Respiratory Research

RESEARCH

Open Access

Therapeutic effect of long-acting muscarinic antagonist for treating uncontrolled asthma assessed using impulse oscillometry

Hiroyuki Sugawara[1,2], Atsushi Saito[1*], Saori Yokoyama[1,2] and Hirofumi Chiba[1]

Abstract

Background In recent years, the incorporation of LAMAs into asthma therapy has been expected to enhance symptom control. However, a significant number of patients with asthma continue to experience poorly managed symptoms. There have been limited investigations on LAMA-induced airway alterations in asthma treatment employing IOS. In this study, we administered a LAMA to patients with poorly controlled asthma, evaluated clinical responses and respiratory function, and investigated airway changes facilitated by LAMA treatments using the IOS.

Methods Of a total of 1282 consecutive patients with asthma, 118 exhibited uncontrolled symptoms. Among them, 42 switched their treatment to high-dose fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) (ICS/LABA/LAMA). The patients were then assessed using AHQ-33 or LCQ and ACT. Spirometry parameters (such as FEV_1 or MMEF) and IOS parameters (such as R20 or AX) were measured and compared before and after exacerbations and the addition of LAMA.

Results Of the 42 patients, 17 who switched to FF/UMEC/VI caused by dyspnea exhibited decreased pulmonary function between period 1 and baseline, followed by an increase in pulmonary function between baseline and period 2. Significant differences were observed in IOS parameters such as R20, R5-R20, Fres, or AX between period 1 and baseline as well as between baseline and period 2. Among the patients who switched to inhaler due to cough, 25 were classified as responders (n = 17) and nonresponders (n = 8) based on treatment outcomes. Among nonresponders, there were no significant differences in spirometry parameters such as FEV_1 or PEF and IOS parameters such as R20 or AX between period 1 and baseline. However, among responders, significant differences were observed in all IOS parameters, though not in most spirometry parameters, between period 1 and baseline. Furthermore, significant differences were noted between baseline and period 2 in terms of FEV_1, %MMEF, %PEF, and all IOS parameters.

Conclusion ICS/LABA/LAMA demonstrates superiority over ICS/LABA in improving symptoms and lung function, which is primarily attributed to the addition of LAMA. Additionally, IOS revealed the effectiveness of LAMA across all airway segments, particularly in the periphery. Hence, LAMA can be effective against various asthma phenotypes characterized by airway inflammation, even in real-world cases.

Keywords Bronchial asthma, Impulse oscillometry system (IOS), Pulmonary function test, Long-acting muscarinic antagonist (LAMA)

*Correspondence:
Atsushi Saito
a-saito@sapmed.ac.jp
Full list of author information is available at the end of the article

Background

Asthma is a heterogeneous disease commonly characterized by chronic airway inflammation. The frequency and intensity of asthma symptoms, such as wheezing, chest tightness, shortness of breath, and cough, typically vary and contribute to the asthma burden [1]. Poor symptom control is strongly associated with an increased risk of asthma exacerbations [2]. However, other independent risk factors have also been identified, including a history of ≥1 exacerbation in the previous year, poor treatment adherence, incorrect inhaler technique, chronic sinusitis, and smoking, all of which can be assessed in primary care [3]. Exacerbations represent a change in symptoms and lung function from the patient's usual status [4]. Decreased expiratory airflow can be quantified by lung function parameters such as peak expiratory flow (PEF) and forced expiratory volume in 1 s (FEV_1), compared with the patient's previous lung function or predicted values. Lung function should be assessed upon diagnosis or treatment initiation and after treatment, with recordings made at least every 1–2 years.

According to the International cross-sectional and longitudinal assessment on asthma control (LIAISON), among 8111 patients, 3526 (43.5%) presented with controlled asthma, 1462 (18.0%) with partly controlled asthma, and 3123 (38.5%) with uncontrolled asthma [5]. A Japanese internet survey reported that of 992 patients, 348 (35.1%) had controlled asthma, 494 (49.8%) had partly controlled asthma, and 150 (15.1%) had uncontrolled asthma based on the Global Initiative for Asthma criteria [6]. Moreover, a global study revealed that asthma undertreatment still occurs worldwide [7].

Recently, several triple therapy combinations [inhaled corticosteroid (ICS)–long-acting β_2 agonist (LABA)–long-acting muscarinic antagonist (LAMA)] in a single inhaler (SITT) have been introduced to the market. Moreover, the 2021 Global Initiative for Asthma recommends adding LAMA to the treatment regimen of patients aged ≥18 years who still experience symptoms or exacerbations despite adherence to inhaled LABA combined with medium- or high-dose ICS [1]. Recent studies have shown that adding LAMA to ICS/LABA is effective in asthma control, and SITT with high-dose ICS is more effective than that with medium-dose ICS in terms of improving lung function and reducing severe exacerbations [8, 9]. Therefore, triple therapy is recommended as a second-line treatment for patients with uncontrolled asthma who have received ICS/LABA therapy.

The impulse oscillometry system (IOS) can be used to assess the function of both large and small airways using the forced oscillation technique. IOS can detect subtle airway changes earlier than spirometry [10–12]. Our previous studies have revealed that phenotypic differences in IOS parameters could be associated with the efficacy of ICS in asthma [13, 14]. However, only few studies have evaluated LAMA-induced airway changes with IOS for treating asthma.

In real-world asthma treatment, if a patient is diagnosed with uncontrolled asthma caused by dyspnea or cough, it may be necessary to switch from ICS/LABA to ICS/LABA/LAMA. Therefore, the current study aimed to assess the efficacy of LAMA in asthma treatment and its mechanism of action within the airways. Additionally, we examined the types of asthma effectively treated with LAMA based on pulmonary function assessed using spirometry and IOS.

Method

Patients and treatment

This was a single-center retrospective observational study conducted at a primary care setting. A total of 1282 consecutive patients with asthma who visited the Sugawara Internal Medicine and Respiratory Clinic between April 2021 and March 2023 were screened during the same period. Among them, 1164 presented with well- or partly controlled asthma, whereas 118 presented with uncontrolled asthma. Despite dual therapy with high-dose ICS/LABA, 42 out of 73 patients with uncontrolled asthma were treated with LAMA. They received SITT (fluticasone furoate/umeclidinium bromide/vilanterol trifenate [FF/UMEC/VI]). Because the inclusion criteria included patients treated with high-dose ICS/LABA presenting uncontrolled asthma, these patients were eligible for this study (Fig. 1). All patients had previously been diagnosed with asthma based on a history of respiratory symptoms such as wheezing, shortness of breath, chest tightness, and cough, which typically varied in frequency and intensity, and were treated according to the Global Strategy for Asthma Management and Prevention [1]. In total, 42 patients with uncontrolled asthma that had been well-controlled in the stable period (period 1) received FF/UMEC/VI (at baseline), followed by an assessment after 2 months (period 2, Fig. 2). The main symptoms of uncontrolled asthma were dyspnea in 17 patients and cough in 25 patients. Among the 17 patients with dyspnea-induced uncontrolled asthma, 7 were switched from FF/VI and 10 from non-FF/VI. Among the 25 patients with cough-induced uncontrolled asthma, 17 were classified as responders (9 who switched from FF/VI and 8 from non-FF/VI) and 8 as nonresponders (2 who switched from FF/VI and 6 from non-FF/VI). Regarding to the criteria for responders in this study, we considered the LCQ score of 2.56 or more after treatment were represent significant improvement as previous paper [20].

