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The use of a long-acting muscarinic antagonist in the treatment of asthma: A tertiary asthma center experience

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Abstract
Introduction: We aimed to investigate the frequency and sociodemographic and clinical distinguishing features of asthmatic patients in whom long-acting muscarinic antagonists (LAMA) were added to maintenance therapy in our clinic.
Methods: In this cross-sectional study, data on sociodemographic, phenotypic, and clinical characteristics of patients with asthma using Steps 4 and 5 medications, who were followed up in our center for at least 1 year, were obtained from file records. Whether the patients received add-on LAMA for at least 6 months was also noted.
Results: A total of 279 patients with asthma using Steps 4 and 5 medications (female/male: 215/64) with a mean age of 50.84 ± 12.42 years were included in the study. Seventy-nine (28.3%) patients (female/male: 60/19) with a mean age of 52.45 ± 11.61 years used LAMA as an add-on treatment; 28 (37.8%) at Step 4 and 51 (24.8%) at Step 5. In Steps 4 and 5, there was no difference in terms of age, sex, body mass index, smoking status, being allergic or eosinophilic, phenotype, and asthma onset between patients with and without add-on LAMA. Asthma control in the previous year was better, and minimum forced expiratory volume in 1s (FEV1) was lower in patients with LAMA than in those without in Step 4 ($P = 0.001$ and $P = 0.030$, respectively). In Step 5, the rate of being well-controlled was higher in those without add-on LAMA ($P < 0.001$). The number of exacerbations in the previous year was higher, and minimum and maximum FEV1 were lower in patients with add-on LAMA ($P < 0.001$ and $P < 0.001$, respectively).
Conclusion: Our study showed that add-on LAMA treatment was effective in increasing asthma control in patients using Step 4 medication independent of baseline characteristics and asthma phenotype.

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Introduction

Long-term management of asthma aims to provide symptom control and reduce future risks including exacerbations, persistent airway limitation, and side effects of treatments in particular. In this respect, a stepwise approach based on the dosage of inhaled corticosteroids (ICS) is recommended. If disease control is not achieved despite a moderate-high dose of ICS and long-acting beta-agonist (LABA) therapy in Steps 4 and 5, add-on therapies are considered following the elimination of modifiable risk factors.[1]

Long-acting muscarinic antagonists (LAMAs) antagonize the action of acetylcholine by inhibiting muscarinic M1 and M3 receptors in the airways, resulting in smooth muscle relaxation and reduction in airway inflammation, mucus secretion, and asthma-related airway remodeling.[2,3] In clinical studies, the addition of tiotropium, which is one of the LAMAs and acts mainly on M_3 muscarinic receptors located on smooth muscle cells and submucosal glands, to a medium or high dose of ICS and a second controller therapy, was shown to increase peak and trough forced expiratory volume in 1 s (FEV1) values and delay the time of next asthma exacerbation.[4,5] In 2015, the United States Food and Drug Administration (FDA) approved tiotropium for the maintenance treatment of asthma in patients aged ≥ 12 years.[6] Based on clinical studies, the Global Initiative for Asthma (GINA) 2015 recommended adding tiotropium to the treatment of patients who were not under control with medium-dose ICS and LABA in Step 4, and in patients whose asthma was not controlled with high-dose ICS and LABA in Step 5.[7] In real-life studies, the administration of tiotropium as add-on therapy in patients with severe asthma was associated with improved asthma control and lung function. It was shown to significantly reduce the number of emergency room visits and hospitalizations.[8,9] Recently, the effectiveness of fixed-dose combinations of mometasone furoate/indacaterol/glycopyrronium, beclometasone dipropionate/formoterol fumarate/glycopyrronium, and fluticasone furoate/vilanterol/umeclidinium was demonstrated in severe asthma.[10-13] Regarding the clinical trials, the triple combination of ICS/LABA/LAMA was added in Step 5 to the previous recommendations in GINA 2021.[14] Add-on LAMA therapy has been recommended irrespective of the basal asthma phenotype. There is no specific recommendation for which patient group LAMA should be added.[14] Besides that, there is scant data in the literature on the frequency and characteristics of patients with asthma using LAMA.

In this context, the objectives of this study were to determine the frequency of patients using LAMA and to define the sociodemographic and clinical characteristics of these patients in our asthma follow-up center specialized in the management of severe asthma, which has a large and diverse patient population. We also aimed to examine the features that distinguished patients who used LAMA, if any, from patients who were followed up with Steps 4 and 5 medication but did not use LAMA. Thus, additional data will be obtained on the indications of LAMA in the treatment of patients constituting the severe asthma group.

