, including geriatric

Table 3 Correlations Between Changes in R5-19 (ΔR5-19) and Changes (Δ) in Functional Parameters

Parameter	ΔR5-19	
	r	p
ΔFres, Hz	0.54	<0.0001
ΔAX, cmH_2O/L	0.85	<0.0001
ΔX5, $cmH_2O/L/s$	0.41	0.0007
ΔRV/TLC, %	0.26	0.009
ΔRV, % predicted	0.24	0.017
ΔFRC, % predicted	0.12	0.23
ΔFEV_1, L	−0.41	<0.0001
ΔFEV_1, % predicted	−0.38	0.0002
ΔFVC, L	−0.19	0.06
$\Delta FEV_1/FVC$	−0.44	<0.0001
ΔFEF25-75, % predicted	−0.45	<0.0001

Abbreviations: AX, area of reactance; FEF25-75%, forced expiratory flow at 25–75% of FVC; FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity; Fres, frequency resonance; R5-19 (difference between resistance at 5Hz and 19Hz); X5, reactance.

Table 4 Correlations Between Changes in CAT and SGRQ Scores and Changes (Δ) in Functional Parameters

Parameter	ΔCAT Score		ΔSGRQ Score	
	r	p value	r	p value
ΔR5-19, $cmH_2O/L/s$	0.40	<0.0001	0.21	0.04
ΔFres, Hz	0.28	0.005	0.18	0.08
ΔAX, cmH_2O/L	0.35	0.005	0.18	0.15
ΔX5, $cmH_2O/L/s$	0.10	0.43	0.03	0.81
ΔRV/TLC, %	0.11	0.26	0.12	0.23
ΔRV, % predicted	0.053	0.61	0.09	0.36
ΔFRC, % predicted	0.12	0.25	0.05	0.58
ΔFEV_1, L	−0.39	0.0001	−0.18	0.07
ΔFEV_1, % predicted	−0.38	0.0002	−0.18	0.08
ΔFVC, L	0.11	0.27	−0.18	0.09
$\Delta FEV_1/FVC$	−0.46	<0.0001	−0.25	0.01
ΔFEF25-75%, % predicted	−0.29	0.004	−0.05	0.59

Abbreviations: AX, area of reactance; FEF25-75%, forced expiratory flow at 25–75% of FVC; FEV_1, forced expiratory volume in 1 sec; FVC, forced vital capacity; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; Fres, frequency resonance; MEF, mid-expiratory flow; R5-19 (difference between resistance at 5Hz and 19Hz); SGRQ, Saint George's Respiratory Questionnaire; X5, reactance.

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(≥65 years) and advanced elderly (≥80 years) patients with COPD and healthy volunteers, showed a good performance for FOT compared to spirometry, with significant increases in resonant frequency (Fres), respiratory resistance (R5-20), and reactance (X5) seen in both groups with COPD.[37] Impulse oscillometry may be of value in detecting COPD pathological alterations early as it was able to capture symptomatic individuals with preserved spirometry.[38] Exploring relationships between peripheral airway function by impulse oscillometry, CT and spirometry in COPD patients in a cross-sectional study, R5-20 and X5 were correlated with the SGRQ and the MRC scores and these relationships were significantly stronger than FEV_1 and CT findings.[33] Also, in subjects with chronic respiratory symptoms and preserved pulmonary function, oscillometry correlated better with CAT and mMRC scores,[39] and was more sensitive to diagnose SAD than FEF 25–75%.[40]

In the MASCOT study we have shown that extrafine triple therapy remarkably improved R5-19 in a single month, while R5-19 exhibited a good correlation with symptomatic improvement assessed by CAT, compatible with FEV_1 and better than FEF25-75% and RV/TLC% indices. Moreover, R5-19 was the only SAD parameter correlated with SGRQ. A limited number of previous studies have demonstrated a role for oscillometry in evaluating treatment effects in COPD patients. In a study exploring the efficacy of the combination of indacaterol/glycopyrronium versus tiotropium in moderate to severe COPD, Molino et al found that oscillometry was more sensitive than spirometry for monitoring outcome measures of airway obstruction.[41] In a small proof of concept study adding tiotropium or aclidinium on top of ICS/LABA, peripheral airway resistance (R5–R20) significantly improved with aclidinium, while both treatments led to significant improvement in Fres but not in R5.[42] Extrafine formulation of beclomethasone/formoterol, in a small 3-month study by Pisi et al, was found to improve SAD assessed by R5-20 and RV/TLC in patients with severe COPD and the improvement correlated with CAT.[21] The association of improvement in SAD and overall in lung function parameters with patients' health status that is shown after 4 weeks of treatment in the MASCOT study further supports the role of small airways on patients' quality of life,[12] and builds on the body of evidence that improvement in patients' lung function including SAD as early as 4 weeks may have significant measurable impact on their lives.[43] As SAD may contribute to air-trapping (also evaluated by RV/TLC in our study) and pulmonary hyperinflation, the early improvement of SAD at 4 weeks may represent a plausible explanation for the improvement in health status of our patients.

