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Effects of umeclidinium bromide in the management of small airway disease: a pilot study

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Abstract

Umeclidinium bromide is a long-acting muscarinic antagonist that selectively inhibits muscarinic receptors, preventing bronchoconstriction and promoting sustained bronchodilation. This study aimed to assess the bronchodilatory efficacy of umeclidinium bromide, specifically in terms of its impact on airflow limitation, exertional dyspnea, and indices of lung hyperinflation. We analyzed 50 patients (21 males, 29 females) with a mean age of 67.3 ± 9.59 years, all presenting with a preserved Tiffenau Index [forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC): $74.49 \pm 2.58\%$] but reduced forced mid-expiratory flow [forced mid-expiratory flow (FEF₂₅₋₇₅): $37.85\% \pm 7.04\%$]. Patients exhibited an increased Motley Index ratio ($135.24 \pm 9.78\%$), a mean FEV1 of 2.00 ± 0.57 L, an FVC of 2.70 ± 0.57 L, an airway resistance (Raw) of $225.52 \pm 56.66\%$, and a total lung capacity of $98.08 \pm 8.26\%$. Functional exercise capacity was evaluated using the 6-minute walking test (6MWT), with a mean distance of 308.48 ± 31.91 m. Dyspnea severity was assessed using the modified Medical Research Council dyspnea scale (mMRC) (mean score: 1.80 ± 0.73). Post-treatment assessments demonstrated a significant increase in FVC ($p=0.04$), FEF₂₅₋₇₅ ($p<0.001$), and a significant decrease in total airway resistance ($p<0.001$), along with a marked reduction in the Motley Index ratio ($p<0.001$). Patients exhibited an increase in the distance covered during the 6MWT ($p<0.001$) and a reduction in dyspnea severity, as reflected by improvements in the mMRC scale ($p<0.001$). Umeclidinium bromide was effective in mitigating lung hyperinflation, improving exercise capacity, and reducing dyspnea.

Key words: small airway disease, umeclidinium, lung function, dyspnea, exercise.

Introduction

Recently, several novel anti-cholinergic therapies have been approved for use in chronic obstructive pulmonary disease (COPD), aiming to enhance efficacy by specifically targeting muscarinic acetylcholine receptor (mAChR) subtypes while also improving safety profiles [1]. COPD is characterized by increased parasympathetic activity, which can be partially reversed by anti-cholinergic therapy, leading to improved airflow limitation [2,3]. The ideal anti-cholinergic agent for COPD should antagonize M1 and M3 receptors while showing minimal affinity for M2 receptors, which counteract β_2 -adrenoceptor-mediated relaxation pathways.

Umeclidinium bromide is a LAMA that selectively targets M3 receptors, thereby preventing bronchoconstriction and promoting airway dilation. Its high affinity for M3 receptors results in slow dissociation, ensuring sustained bronchodilation. By blocking the M3 receptor, umeclidinium inhibits acetylcholine's effects, leading to smooth muscle relaxation and improved airflow [4,5]. Umeclidinium has been shown to reduce bronchoconstriction and alleviate symptoms in both COPD and asthma [6,7]. The effective half-life following once-daily inhalation is approximately 11 hours.

Small airways (SA), defined as tracheobronchial branches with a diameter of less than 2 mm, play a crucial role in pulmonary mechanics beyond their function as mere conduits. Their involvement in obstructive lung diseases, such as asthma and COPD, is closely associated with disease progression [8]. Physiologically, these airways exhibit laminar airflow, in contrast to the turbulent flow observed in proximal airways. As branching increases, airflow progressively decreases, reaching near-zero at the transition zone, where gas exchange occurs through passive diffusion [9]. This characteristic airflow pattern promotes the deposition of inhaled particles, rendering SA particularly susceptible to damage from irritants and inflammatory agents. Notably, in emphysema, alveolar destruction is often preceded by SA damage [10].

Small airway disease (SAD) is characterised by inflammation of the smallest bronchi and bronchioles, accompanied by cellular infiltration, goblet cell metaplasia, and fibrosis, which leads to increased wall thickness and tortuosity, thereby increasing airway resistance and causing expiratory airflow limitation, lung hyperinflation, and air trapping [11,12]. In this study, we examined a specific patient phenotype exhibiting a normal forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) ratio but reduced forced mid-expiratory flow (FEF₂₅₋₇₅), a parameter sensitive to small airway obstruction. We also assessed residual volume (RV)/total lung capacity (TLC) ratio as a marker of lung hyperinflation and evaluated exercise tolerance using the six-minute walking test (6MWT).