Materials and Methods

Study design and study population

The study was planned as an observational, descriptive, cross-sectional study in accordance with the Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee (Cod: 2023/137).

Data were collected from file records of all patients with asthma who had been on follow-up in our asthma clinic. Our center is experienced in the field of asthma diagnosis and management and is one of the leading referral centers in our country. Patients are examined every day of the week, and the total number of registered patients is over 700 with about 100 new registries annually. A physician and a nurse are assigned to the asthma outpatient clinic in which four professors provide supervision and consultation. Patients with asthma on the treatments of GINA Steps 4 and 5 with at least 1 year follow-up in our center were included after obtaining written permission. It was also noted whether the patients were using LAMA or not. In order to consider patients as "using LAMA," they should have been on LAMA for at least 6 months.

The LAMA used by the study group was tiotropium because it was the only one approved for asthma and the only LAMA available in our country before 2021.

Clinical data collection

The file review phase of the study was conducted between April 2023 and May 2023. During these dates, the records of patients who had followed up at our center for at least 1 year were reviewed. The data collected included the sociodemographic features of the patients, phenotypic features and clinical presentations of asthma, the presence of allergic and systemic comorbidities, and asthma treatment steps. Clinical follow-up parameters including asthma control test (ACT) scores, asthma exacerbations and hospitalizations in the previous year, and pulmonary function test results were also included. The use of tiotropium as add-on therapy, the treatment step at which tiotropium was initiated, and the current treatment to which tiotropium was added were evaluated. Following data evaluation, the characteristics of the patients using add-on tiotropium were documented as well as their disease features. The outcomes of the patients who did and did not receive tiotropium at Steps 4 and 5 were compared within steps for each step.

Definitions

Phenotypic evaluation

Allergic: Patients who were sensitive to at least one inhalant allergen consistent with their history and clinical features in a skin prick test and/or sp IgE measurement.

Eosinophilic: Patients who had a blood eosinophil count of 300/μL or higher in the oral corticosteroid (OCS)-free period or 150/μL or higher under OCS at least twice during the follow-up period.

Non-eosinophilic: Patients who did not fulfil the eosinophilic requirements were considered non-eosinophilic.

Phenotypic groups: Formed according to eosinophilic/non-eosinophilic and allergic/nonallergic status as follows: allergic eosinophilic (AE), nonallergic eosinophilic (NAE), allergic non-eosinophilic (ANE), nonallergic non-eosinophilic (NANE).

Based on age at asthma onset
Early-onset asthma: Diagnosed before the age of 18 years; Adult-onset: Asthma diagnosed between the age of 18 and 40 years.

Late-onset: After the age of 40 years.

Asthma control status at the last visit
Patients were checked in terms of control status according to the following criteria:

1. Having an ACT score of ≥ 20 at the last visit
2. FEV1 variability of less than 12% between visits in the past year
3. Having no history of asthma exacerbation in the previous year.

Well-controlled patients had to meet all three criteria. Partial-controlled patients did not meet one or two of the criteria. Uncontrolled patients met none of the criteria.

Asthma exacerbation
It is defined as the worsening of asthma symptoms, which requires systemic steroid use for at least 3 days.

Pulmonary function test
Minimum forced expiratory volume in 1 s (FEV1min): lowest FEV1 value during follow-up.
Maximum forced expiratory volume in 1 s (FEV1max): highest FEV1 value during follow-up.

Measurements

Skin prick test
Skin prick tests were performed using common aeroallergen extracts (*Dermatophagoides pteronyssinus*; *Dermatophagoides farinae*; mixtures of grass pollens [Dactylis, Festuca, Lolium, Phleum, Poa], tree pollens [Alnus, Betula, Corylus], and cereal pollens [Avena, Triticum, Hordeum, Secale]; weed pollens [Artemisia vulgaris; Parietaria judaica]; molds [*Aspergillus fumigatus*; Cladosporium; *Alternaria alternata*]; and cat and dog epithelia) (ALK, Abello, Spain).

Prick tests were considered positive if at least 3 mm or more edema accompanied by erythema occurred in early readings at the 15th minute with validation by positive (histamine 10 mg/mL) and negative controls (saline).

Specific IgE
The ImmunoCAP fluoroenzyme immunoassay system (Phadia, Uppsala, Sweden) was used for specific IgE testing. Values equal to or higher than 0.35 kU/L were defined as positive.

Pulmonary function test
FEV1, forced vital capacity (FVC), peak expiratory flow (PEF), and maximum mid-expiratory flow (MMF) were measured using a spirometry device (ZAN 100, Germany) and evaluated according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.