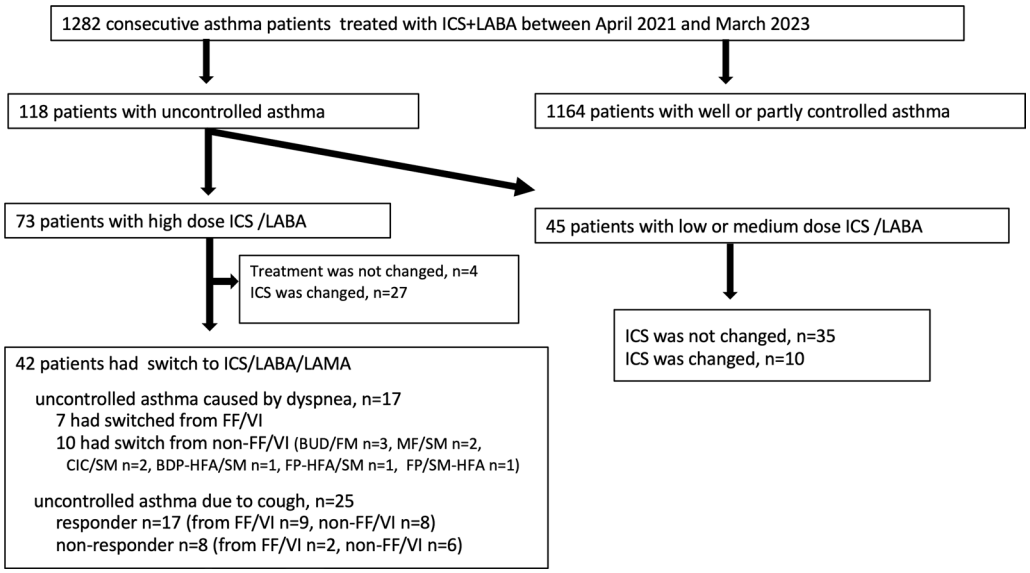

Fig. 1 Flowchart of the 1282 consecutive patients treated with ICS/LABA between April 2021 and March 2023. Of these patients, 118 who presented with uncontrolled asthma switched treatment. Moreover, 42 patients taking high-dose ICS/LABA switched to high-dose ICS/LAMA/LABA

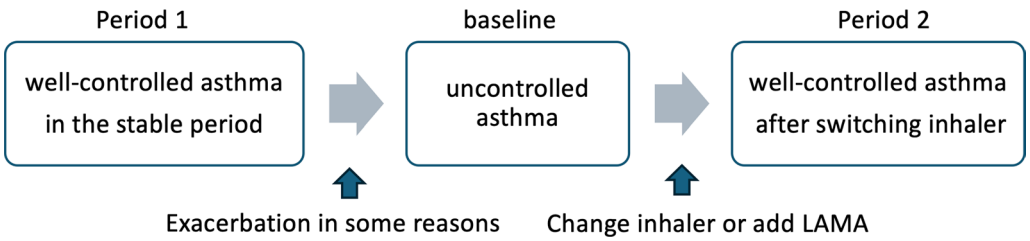

Fig. 2 Definition of period 1, baseline, and period 2. Baseline was defined as the time of diagnosis of uncontrolled asthma, period 1 was defined as the time of diagnosis of controlled asthma before switching inhaler within 1 year, and period 2 was defined as 2 months after switching to triple therapy, indicating well controlled asthma

Therapeutic efficacy was assessed using the Japanese Health Questionnaire-33 (AHQ) or the Leicester Cough Questionnaire (LCQ) at baseline and every 2 weeks or 2 months after treatment and the Asthma Control Test (ACT) at baseline and every 4 weeks after treatment. The experimental protocols and the research purpose were explained to all participants. The current study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Ethical Committee of the Sapporo Medical Association.

Measurements of IOS parameters and pulmonary function

A commercially available impulse oscillometry device (MasterScreen IOS, Jaeger, Germany) was used in accordance with the manufacturer's recommendations [10]. The following parameters were evaluated: resistance at 5 Hz (R5, indicating total airway resistance), resistance at 20 Hz (R20, representing central airway resistance), difference between R5 and R20 (R5–R20, reflecting frequency dependence of resistance primarily sensitive to heterogeneous narrowing in the peripheral airways), reactance at 5 Hz (X5, reflecting the elastance of the lung parenchyma and chest wall in response to volume change), resonant frequency (Fres), and integrated area of low-frequency X (AX). The use of Fres and AX for detecting the degree of obstruction in the peripheral airways has been previously proposed [15–17]. Following the IOS evaluation, pulmonary function tests were performed using spirometry (MasterScreen IOS, Jaeger, Germany). The tests were conducted to prevent the negative effects of forced expiration on the airways. The following parameters were assessed: percentage predicted forced vital capacity (%FVC), percentage predicted forced expiratory volume in 1 s (%FEV_1), FEV_1/FVC ratio, percentage predicted maximal mid-expiratory flow (%MMEF), and percentage predicted PEF (%PEF).

For the IOS parameters, only a few predicted values were available, and the asthma subtypes classified using

IOS were defined using the equations reported by Vogel et al. [18]. According to the percentage predicted value of the IOS, four groups were established as follows: the central type, defined as R20 ≥ 100% and R5–R20 < 100%; the peripheral type, defined as R20 < 100% and R5–R20 ≥ 100%; the mixed type, defined as R20 ≥ 100% and R5–R20 ≥ 100%; and the resistless type, defined as R20 < 100% and R5–R20 < 100% [13, 14].

AHQ, LCQ, and ACT

The AHQ was administered for asthma with dyspnea, whereas the LCQ was administered for asthma with cough. Additionally, the ACT was administered. The Japanese version of the AHQ, an asthma-specific, health-related quality of life questionnaire, has been previously developed [19]. The clinical validity of the AHQ was evaluated, and the results showed that it was reliable and valid for discriminative purposes, instilling confidence in its use in clinical research. The AHQ comprises six subscales (asthmatic symptoms, emotions, daily activities, factors that worsen symptoms, social activities, and economics). Furthermore, it consists of 32 items (graded 0–4) and one face scale (graded 1–5). A higher AHQ score reflects a poorer health status across these 33 items.