Importantly, small airway dysfunction may precede the development of conventional spirometric airflow obstruction and may therefore be present in symptomatic individuals with a preserved FEV₁/FVC ratio. This phenotype may be particularly relevant in individuals exposed to established respiratory risk factors, including cigarette smoke and other inhaled noxious agents. Despite preserved conventional spirometric indices, these subjects may exhibit peripheral airflow limitation, air trapping, exertional dyspnea, and impaired exercise tolerance. From a treatable-traits perspective, these findings provided the rationale for exploring whether pharmacological bronchodilation could improve lung mechanics and symptoms before overt spirometric obstruction becomes detectable.

The primary objective was to investigate the relationship between small airway changes and the bronchodilatory efficacy of umeclidinium bromide.

Materials and Methods

This retrospective observational study included patients in a stable clinical phase who were evaluated at the Respiratory Pathophysiology Unit at 'Magna Græcia University' in Catanzaro, Italy, and at 'Annunziata Hospital' in Cosenza, Italy, between January 2023 and June 2023. Patients presenting with exertional dyspnea and reduced exercise tolerance were retrospectively identified through review of clinical and pulmonary function records. Smoking exposure was recorded when available; however, detailed information regarding current versus former smoking status and cumulative tobacco exposure expressed as pack-years was not systematically available because of the retrospective study design. Pulmonary function was assessed using spirometry in accordance with European Respiratory Society guidelines [13]. Exercise tolerance was evaluated via the 6MWT, and symptoms were quantified using the modified Medical Research Council dyspnea scale (mMRC) [14]. Patients were excluded if they had experienced bronchial exacerbations in the preceding month or had other respiratory diseases or uncontrolled comorbidities, such as severe cardiovascular disease or malignancies. Conventional spirometric airflow obstruction was defined as an FEV₁/FVC ratio <0.70. However, patients meeting this criterion were not the target population of the present study. The study specifically included symptomatic patients with a preserved FEV₁/FVC ratio (≥ 0.70) but evidence of small airway dysfunction. For the purposes of this exploratory study, FEF_{25–75} <60% predicted was used as an operational marker of small airway dysfunction and RV/TLC ratio >120% as indicative of lung hyperinflation. Given the known variability and volume dependence of FEF_{25–75}, this parameter was not interpreted in isolation; patient selection

additionally required a preserved FEV₁/FVC ratio, increased RV/TLC, and exertional respiratory symptoms.

All patients with reduced FEF_{25–75}, a normal FEV₁/FVC ratio, and increased RV/TLC ratio with exertional dyspnea were treated with umeclidinium bromide (55 µg once daily) for six months. Umeclidinium was prescribed as part of routine clinical management and independently of the subsequent retrospective inclusion of patients in the study. No additional therapies were administered during this period. Smoking history was considered a relevant clinical risk factor but was not a prerequisite for treatment initiation. The decision to prescribe umeclidinium was based on the presence of respiratory symptoms together with functional evidence of small airway dysfunction and air trapping. Treatment adherence was assessed by pharmacy refill records during follow-up. Adverse events were assessed through review of medical records, in addition to spontaneously reported events occurring during the treatment period.

Functional and clinical parameters were recorded at baseline and after six months of treatment. Clinical and functional assessments were performed at baseline, before initiation of umeclidinium, and repeated after six months of treatment. At both time points, spirometric parameters included FVC, FEV₁, FEV₁/FVC, FEF_{25–75}, and PEF. Body plethysmography was used to assess total airway resistance (sR_{tot}), TLC, and RV/TLC. Exercise capacity was evaluated using the 6MWT, and dyspnea severity was assessed using the mMRC scale. Complete paired baseline and six-month data were available for all 50 patients for the variables included in the analysis.

Given the mild functional impairment, we opted for a safe and effective LAMA-based treatment as part of an institutional protocol aimed at minimizing bronchodilator use, such as salbutamol, and reducing hyperinflation. Lung function assessments were conducted using the Vmax 22 Pulmonary Function System (Sensormedics). Spirometry was performed in accordance with the 2019 American Thoracic Society/European Respiratory Society (ATS/ERS) technical standard [13]. The study was approved by the local Ethical Committee of the Calabria Region (N. 12/2018) and all participants gave written informed consent.