The MASCOT study confirmed in a real world setting the results of the TRIBUTE randomized trial of extrafine triple therapy that showed larger improvement in FEV_1 from baseline with BDP/FF/G than with indacaterol/glycopyrronium at weeks 12 and 40, with improvements in the SGRQ total score, in exacerbating COPD patients.[19] Although an open-label switch study from LABA/LAMA, MASCOT showed an improvement of 140 mL in FEV_1, with mean improvements in the CAT and SGRQ scores of −4.08 and −8.75 points at 4 weeks, that are more pronounced than those observed in randomized trials.

Our results are in line with recently published real world data for extrafine triple therapy. The TRITRIAL study showed significantly reduced CAT total score, and improved quality of life, sleep quality and adherence to treatment, at six and twelve months in patients receiving BDP/FF/G.[22] Similar observational studies were conducted in German (The TriOptimize study)[23] and Austrian patients (TRICOP).[24] In the TRIWIN[25] and the TRIBUNE[26] real-life studies in Greek real-world settings, extrafine triple therapy achieved improved outcomes on health status, lung function and rescue medication after 24 weeks. At 6 months 79.8% of patients in TRIWIN and 85.9% in TRIBUNE reached the MCID of 2 points in CAT, whereas in our study we showed that 78% of patients reached the CAT MCID in as early as 4 weeks.

A major strength of our study is that it covers the majority of physiologic evaluations of small airways dysfunction. SAD can be evaluated also with imaging techniques (eg chest HRCT), however these are not widely used in routine clinical practice and carry certain risks for the patients. The direct switch from LABA/LAMA to extrafine triple therapy is an additional strength of MASCOT, as it evaluates patients in a real clinical setting, with minimal exclusion criteria. The 4-week duration of the study could be considered as a limitation, however our aim was to explore the prompt effect of triple therapy in functional and health status outcomes using a rigorous evaluation of SAD. A potential limitation is that the effectiveness of the extrafine triple pMDI on SAD may be blurred from the effectiveness of triple vs LABA +LAMA combinations; however, in this study we have followed standard clinical practice, as at the time of the study design and protocol development the combination of BDP/FF/G was the only formulation indicated for COPD in Greece. Another limitation is the use of the fixed FEV_1/FVC ratio of <0.70 for the diagnosis of COPD, and this may lead to

potential underdiagnosis in younger and overdiagnosis in older individuals;[44] however, our study was designed to follow standard clinical practice and recent recommendations.[3,4,45] Our study compared the effects of treatment change and reported functional and clinical changes from baseline, so it did not have a placebo arm; however, the mainstay of the study remain the objective pulmonary function and oscillometry measurements. Moreover, this is in line with ethics and good clinical practice as MASCOT included symptomatic COPD patients with a history of exacerbations. Given the small study duration and the absence of a control arm, we acknowledge that MASCOT is a hypothesis generating study that needs to be confirmed in longer controlled trials of extrafine triple versus dual or non-extrafine triple therapies, that may evaluate the association of SAD improvement with exacerbation prevention and long-lasting improvement in health status.

In conclusion, in MASCOT we showed that initiation of extrafine triple therapy after direct switch from LABA/LAMA in symptomatic or exacerbating COPD patients led to significant improvements of SAD assessed by multiple modalities, including oscillometry. This early improvement at 4 weeks in a real-life setting was also reflected in clinically important improvement in health status and quality of life of COPD patients. Our study further highlights the clinical importance of diagnosing and targeting SAD in COPD and the early effectiveness of extrafine triple therapy in this "silent" part of the airways. Our results need to be confirmed in longer studies that will evaluate the potential association of physiological improvement with exacerbation prevention and quality of life.

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Disclosure

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