Cough-specific QOL was evaluated using the Japanese version of the LCQ (J-LCQ), which was translated from the original version and validated. It comprises 19 questions covering three subdomains (physical, social, and psychological). Total scores range from 3 to 21, with higher scores indicating better QOL. A significant correlation between J-LCQ and subjective cough severity and frequency was assessed [20, 21]. The use of the J-LCQ was approved by Surinder Birring, Akio Niimi, and Haruhiko Ogawa. The ACT is a validated, patient-completed measure of asthma control comprising five questions rated on a 5-point scale. It is used to assess activity limitation, shortness of breath, night-time symptoms, use of rescue medication, and overall rating of asthma control within the last 4 weeks [22]. A total ACT score of ≥ 20 is considered the optimal cutoff point for well-controlled asthma.

Statistical analysis

Data are expressed as means ± standard error of the mean. Differences between before and at baseline or between at baseline and after treatment were compared using paired or unpaired *t*-tests. Categorical variables were tested using the chi-square test. A P-value of < 0.05 was considered statistically significant. Microsoft Excel 2007 (Microsoft Corporation, USA), the Excel Statistical Program File (ystat2008.xls, Igakutosho-shuppan Ltd., Tokyo, Japan), and GraphPad Prism v7 software (GraphPad, Inc., San Diego, CA, USA) were used for data analysis and graph generation. Spearman's correlation and JMP 13.0 (SAS Institute, Cary, NC, USA) were used to evaluate the coefficients of determination (ρ), residuals, and significance (p) to identify associations between pulmonary function test and IOS indices.

Results

Characteristics and pulmonary function of patients with uncontrolled asthma caused by dyspnea at baseline

Table 1 and Table S1 show the characteristics of 17 patients with asthma (FF/VI group: 7 patients switched from FF/VI, non-FF/VI group: 10 patients switched from non-FF/VI due to dyspnea). The mean age of the participants was 60.6 years (FF/VI group: 55.1 years, non-FF/VI group: 64.5 years). The male-to-female ratio was 4:13 (FF/VI group: 1:6, non-FF/VI group: 3:7). Seven patients had a smoking history. There were no significant differences between the FF/VI and non-FF/VI groups in terms of age, sex, body mass index, smoking status, atopy, blood eosinophil count, serum IgE level, and AHQ score. However, the ACT score of the non-FF/VI group was lower than that of the FF/VI group. According to spirometry assessment, the non-FF/VI group had lower FEV_1/FVC, %MMEF, and PEF. In contrast, the IOS evaluation showed no significant differences in all parameters between the two groups (Table 1 and Table S1).

Comparison of pulmonary function and therapeutic effects in the treatment of patients with uncontrolled asthma caused by dyspnea

Baseline was defined as the time of uncontrolled asthma diagnosis, period 1 as the time of well-controlled asthma diagnosis within 1 year from baseline, and period 2 as 2 months after switching inhalers to triple therapy with well-controlled asthma (Fig. 2). In all patients compared between baseline and period 2, AHQ values significantly decreased, whereas ACT scores significantly increased (Table 1). Additionally, all patients exhibited significantly decreased pulmonary function based on spirometry results at baseline compared with period 1. Furthermore, spirometry parameters, except FEV_1/FVC, improved close to their initial values after switching inhalers (Fig. 3, Table 1). For the FF/VI group, FEV_1, $\%FEV_1$, and %FVC decreased at baseline and increased after adding LAMA. In contrast, spirometry values other than FEV_1/FVC worsened at baseline and improved after switching inhalers. The non-FF/VI group had a lower %MMEF than the FF/VI group before switching therapy. Moreover, there were significant differences in FEV_1, %MMEF, and %PEF at baseline between the two groups. However, after switching therapy, FEV_1, %MMEF, and %PEF did not significantly differ between the two groups (Table S1).

Table 1 Baseline characteristics and pulmonary function of patients with uncontrolled asthma caused by dyspnea

Treatment switch from	All				
	Period 1	Baseline	Period 2	Period1 vs baseline p-value	Baseline vs period2 p-value
n		17			
Characteristics of the patients					
Age (y)		60.6 (4.6)			
Sex (male:female), n		4:13			
BMI (kg/m^2)		24.9 (1.2)			
Smoking status (smoker:never smoker), n		7:10			
Atopy (atopy:non-atopy), n		11:6			
Blood eosinophil count (cells/uL)		354.4 (95.6)			
Serum IgE (U/L)		730.9 (260.2)			
Thearpeutic evaluation					
AHQ		32.8 (3.9)	12.7 (2.4)		< 0.001**
ACT		19.6 (0.7)	24.2 (0.2)		< 0.001**
Spirometry					
FEV1 (L)	2.28 (0.22)	1.96 (0.24)	2.26 (0.23)	< 0.001**	< 0.001**
%FEV1 predicted	95.6 (4.5)	81.3 (4.5)	96.2 (4.6)	< 0.001**	< 0.001**
%FVC predicted	99.9 (4.3)	87.8 (3.9)	102.0 (4.4)	< 0.001**	< 0.001**
FEV1/FVC ratio	78.6 (2.4)	75.1 (2.5)	77.2 (2.5)	0.021*	0.21
%MMEF predicted	67.6 (6.8)	48.1 (7.8)	64.9 (7.7)	< 0.001**	0.001**
%PEF predicted	100.4 (5.5)	81.7 (6.5)	98.7 (6.6)	< 0.001**	< 0.001**
Impulse oscillometry					
R5, (kPa/L/s)	0.32 (0.01)	0.39 (0.02)	0.30 (0.01)	0.003**	0.001**
R20 (kPa/L/s)	0.26 (0.01)	0.32 (0.02)	0.25 (0.01)	0.005**	0.001**
R5–R20, kPa/L/s	0.06 (0.01)	0.08 (0.02)	0.06 (0.01)	0.03*	0.017*
X5 (kPa/L/s)	− 0.12 (0.01)	− 0.19 (0.03)	− 0.13 (0.01)	0.013*	0.014*
Fres (Hz)	13.9 (1.2)	16.0 (1.4)	13.9 (1.2)	0.002**	0.004**
AX (kPa/L)	0.51 (0.10)	1.02 (0.21)	0.57 (0.11)	0.004**	0.004**

Data are presented as mean (SEM) or number (percentage). Differences between groups were tested using the paired t-test, unpaired t-test, or chi-square test. *: p < .05, **: p < .01

The absolute values of most IOS parameters at baseline were higher than those in period 1. Patients exhibited lower absolute values after switching than at baseline, a trend similar to the spirometry results (Fig. 3, Table 1). In the FF/VI group, there was a minimal decrease in the numerical value at baseline, and a significant improvement was observed in X5, Fres, and AX. The absolute values of the non-FF/VI group were significantly higher at baseline and lower after switching inhalers. However, there was no significant difference in IOS parameters, except R20, between the FF/VI and non-FF/VI groups (Table S1).