Statistical analysis

Statistical analysis was conducted with SPSS for Windows, version 9.0.0 (SPSS, Inc., Chicago, IL, USA). Continuous variables were summarized as mean ± standard deviation (SD) when normally distributed and as median and interquartile range (IQR) when non-normally distributed. For paired comparisons, the normality of within-subject differences was assessed

using the Shapiro–Wilk test and inspection of Q–Q plots. Normally distributed paired differences were analyzed using the paired Student's t-test, whereas non-normally distributed paired differences were analyzed using the Wilcoxon signed-rank test. A two-sided P value <0.05 was considered statistically significant.

Results

A total of 50 patients were screened, including 21 males and 29 females, with a mean age of 67.3 ± 9.59 years (Table 1). The mean Tiffenau index (FEV_1/FVC) was $74.49\% \pm 2.58\%$, while FEF_{25-75} was significantly reduced to $37.85\% \pm 7.04\%$. The RV/TLC ratio (Motley index) was elevated at $135.24\% \pm 9.78\%$, with FEV_1 recorded at 2.00 ± 0.57 L and FVC at 2.70 ± 0.57 L. All patients displayed small airway obstruction with associated air trapping. Thirty-one patients were smokers. Reduced exercise tolerance correlated with increased respiratory symptoms, as evidenced by the 6MWT distance of $308.48 \text{ m} \pm 31.91 \text{ m}$ and mMRC score of 1.80 ± 0.73 . Following umeclidinium treatment, significant improvements were noted in lung function, with an increase in FVC to 3.02 ± 0.79 L compared to 2.70 ± 0.57 L ($P = 0.04$) and FEF_{25-75} increased to $49.98\% \pm 7.46\%$ from $37.85\% \pm 7.04\%$ ($P < 0.001$) (Table 2). Hyperinflation indices improved, showing a reduction in the RV/TLC ratio to $107.43 \pm 8.53\%$ from $135.24 \pm 9.78\%$ ($P < 0.001$). Patients also experienced improved exercise tolerance, evidenced by the significant increase in 6MWT distance to $347.80 \text{ m} \pm 35.80 \text{ m}$ from $308.48 \text{ m} \pm 31.91 \text{ m}$ ($P < 0.001$) and a reduction in dyspnea, as indicated by the mMRC score of 0.62 ± 0.64 compared to 1.80 ± 0.73 ($P < 0.001$) (Table 2). Although FEV_1 improved numerically from 2.00 ± 0.57 L to 2.19 ± 0.56 L, this did not reach statistical significance. Smokers exhibited more severe small airway obstruction, as evidenced by lower FEF_{25-75} values of $33.65 \pm 3.92\%$ compared to $44.69 \pm 5.44\%$ ($P < 0.001$). No adverse effects were reported following the administration of umeclidinium.

Discussion

SA are not merely conduits for airflow; they also represent a crucial determinant of pulmonary mechanics. Lacking cartilaginous support, SA collapse during maximal expiration, leading to air trapping and the formation of residual volume (RV) [15,16]. This physiological air trapping is vital, as RV ensures the maintenance of gas exchange even under extreme conditions. However, SA dysfunction can lead to premature closure, resulting in increased RV and the development of pulmonary hyperinflation. This pathophysiological feature limits exercise

capacity and contributes to exertional dyspnea in patients with COPD [17,18]. Studies have demonstrated that small airway dysfunction (SAD) progressively worsens as COPD advances and is closely associated with an impaired quality of life (10).