Statistical analysis

Statistical analyses were performed using the SPSS version 23 software (SPSS, Chicago, III, USA).

The normality of distribution was assessed using the Kolmogrov–Smirnov method. Frequency of distribution was analyzed, and descriptive statistics was calculated using mean and standard deviation for normally distributed variables, and median and interquartile range for non-normally distributed variables. Classified categoric variables were compared using Fisher's exact test or Pearson's chi-square (x^2) test, as appropriate. Comparisons of variables between groups were performed using Student's t-test/Mann–Whitney U test, and one-way analysis of variance (ANOVA). P-values less than 0.05 were considered statistically significant.

Results

In total, 279 patients with asthma received Step 4 (26.5%, n = 74) and Step 5 (73.5%, n = 205) treatment with at least 1-year of follow-up in our clinic. The mean age was 50.84 ± 12.42 years, and 77.1% (n = 215) were females. A total of 79 (28.3%) patients (female/male: 60/19) with a mean age of 52.45 ± 11.61 years used tiotropium as add-on therapy (Figure 1). All patients had regular follow-ups with a median visit number of five per year.[1-15] The median follow-up period of the patients in our center was 7 (min-max: 1–34) years. Most patients were overweight (39.2%, n = 31) or obese (43.0%, n = 34) and had adult (53.2%, n = 42) or late-onset (38.0%, n = 30) asthma. More than half were nonallergic (64.6%, n = 51) and eosinophilic (70.9%, n = 56). The mean ACT score was 20.88 ± 4.70 at the last visit, and more than half of the patients were well-controlled or partially controlled (34.2%, n = 27 and 36.7%, n = 27 respectively) in the previous year (Table 1). The most common allergic comorbidities were allergic rhinitis (30.7%, n = 24), nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (NERD) (16.5%, n = 13), venom allergy (5.1%, n = 4), and urticaria (5.1%, n = 4). Chronic rhinosinusitis (34.2%, n = 27), nasal polyposis (25.3%, n = 20), gastroesophageal reflux (19.0%, n = 15), hypertension (13.9%, n = 11), and diabetes mellitus (8.9%, n = 7) were mostly seen as systemic comorbidities.

Tiotropium initiation was higher in patients using Step 4 medication compared to those using Step 5 medication (n = 28, 37.8% vs n = 51, 24.8%) (P = 0.034).

Tiotropium was used as add-on therapy at Step 4 in 28 patients, constituting 37.8% of the patients who received Step 4 treatment and 35.4% of the patients with add-on tiotropium (Figure 1). The mean age was 54.05 ± 10.45, and 89.3% (n = 25) were females. More than half of the patients were eosinophilic (57.1%, n = 16) and most were nonallergic (71.4%, n = 20). The nonallergic eosinophilic group was the most (39.3%, n = 11), followed by the nonallergic non-eosinophilic group (35.7%, n = 10). When the patients who did (n = 28) and did not (n = 46) receive tiotropium at