Characteristics, comparison of pulmonary function, and therapeutic effects in the treatment of patients with uncontrolled asthma caused by cough

Twenty-five patients with uncontrolled asthma caused by cough switched to FF/UMEC/VI inhalers at baseline (Table 2, Fig. 4). Based on treatment outcomes, the patients were classified as responders (n = 17) and nonresponders (n = 8). There were no significant differences in characteristics and LCQ scores at baseline between the two groups. Among nonresponders, there were no significant differences in spirometry and IOS parameters between period 1 and baseline. Due to ethical reasons, pulmonary function tests were not performed on nonresponders who did not exhibit improvement in cough after triple therapy. Conversely, among all responders, all IOS parameters significantly differed between period 1 and baseline. However, no significant difference was observed in spirometry parameters other than %PEF. Thus, IOS seems capable of revealing differences between responders and nonresponders. In period 2, after switching to triple therapy, responders had significantly elevated FEV_1, $\%FEV_1$, %MMEF, and %PEF based on spirometry and

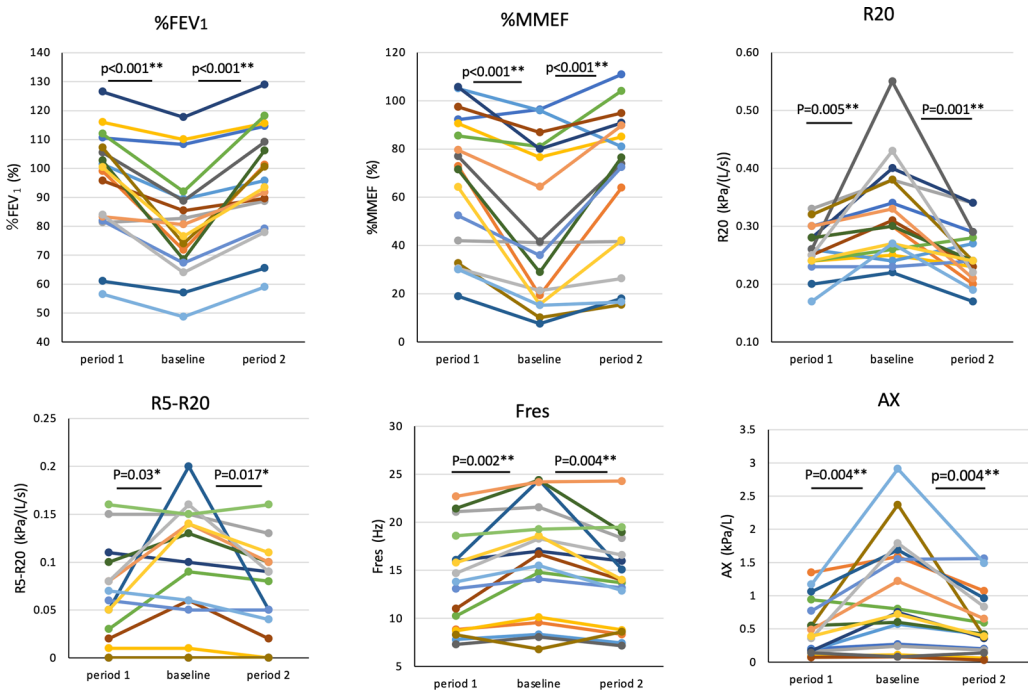

Fig. 3 Comparison of spirometry and impulse oscillometry data in patients with uncontrolled asthma caused by dyspnea. The differences between period 1 and baseline or between baseline and period 2 were analyzed using the unpaired *t*-test, *: $p < 0.05$, **: $p < 0.01$

increased R5, R20, X5, Fres, and AX based on the IOS evaluation. When responders were categorized into the FF/VI and non-FF/VI groups, significant differences were observed in IOS variables such as R5-R20, Fres, and AX compared to spirometry parameters (Table S2).

Comparison of therapeutic effects based on asthma subtypes classified via impulse oscillometry

Patients with uncontrolled asthma (n = 42) were classified into four subtypes according to the IOS parameters, as in our previous study (Fig. 5). Among 17 patients with uncontrolled asthma caused by dyspnea, 7 exhibited the central type, 7 the peripheral type, and 3 the mixed type. Patients with all subtypes showed increased FEV_1, and there was no significant difference in terms of the change in FEV_1 between the subtypes. Seventeen patients with uncontrolled asthma caused by cough, who experienced symptom improvement with LAMA, were classified as follows: 3 with the central type, 8 with the peripheral type, 1 with the mixed type, and 5 with the resistless type. These patients showed improved LCQ scores, and no significant difference was observed in terms of the change in LCQ between the subtypes.

Discussion

For a long time, muscarinic antagonists were considered effective only for chronic obstructive pulmonary disease (COPD), not for asthma, primarily due to the perceived minimal cholinergic component of bronchoconstriction compared to the direct constrictor effects of inflammatory mediators or leukotrienes [23]. However, studies on tiotropium as a LAMA have demonstrated that LAMAs are as effective as LABAs in terms of bronchodilation, patient-reported outcomes, and exacerbations [24, 25]. Recently, the efficacy of LAMAs as add-on therapy in patients with asthma experiencing persistent symptoms or exacerbations despite optimized ICS/LABA treatment has been evaluated [26]. IOS parameters have been found to be more sensitive in predicting poor symptom control and exacerbations than spirometry in patients with asthma [27–29]. Additionally, a recent randomized controlled trial investigating persistent asthma with triple therapy revealed improvement in small airway resistance by reducing the trough IOS index R5–R20 [30]. However, few studies have examined the association between IOS parameters and asthma outcomes in patients receiving additional LAMA therapy. Randomized clinical studies investigating SITT in asthma treatment (TRIMARAN combined with TRGGER, IRIDIUM, ARGON, and CAPTAIN) [31–34] have shown that SITT has a more

Table 2 Baseline characteristics and pulmonary function of patients with uncontrolled asthma caused by cough who were nonresponders and responders to LAMA