SAD negatively impacts exercise-induced hyperpnea in COPD patients. It has been shown that the degree of ventilation inhomogeneity at rest, an indicator of SAD, is strongly correlated with the development of dynamic hyperinflation and ventilatory inefficiency during exercise in these patients [19,20]. Furthermore, SA dysfunction can play a role in acute asthma exacerbations, potentially leading to a severe phenomenon known as excessive bronchoconstriction [12,21]. In our study, we specifically selected umeclidinium, a muscarinic antagonist with selective activity for the M3 receptor, because it provides effective bronchodilation and symptom relief while maintaining a favourable safety profile. Clinical studies have demonstrated that both umeclidinium and tiotropium exhibit rapid association and dissociation kinetics with M2 and M3 receptors. However, the dissociation from M3 muscarinic acetylcholine receptors (mAChRs) is significantly slower than from M2 mAChRs for both drugs, with umeclidinium exhibiting a dissociation time of 82 minutes compared to 9 minutes for M2, and Tio showing 273 minutes compared to 39 minutes, respectively [22,23]. Our findings highlight the efficacy of umeclidinium in alleviating respiratory symptoms, as evidenced by a significant reduction in mMRC, and in enhancing exercise capacity, demonstrated by increased distances covered in the walking test. The reduction in dynamic hyperinflation in our patients is reflected in the significant decrease in the RV/total lung capacity (TLC) ratio and, indirectly, by the reduction in lung resistance and forced expiratory flow (FEF₂₅₋₇₅). Addressing dynamic hyperinflation early not only improves respiratory symptoms and mechanics but also mitigates the cardiovascular implications associated with it. Chronic exposure of small airways to toxic substances, including cigarette smoke, leads to significant remodelling in response to injury. This remodelling involves increased airway wall thickness, heightened inflammatory cell density, fibrosis, smooth muscle hyperplasia, and mucus plugging—all hallmark features of COPD that contribute to SAD. These mechanisms may help identify subclinical COPD patients with SAD before overt lung function impairment occurs, as evidenced by early declines in FEF₂₅₋₇₅ and increased RV/TLC ratios [24,25].

Smoking history is a well-established risk factor for COPD. Our study demonstrated that smokers exhibited greater small airway obstruction compared to non-smokers, suggesting that declines in FEF₂₅₋₇₅ and the indirect increase in the RV/TLC ratio may serve as early indicators of minor airway damage. Therefore, we emphasize that respiratory function parameters,

including increased RV/TLC ratios, reduced FEF₂₅₋₇₅, and clinical symptoms, can aid in the early diagnosis and prediction of COPD, which is crucial for improving patient prognosis.

It is essential to recognize that characterizing and targeting SAD is only one aspect of a broader strategy to evaluate the phenotypic variations of COPD patients [26], thereby enabling the provision of the most effective and appropriate targeted therapies. Future advancements in assessing the extent of small airway involvement, along with the development of novel drugs, formulations, and inhalers targeting small airways, will enhance our management of small airway disease in COPD patients [27,28]. Our study highlights the effectiveness of bronchodilators, such as long-acting muscarinic antagonists (LAMAs), in this specific patient phenotype, suggesting that individuals with particular characteristics can derive significant benefits from these medications, thereby improving disease management. It is noteworthy that the most recent ATS/ERS guidelines on the interpretation of pulmonary function tests explicitly emphasize the necessity of assessing, alongside the forced expiratory volume in one second/forced vital capacity (FEV₁/FVC) ratio, expiratory flow rates at low lung volumes, such as FEF₂₅₋₇₅, FEF₅₀, and FEF₇₅, as well as maximal expiratory volumes at three and six seconds (FEV₃ and FEV₆), as spirometric markers of SA obstruction. However, a universally accepted functional definition of SA obstruction is still lacking, with spirometry being the most commonly used tool for its assessment.

In our study, patients presenting to our outpatient clinics with symptoms of dyspnea underwent a complete spirometric evaluation. Despite normal FEV₁/FVC ratios, further assessment revealed reduced FEF₂₅₋₇₅, increased pulmonary resistance, and elevated Multiple Breath Washout (MBW)-derived indices, which enabled the initiation of inhalation therapy aimed at improving respiratory symptoms. Similarly, Xiao D et al., in a study involving more than 50,000 subjects from the general population, defined SA obstruction as the presence of at least two out of three flow parameters (FEF₂₅₋₇₅, FEF₅₀, and FEF₇₅) below 65% of the predicted value [29]. Using this criterion, SA obstruction was associated with various risk factors, including active and passive smoking, biomass combustion exposure, particulate matter exposure, and a history of chronic childhood cough. The presence of cholinergic innervation in human peripheral airways remains a topic of debate. However, even if parasympathetic innervation is sparse or absent in SA, non-neuronal cholinergic mechanisms predominate at this level [30]. M3 muscarinic receptors in peripheral airways are expressed and activated by non-neuronal acetylcholine (ACh), which is released from epithelial cells expressing choline acetyltransferase in response to inflammatory stimuli or exposure to cigarette smoke.

The role of the epithelium in synthesizing and releasing non-neuronal ACh is crucial for modulating airway smooth muscle tone. Furthermore, ACh stimulates cells surrounding the small airway smooth muscle in an autocrine or paracrine manner, thereby influencing inflammation and airway remodelling [31,32]. Indeed, various airway-resident cells, including bronchial epithelial cells, neutrophils, lymphocytes, macrophages, and fibroblasts, express muscarinic receptors. LAMAs reduce the release of non-neuronal ACh by modulating the activity of organic cation transporters.