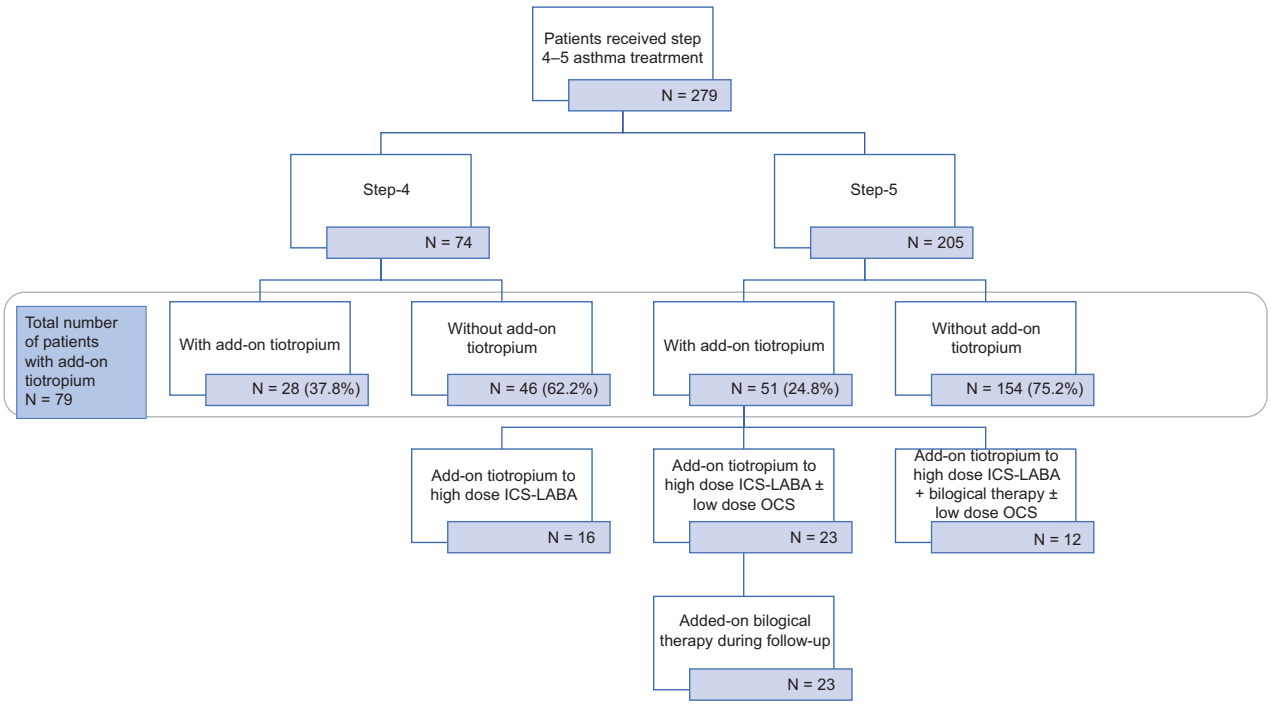

Figure 1 Flow chart of the study.

Table 1 Demographic features of the patients used tiotropium (n = 79).

Sex	Female	75.9 (60)
% (n)	Male	24.1 (19)
Age (mean ± SD)	52.45 ±11.61 years	
Allergy % (n)	Allergic	35.4 (28)
	Nonallergic	64.6 (51)
Blood eosinophilia % (n)	Eosinophilic (≥300 cells/μL)	70.9 (56)
	Non-eosinophilic (<300 cells/μL)	29.1 (23)
Phenotype % (n)	AE	25.3 (20)
	ANE	8.9 (7)
	NAE	44.3 (35)
	NANE	21.5 (17)
Obesity % (n)	Obese (BMI ≥ 30)	43.0 (34)
	Overweight (BMI = 25–29.9)	39.2 (31)
	Normal (BMI < 25)	17.7 (14)
BMI (mean ± SD)	29.74 ± 5.74	
Age of asthma onset, (mean ± SD)	35.16 ± 12.04 years	
Asthma onset % (n)	Early onset	8.9 (7)
	Adult onset	53.2 (42)
	Late onset	38.0 (30)
Disease duration, median (min-max)	17 years (1–34)	
Follow-up duration, median (min-max)	7 years (1–34)	
History of smoke % (n)	Nonsmoker	68.4 (55)
	Smoker	7.6 (6)
	Ex-smoker	24.1 (18)
Asthma control % (n)	Well	34.2 (27)
	Partial	36.7 (29)
	Uncontrolled	29.1 (23)
ACT score (mean ± SD)	20.88 ± 4.70	

ACT, asthma control test; AE, allergic eosinophilic; ANE, allergic non-eosinophilic; BMI, body mass index; NAE, nonallergic eosinophilic; NANE, nonallergic non-eosinophilic; SD, standard deviation.

Step 4 were compared, there was no difference between the two groups in terms of age, sex, being eosinophilic or allergic, BMI, asthma onset, history of smoking, and number of asthma exacerbations in the previous year (Table 2). Although the patients with add-on tiotropium were mostly in the NAE and NANE groups, the distribution of patients in phenotypic groups was more homogeneous than those who did not receive tiotropium; however, there was no statistical difference between the two groups in terms of phenotypes (P = 0.082). Asthma control scores at the last visits were similar in both groups (P = 0.088), but when we looked at the control status in the previous year, patients who received tiotropium were more controlled than those who did not (P = 0.001). The patients who received tiotropium had lower minimum FEV1 scores during the follow-up period (P = 0.030) (Table 2).

Fifty-one patients received tiotropium at Step 5; 24.8% of the patients received Step 5 treatment, and 64.6% of the patients received add-on tiotropium. In 16 patients, tiotropium was added to high-dose ICS-LABA; and in 23 patients, tiotropium was added to high-dose ICS-LABA ± OCS, but these patients eventually switched to biologic therapy. The remaining 12 patients with add-on tiotropium were on biologic therapy in addition to high-dose ICS-LABA ± OCS (Figure 1). Among the patients who followed up with Step 5 treatment in our clinic, compared with the patients with and without add-on tiotropium (n = 51 and n = 154, respectively), there was no difference between the two groups in terms of age, sex, blood eosinophil count, atopy, asthma phenotypes, BMI, age of asthma onset, and smoking history (Table 3). ACT scores of the patients with and without add-on tiotropium were similar (P = 0.362). Patients

Table 2 Comparison of the features of patients with and without add-on tiotropium in Step 4.