	Non-responder					Responder					p-value	
	All					All						
	Period1	Baseline	Period2	Period1 vs baseline	Baseline vs period2	Period1	Baseline	Period2	Period1 vs baseline	Baseline vs period2	Nonresponder vs responder	
				p-value	p-value				p-value	p-value	period1	baseline
n		8					17					
Characteristics of the patients												
Age		52.4 (4.6)					56.1 (4.7)					0.63
Sex;male:female		4:4					4:13					0.39
BMI		26.5 (1.9)					26.9 (1.4)					0.88
Smoking status, n; Smoker:Nonsmoker		4:4					5:12					0.58
Atopy:non-atopy		4:4					8:9					0.77
Blood eosinophil count, cells/uL		135.3 (28.6)					169.7 (23.7)					0.4
Serum IgE, U/L		1122 (874.0)					138.5 (40.1)					0.11
Thearpeutic evaluation												
LCQ		13.4 (0.8)	13.1 (1.2)		0.88		12.7 (2.6)	19.4 (0.3)		< 0.001**		< 0.001**
Spirometry												
FEV1	2.96 (0.24)	2.92 (0.25)	–	0.69	–	2.63 (0.21)	2.60 (0.21)	2.67 (0.21)	0.2	0.012*	0.36	0.37
%FEV1	103.2 (7.4)	99.8 (6.4)	–	0.21	–	109 (3.7)	108.5 (3.8)	112.8 (4.2)	0.71	0.003*	0.44	0.23
%FVC	107.3 (7.8)	104.4 (6.4)	–	0.38	–	105.3 (3.5)	106.0 (3.4)	108.4 (3.8)	0.78	0.26	0.78	0.8
FEV1/FVC	81.3 (2.7)	80.5 (2.7)	–	0.61	–	85.3 (1.3)	83.8 (1.3)	85.1 (1.2)	0.11	0.22	0.13	0.22
%MMEF	80.3 (15.9)	75.6 (13.3)	–	0.41	–	87.2 (6.8)	84.4 (7.3)	97.8 (7.1)	0.26	0.008**	0.64	0.54
%PEF	115.9 (7.9)	120.1 (7.8)	–	0.35	–	117.9 (3.8)	110.7 (4.4)	121.8 (4.6)	0.003**	0.003**	0.8	0.26
Impulse oscillometry												
R5	0.28 (0.02)	0.31 (0.03)	–	0.24	–	0.31 (0.02)	0.36 (0.03)	0.30 (0.02)	0.001**	< 0.001**	0.35	0.33
R20	0.24 (0.01)	0.26 (0.02)	–	0.51	–	0.26 (0.02)	0.29 (0.02)	0.23 (0.02)	0.02*	0.001**	0.47	0.43
R5–R20	0.05 (0.01)	0.06 (0.02)	–	0.2	–	0.05 (0.01)	0.07 (0.02)	0.06 (0.01)	0.011*	0.06	0.68	0.48
X5	−0.12 (0.01)	−0.13 (0.01)	–	0.37	–	−0.13 (0.02)	−0.16 (0.02)	−0.13 (0.01)	0.001**	0.014*	0.58	0.34
Fres	13.1 (1.2)	13.9 (1.4)	–	0.31	–	13.4 (0.9)	16.0 (1.2)	13.8 (0.9)	0.001 **	0.003**	0.78	0.3
AX	0.40 (0.09)	0.52 (0.14)	–	0.11	–	0.54 (0.15)	0.82 (0.21)	0.52 (0.12)	0.001**	0.011*	0.54	0.34

Data are expressed as mean (SEM) or number (percentage). Differences between groups were tested using the paired t-test, unpaired t-test, or chi-square test. *: $p < .05$, **: $p < .01$

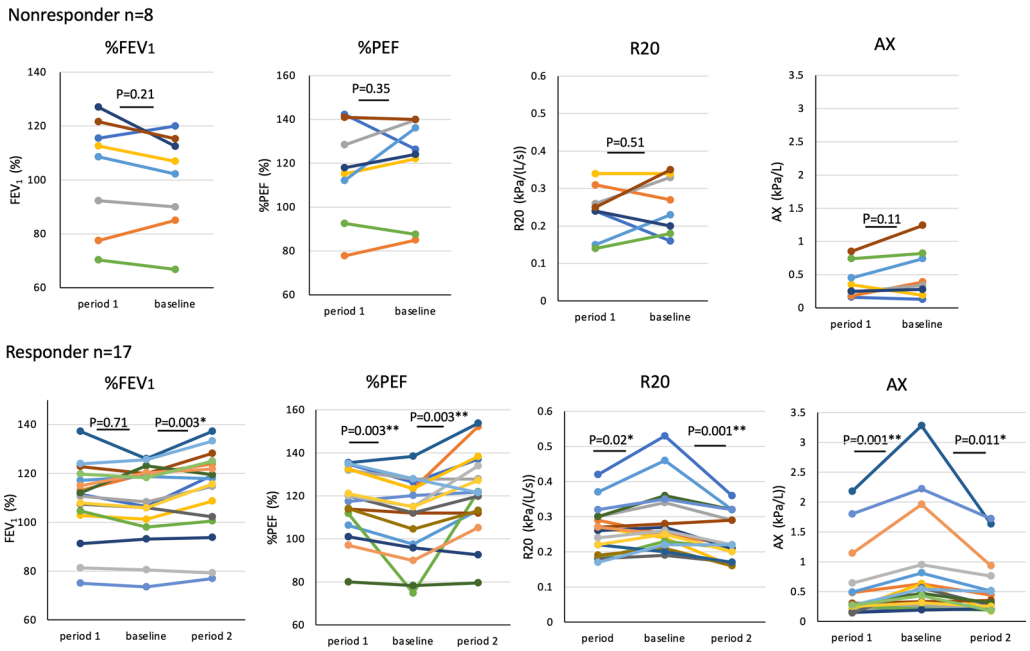

Fig. 4 Comparison of spirometry and impulse oscillometry data in patients with uncontrolled asthma caused by cough. The differences between period 1 and baseline or between baseline and period 2 were analyzed using the unpaired *t*-test, *: $p < 0.05$, **: $p < 0.01$