Therefore, small airways are fundamental not only for conducting airflow but also as key determinants of pulmonary mechanics [32]. Their involvement in obstructive lung diseases, such as asthma and COPD, parallels disease progression. Thus, assessing small airway function may be clinically relevant not only in patients with established obstructive disease but also in symptomatic individuals at risk of developing it. In clinical practice, small airway dysfunction may be evaluated using spirometric, oscillometric, and other physiological measurements; however, no universally accepted functional definition currently exists. In particular, FEF₂₅₋₇₅ is characterized by substantial interindividual variability and is influenced by lung volumes and FVC, limiting its specificity when used as an isolated marker of small airway dysfunction. Therefore, in the present study, FEF₂₅₋₇₅ <60% predicted was considered an operational criterion and was interpreted within a broader clinical and functional phenotype, including preserved FEV₁/FVC, increased RV/TLC, and exertional symptoms. Future studies should aim to establish standardized criteria for small airway dysfunction by integrating clinical, functional, radiological, and oscillometric parameters across different patient populations.

Conclusions

Despite the small sample size, the lack of appropriate sample size and power calculations, the absence of both a control arm and a randomisation procedure, and the single-centre nature of this study, we aim to emphasise the importance of precision medicine. The "Treatable Traits" approach represents a novel strategy in which patients undergo an individualized assessment for a defined set of treatable problems, followed by the implementation of a personalized treatment plan based on this multidimensional evaluation [33,34]. This emerging paradigm in disease management holds significant promise for tailoring care and improving outcomes, particularly in complex cases such as severe asthma, elderly individuals, and patients with multimorbid COPD [35,36]. In our study, the use of umeclidinium in a distinct "new phenotype" of patients resulted in improvements in both respiratory function parameters and

symptomatology, ultimately enhancing patient quality of life. Early intervention, as emphasised in our study, may contribute to improved disease management and slower disease progression. Larger, randomised studies are warranted to validate these findings further.

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Table 1. Demographics and clinical characteristics of enrolled patients.

Characteristic	
Female gender, N (%)	29 (58.0%)
Male gender, N (%)	21 (42.0%)
Age, mean ($\pm$ SD), years	67.3 $\pm$ 9.59
Height, mean ($\pm$ SD), cm	160.5 $\pm$ 8.40
Weight, mean ($\pm$ SD), kg	75.08 $\pm$ 14.57
Smokers (%)	31 (62%)

Table 2. Functional and clinical features of patients at baseline and after treatment with umeclidinium.

	Pre-treatment	Post-treatment	P
FVC, mean ($\pm$ SD), L	2.70 $\pm$ 0.57	3.02 $\pm$ 0.79	0.04
FEV ₁ , mean (SD), L	2.00 $\pm$ 0.57	2.19 $\pm$ 0.56	0.09
FEV ₁ /FVC ratio, mean ($\pm$ SD)	74.49 $\pm$ 2.58	72.72 $\pm$ 1.40	<0.001
FEF ₂₅₋₇₅ , mean ($\pm$ SD), %	37.85 $\pm$ 7.04	49.98 $\pm$ 7.46	<0.001
PEF, mean ($\pm$ SD), %	73.78 $\pm$ 14.44	75.30 $\pm$ 11.23	0.55
sR tot, mean ($\pm$ SD), %	225.52 $\pm$ 56.66	126.51 $\pm$ 30.76	<0.001
TLC, mean ($\pm$ SD), %	98.08 $\pm$ 8.26	98.09 $\pm$ 5.16	0.99
RV/TLC ratio, mean ($\pm$ SD), %	135.24 $\pm$ 9.78	107.43 $\pm$ 8.53	<0.001
6MWT distance, mean ($\pm$ SD), %	308.48 $\pm$ 31.91	347.80 $\pm$ 35.80	<0.001
mMRC, mean ($\pm$ SD)	1.80 $\pm$ 0.73	0.62 $\pm$ 0.64	<0.001

SD, standard deviation; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 s; FEF₂₅₋₇₅, forced mid-expiratory flow between 25% and 75% of FVC; PEF, peak of expiratory flow; sR tot, airway resistance; TLC, total lung capacity; RV, residual volume; 6MWT, six-minute walking test; mMRC, modified Medical Research Council dyspnea scale.