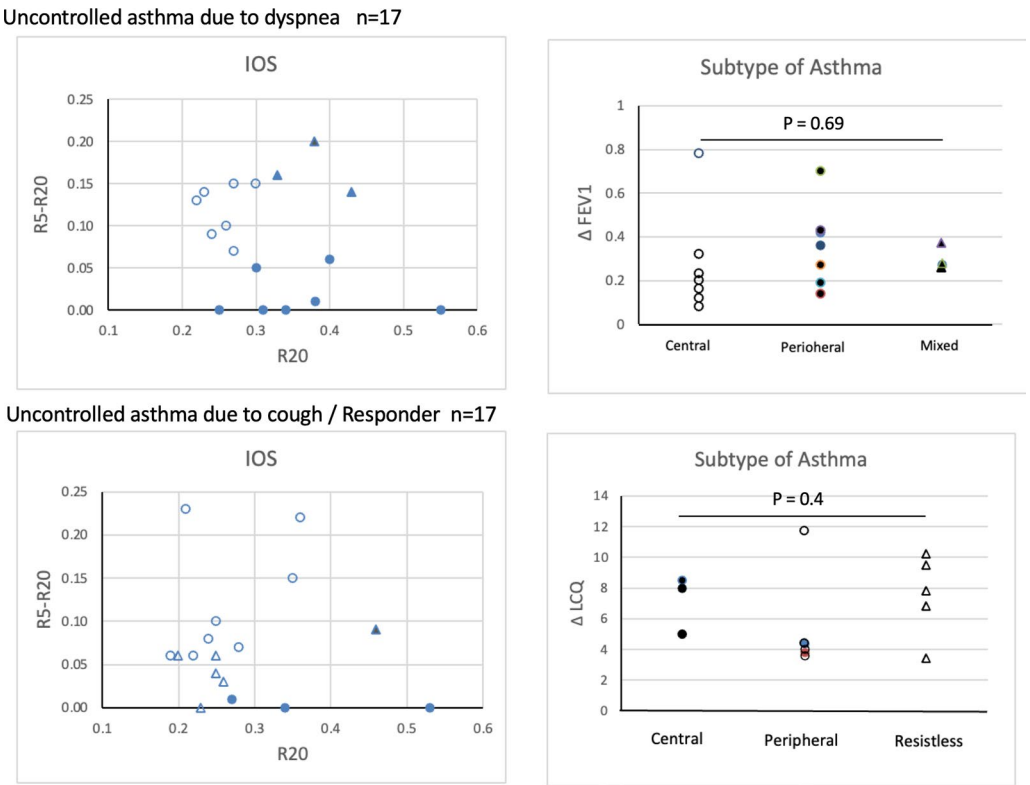

Fig. 5 Comparison of therapeutic effects (Δ FEV_1: change in FEV_1 or Δ LCQ: change in LCQ) in asthma subtypes classified via impulse oscillometry. The asthma subtypes classified with IOS were defined using the equations reported by Vogel et al. According to the percentage predicted value of the IOS, four groups were defined as follows: the central type (open circle), defined as R20 ≥ 100% and R5–R20 < 100%; the peripheral type (closed circle), R20 < 100% and R5–R20 ≥ 100%; the mixed type (closed triangle), R20 ≥ 100% and R5–R20 ≥ 100%; and the resistless type (open triangle), R20 < 100% and R5–R20 < 100%. Differences among the subtypes were analyzed using nonrepeated analysis of variance

consistent effect on pulmonary function than ICS/LABA. However, its benefits against exacerbations were less consistent, although observed in two studies. Therefore, the present study aimed to determine the potential IOS parameters affected by LAMA in the airways, focusing on uncontrolled asthma. To the best of our knowledge, this is the first study to demonstrate an association between uncontrolled asthma symptoms and central and peripheral airway dysfunction, evaluated using IOS parameters, and to show that LAMAs can act on both large and small airways.

In this study, uncontrolled asthma is defined as experiencing three or four of the following asthma symptoms in the past 4 weeks: daytime asthma symptoms occurring more than twice per week, any night waking due to asthma, SABA reliever use for symptoms more than twice per week, and any activity limitation due to asthma, associated with decreased pulmonary function and exacerbation. Asthma exacerbation is characterized by a progressive increase in symptoms such as shortness of breath, cough, wheezing, chest tightness, and a progressive decrease in lung function, representing a deviation from the patient's usual status that necessitates treatment modification [4]. Among the 42 patients with uncontrolled asthma, 17 presented with dyspnea and 25 with cough. Furthermore, comparisons were made between FEV_1 and IOS measurements of patients diagnosed with well-controlled asthma (period 1) and those with uncontrolled asthma (at baseline) as well as between baseline and after switching treatment (period 2).

Among the 17 patients with uncontrolled asthma mainly caused by dyspnea, 7 received additional treatment with LAMA, whereas 10 underwent an ICS modification. The FEV_1 of all 17 patients decreased during the period of uncontrolled asthma symptoms and increased after switching treatments. This pattern was consistent across the two categorized groups, whose inhalation therapies before switching were either FF/VI or non-FF/VI. In the CAPTAIN study, the addition of LAMA alone resulted in a 260 mL increase, and switching from ICS + LABA to SITT led to a 350 mL increase in FEV_1. Our data corroborate these findings. Additionally, we believe that switching to SITT may improve respiratory function through a synergistic interaction among the three drugs, as observed in a recent study [34].

In this study, IOS values were compared across three periods: period 1 (well-controlled asthma), baseline (uncontrolled asthma), and period 2 (well-controlled asthma), yielding R20 values of 0.26, 0.32, and 0.25, respectively. These results indicate significant differences between period 1 and baseline as well as between baseline and period 2. Similarly, AX values were recorded as 0.51 in period 1, 1.02 at baseline, and 0.57 in period 2, also showing significant differences between baseline and period 1 and between baseline and period 2. The switch to SITT demonstrated notable effects on R20, reflecting central airway function, and AX, representing peripheral airway function. Furthermore, it appeared that LAMA influenced R5-R20, X5, Fres, and AX, indicative of small airway functionality. A recent retrospective study on 69 patients with difficult-to-treat asthma revealed that those with poorly controlled asthma exhibited higher R5–R20 and Fres values compared to those with well-controlled asthma [27]. Another study assessing childhood asthma control revealed that R5–R20 is an important IOS-defined small airway parameter associated with uncontrolled asthma [28]. In this study, R20, a key airway parameter, and AX, which represents the peripheral airway, were associated with the addition of LAMA. An in silico study of COPD assessed functional respiratory imaging findings, and the central-to-peripheral airway deposition ratios compared between BDP/GLY/FOR and FF/UMEC/VI were 0.48 vs. 1.96 for ICS, 0.48 vs. 0.97 for LABA, and 0.49 vs. 1.20 for LAMA. Contrary to COPD, FF/UMEC/VI with almost equal central and peripheral deposition for LABA and LAMA components might have a potential clinical advantage in asthma [35]. Our data support the findings that central and peripheral airway dysfunction are associated with asthma development.

Twenty-five patients with uncontrolled asthma caused by cough were treated with LAMA and compared in two groups: responders (n = 17) and nonresponders (n = 8). Neither group presented with a decrease in FEV_1 at baseline compared to Period 1, and the IOS values did not change in nonresponders. However, in responders, R20 was 0.26 (Period 1), 0.29 (at baseline), and 0.23 (Period 2), and AX was 0.54 (Period 1), 0.82 (at baseline), and 0.52 (Period 2), indicating significant differences in both IOS parameters between baseline and period 1 and between baseline and period 2 (Fig. 4). A recent study revealed that tiotropium may alleviate asthmatic cough refractory to ICS/LABA by modulating capsaicin cough reflex sensitivity [36]. In another report, the capsaicin provocation test for patients with chronic cough had a lower capsaicin cough threshold than patients with asthma and healthy controls. However, there were no significant differences in terms of R20 or AX for IOS [37]. Consistent with this result, the current study showed that R20 or AX did not change during well- and uncontrolled asthma in nonresponders refractory to SITT. Additionally, we believe that patients with asthma who present with cough seem to be refractory to treatment if IOS fluctuations are not observed. Furthermore, responders had higher LCQ scores, and they presented with a minimal but significant increase in FEV_1 and significant changes in most IOS parameters than those with uncontrolled

asthma symptoms and those who switched treatment. In the analysis of the subgroup of responders, both the FF/VI and non-FF/VI groups showed significant changes similar to R20, Fres, and AX. These findings suggest that IOS may be valuable in evaluating the effects of LAMA on asthma, complementing the effects of previously reported ICS and LABA.

Moreover, in our previous study, we observed a difference in efficacy between central type (large airway) and peripheral type (small airway) based on IOS parameters in ICS and LABA. Therefore, we also examined changes in FEV_1 and LCQ due to the adding LAMA, and the therapeutic effects on asthma subtypes. However, no difference was observed between the subtypes (Fig. 5). This paradoxically indicates that LAMA may show the potential to improve asthma symptoms and pulmonary function by acting on both peripheral and central airways.

The current study had several limitations. First, being a single-center retrospective study, it is subject to various biases concerning patient selection, drug selection, and other variables. The classification of the two groups as cough-dominant or dyspnea-dominant relied on clinical judgment, which has a weaker scientific basis than numerical classification criteria, representing a study limitation. Regarding drug selection, although we confirmed the absence of differences between the FF/VI and non-FF/VI groups in the first period (stable) and at baseline (uncontrolled asthma), we cannot definitively state that there was no selection bias. Additionally, eight non-responders with uncontrolled asthma caused by cough could not undergo spirometry and IOS evaluation after treatment with FF/UMEC/VI due to ethical reasons. They have the right to abstain from undergoing tests deemed meaningless during the treatment course, as the LCQ indicating low treatment efficacy is considered sufficient. Finally, this small retrospective study included only 42 patients. Furthermore, our follow-up period was short; hence, a long-term prospective study should be performed to confirm these findings. Although the current findings are preliminary, this is the first report showing the efficacy of LAMA in patients with uncontrolled asthma caused by dyspnea or cough. We believe that these findings are important, especially in real-world clinical practice.

Conclusions

Managing patients with uncontrolled asthma treated with high-dose ICS/LABA can often be challenging. In some of these cases, recommending the addition of LAMA, rather than other therapeutic options such as ICS switching or oral steroids, may be preferable. To the best of our knowledge, this is the first report demonstrating that LAMA can alleviate uncontrolled asthma symptoms by targeting both small and large airways, as evaluated through IOS. Furthermore, we have shown that the response of small and large airways to LAMA may be associated with improved respiratory function. Therefore, even in real-world scenarios, LAMA may effectively address various asthma phenotypes characterized by airway inflammation.

Abbreviations

LAMA	Long-acting muscarine antagonist
LABA	Long-acting β2 agonist
ICS	Inhaled corticosteroid
SITT	Single-inhaler triple therapy
FVC	Forced vital capacity
FEV_1	Forced expiratory volume in 1 s
MMEF	Maximum mid-expiratory flow
PEF	Peak expiratory flow
IOS	Impulse oscillometry system
R5	Resistance at 5 Hz
R20	Resistance at 20 Hz
R5–R20	The difference between R5 and R20
X5	Reactance at 5 Hz
Fres	Resonance frequency
AX	Area of low-frequency reactance
AHQ	Asthma Health Questionnaire
LCQ	Leicester Cough Questionnaire
ACT	Asthma Control Test

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12931-024-02921-z.

Supplementary Material 1.

Acknowledgements

Not applicable.

Author contributions

HS developed the study design, conducted the experiments, analyzed and interpreted the data, and wrote the manuscript. AS contributed to data analysis, interpretation, and manuscript revision. SY and HC assisted with data analysis and interpretation and supervised statistical analysis. All authors have read and approved the final manuscript.

Funding

Not applicable.

Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Ethical Committee of the Sapporo Medical Association. All participants were briefed on the experimental protocols and the study's purpose, and informed consent was obtained through an opt-out format on the website.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details
[1]Department of Respiratory Medicine and Allergology, Sapporo Medical University School of Medicine, S1W16 Chuoku Sapporo, Sapporo, Hokkaido 060-8543, Japan. [2]Sugawara Internal Medicine and Respiratory Clinic, Tomakomai 053-0821, Japan.

Received: 25 March 2024 Accepted: 20 July 2024
Published online: 07 August 2024

References

1. Global initiative for Asthma. Global strategy for asthma management and prevention; 2023. www.ginasthma.org.
2. Meltzer EO, Busse WW, Wenzel SE, et al. Use of the asthma Control Questionnare to predict future risk of asthma exacerbation. J Allergy Clin Immunol. 2011;127:167–72. https://doi.org/10.1016/j.jaci.2010.08.042.
3. Loymans RJ, Honkoop PJ, Termeer EH, et al. Identifying patients at risk for severe exacerbations of asthma: development and external validation of a multivariable prediction model. Thorax. 2016;71:838–46.
4. Reddel HK, Taylor DR, Bateman ED, et al. An Official American Thoracic Society/European Respiratory Society Statement: Asthma Control and exacerbations. Standardizing endopoints for clinical asthma clinical practice. Am J Respir Crit Care Med. 2009;180:59–99.
5. Braido F, Brusselle G, Guastalla D, et al. Determinants and impact of suboptimal asthma control in Europe: the international cross-sectional and longitudinal assessment on asthma control (LIAISON) study. Respir Res. 2016;17:51. https://doi.org/10.1186/s12931-016-0374-z.
6. Adachi M, Hozawa S, Nishikawa M, et al. Asthma control and quality of life in a real-life setting: a cross-sectional study of adult asthma patients in Japan (ACQUIRE-2). J Asthma. 2019;56:1016–25. https://doi.org/10.1080/02770903.2018.1514628.
7. Reddel HK, Vestibo J, Agusti A, et al. Heterogeneity within and between physician-diagnosed asthma and/or COPD: NOVELTY cohort. Eur Respir J. 2021;58:2003927. https://doi.org/10.1183/13993003.03927-2020.
8. Papi A, Fabbri LM, Kerstjens HAM, Rogliani P, Watz H, Singh D. Inhaled long-acting muscarinic antagonists in asthma, a narrative review. Eur J Intern Med. 2021;85:14–22.
9. Rogliani P, Ritondo BL, Calzetta L. Triple therapy in uncontrolled asthma: a network meta-analysis of phase III studies. Eur Respir J. 2021;58(3):2004233.
10. Oostveen E, MacLeod D, Lorino H, et al. ERS Task Force on Respiratory Impedance Measurements. The forced oscillation technique in clinical practice: methodology, recommendations and future developments. Eur Respir J. 2003;22(6):1026–41.
11. Bickel S, Popler J, Brton L, Eid N. Impulse Oscillometry, interpretation and practical applications. Chest. 2014;146(3):841–7.
12. King GG, et al. Technical standards for respiratory oscillometry. Eur Respir J. 2020;55(2):1900753. https://doi.org/10.1183/13993003.00753-2019.
13. Sugawara H, Saito A, Yokoyama S, Tsunematsu K, Takahashi H. Comparison of therapeutic effects of inhaled corticosteroids on three subtypes of cough variant asthma as classified by the impulse oscillometry system. Respir Res. 2019;20:41.
14. Sugawara H, Saito A, Yokoyama S, Tsunematsu K, Chiba H, Takahashi H. A retrospective analysis of usefulness of impulse oscillometry system in the treatment of asthma. Respir Res. 2020;21:226.
15. Smith HJRP, Goldman MD. Forced oscillation technique and impulse oscillometry. Eur Respir Monograph. 2005;31:72–105.
16. Goldman MD. Clinical application of forced oscillation. Pulm Pharmacol Ther. 2001;14:341–50.
17. Kaminsky DA, Simpson SJ, Berger KI, et al. Clinical significance and applications of oscillometry. Eur Resp Rev. 2022;31: 210208.
18. Vogel J SU. Impulse Oscillometry Analysis of lung mechanics in general practice and clinic, epidemiological and experimental research. Frankfurt: PMI-Verlagsgruppe; 1994. p. 148–152
19. Arioka H, Kobayashi K, Kudo K, Kabe J. Validation study of a disease-specific module, the asthma health questionnaire (AHQ) using Japanese adult asthmatic patients. Allergol Int. 2005;54:10.
20. Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan MD, Pavord ID. Development of a symptom specific health status measure for patients with chronic cough: leicester cough questionnaire (LCQ). Thorax. 2003;58:339–43.
21. Kanemitsu Y, Niimi A, Matsumoto H, et al. Gastroesophageal dysmotility is associated with the impairment of cough-specific quality of life in patients with cough variant asthma. Allergol Int. 2016;65:320–6.
22. Nathan RA, Sporkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol. 2004;113:59–65.
23. Barnes PJ. Distribution of receptor targets in the lung. Proc Am Thorac Soc. 2004;1:345–51.
24. Buhl R, FitzGerald JM, Busse WW. Tiotropium added-on inhaled corticosteroids versus addition of long-acting b2-agonists for adults with asthma. Respir Med. 2018;143:82–90.
25. Bateman ED, Kornmann O, Schmidt P, et al. Tiotropium is noninferior in maintaining improved lung functioning B16-Arg/Argpatients with asthma. J Allergy Clin Immunol. 2011;128:315–22.
26. Matera MG, Rinaldi B, Berardo C, et al. A review of the pharmacokinetics of M3 muscarinic receptor antagonists used for the treatment of asthma. Expert Opin Drug Metab Toxicol. 2020;16:143–8.
27. Shen Y, Hsieh Y, Huang Y, et al. Assessing the prognostic value of respiratory oscillometry in patients with difficult-to-treat asthma. Sci Rep. 2023;13:2457.
28. Lin L, Chang Y, Yang K, et al. Small airway dysfunction measured by impulse oscillometry and fractional exhaled nitric oxide is associated with asthma control in children. Front Pediatr. 2022;10: 877681.
29. Kraft M, Richardson M, Hallmark B, et al. The role of small airway dysfunction in asthma control and exacerbations: a longitudinal, observational analysis using data from the ATLANTIS study. Lancet Respir Med. 2022;10:661–8.
30. Jabbal S, Kuo CR, Lipworth B. Randomized controlled trial of triple versus dual inhaler therapy on small airways in smoking asthmatics. Clin Exp Allergy. 2020;50:1140–7.
31. Virchow JC, Kuna P, Paggiaro P, et al. Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind parallel group, randomized, controlled phase 3 trials. Lancet. 2019;394:1737–49.
32. Kerstjens HAM, Maspero J, Chapman KR, et al. Once-daily, single-inhaler mometasone-indacaterol-glycopyrronium versus mometasone-indacaterol or twice-daily fluticasone-salmeterol in patients with inadequately controlled asthma (IRIDIUM): a ran- domised, double-blind, controlled phase 3 study. Lancet Respir Med. 2020;8(10):1000–12.
33. Gessner C, Kornmann O, Maspero J, et al. Fixed-dose combination of indacaterol/glycopyrronium/mometasone furoate once-daily versus salmeterol/fluticasone twice-daily plus tiotropium once- daily in patients with uncontrolled asthma: a randomised, phase IIIb, non-inferiority study (ARGON). Respir Med. 2020;170: 106021.
34. Lee LA, Bailes Z, Barnes N, et al. Efficacy and safety of once-daily single-inhaler triple therapy (fluticasone furoate/umeclidinium/ vilanterol (FF/UMEC/VI) versus FF/VI in patients with inadequately controlled asthma: a double-blind, randomised, Phase IIIA trial (CAPTAIN study). Lancet Respir Med. 2020;9:3–5.
35. Usmani O, Scichilone N, Mignot B, Belmans D, et al. Airway deposition of extrafine tripl therapy in pstients with COPD: a model approach based on Functional Respiratory Imaging Computerv simulations. Int J Chronic Obstruct Pulm Dis. 2020;15:2433–40.
36. Fukumitsu K, Kanemitsu Y, Asano T, et al. Tiotropium attenuates refractory cough and capsaicin cough reflex sensitivity in patients with asthma. J Allergy Clin Immunol Pract. 2018;6:1613–20.
37. Johansson EL, Gustafsson P, Millqvist E, et al. Small and large airways' reactions to inhaled capsaicin in patients with chronic idiopathic cough, or asthma and healthy control subjects. Exp Lung Res. 2019;45:55–64.

Publisher's Note