		With add-on tiotropium (n = 28)	Without add-on tiotropium (n = 46)	P
Age (mean ± SD)		54.05 ± 10.45	51.09 ± 12.35	0.290
Female % (n)		89.3 (25)	91.3 (42)	0.999
Allergy % (n)	Allergic	28.6 (8)	45.7 (21)	0.225
	Nonallergic	71.4 (20)	54.3 (25)	
Blood eosinophilia % (n)	Eosinophilic (≥ 300cells/μL)	57.1 (16)	39.1 (18)	0.205
	Non-eosinophilic (<300 cells/μL)	42.9 (12)	60.9 (28)	
Phenotype % (n)	AE	17.9 (5)	15.2 (7)	0.082
	ANE	7.1 (2)	30.4 (14)	
	NAE	39.3 (11)	23.9 (11)	
	NANE	35.7 (10)	30.4 (14)	
Obesity % (n)	Obese (BMI ≥ 30)	46.4 (13)	58.7 (27)	0.451
	Overweight (BMI = 25-29.9)	32.1 (9)	19.6 (9)	
	Normal (BMI < 25)	21.4 (6)	21.7 (10)	
BMI		29.60 ± 5.65	30.96 ± 6.14	0.344
The onset age of asthma (mean ± SD)		37.17 ± 11.90	34.54 ± 10.58	0.325
Asthma onset % (n)	Early onset	7.1 (2)	6.5 (3)	0.779
	Adult onset	57.1 (16)	65.2 (30)	
	Late-onset	35.7 (10)	28.3 (13)	
History of smoke % (n)	Nonsmoker	71.4 (20)	69.6 (32)	0.154
	Smoker	17.9 (5)	6.5 (3)	
	Ex-smoker	10.7 (3)	23.9 (11)	
Asthma control	Well	42.9 (12)	54.3 (25)	0.001
	Partial	32.1 (9)	2.2 (1)	
	Uncontrolled	25.0 (7)	43.5 (20)	
ACT (mean ± SD)		20.50 ± 4.54	22.11 ± 3.42	0.088
Number of visits per year median (min-max)		4 (1-13)	3 (1-5)	<0.001
Number of asthma exacerbations median (min-max)		0 (0-3)	0 (0-2)	0.164
Pulmonary function tests	FEV1 min %	70.15 ± 19.18	78.26 ± 20.30	0.101
(mean ± SD)	FEV1 min mL	1.91 ± 0.65	0.030	
	FEV1/FVC min	72.43 ± 11.29	0.209	
	FEV1 max %	92.04 ± 19.43	0.099	
	FEV1 max mL	2.22 ± 0.64	0.065	
	FEV1/FVC max	76.50 ± 8.79	0.250	

ACT, asthma control test; AE, allergic eosinophilic; ANE, allergic non-eosinophilic; BMI, body mass index; FEV1, forced expiratory volume in 1 s; FVC: forced vital capacity; NAE, nonallergic eosinophilic; NANE, nonallergic non-eosinophilic; SD, standard deviation.

with add-on tiotropium at Step 5 experienced more frequent asthma exacerbations than those without tiotropium (P < 0.001), and therefore being well-controlled was more common in patients without add-on tiotropium. The rate of being partially controlled was higher in the group with add-on tiotropium (P < 0.001). The patients with add-on tiotropium had lower pulmonary function test values than those without add-on tiotropium (P < 0.001). The mean minimum FEV1 of patients with add-on tiotropium was 1.38 ± 0.55 L (56.49 ± 20.52%), whereas it was 1.99 ± 0.75 L (75.69 ± 18.31%) for patients without tiotropium. The mean maximum FEV1 value of patients with add-on tiotropium was 1.85 ± 0.67 L (72.55 ± 25.52%), and it was 2.48 ± 0.86 L (93.81 ± 18.40%) in the patients without add-on tiotropium (Table 3).

The patients were divided into three groups, Groups 1-3, according to the treatment stage in which tiotropium was added at Step 5. In Group 1 (n = 16), tiotropium was added to high-dose ICS-LABA. In Group 2 (n = 23), which included patients who had tiotropium added to high-dose ICS-LABA and/or low-dose OCS; 4 patients received omalizumab and 19 patients received mepolizumab as biological treatments during follow-up. In Group 3 (n = 12), tiotropium was added to high-dose ICS-LABA and with biologic treatment already being received and/or low-dose OCS. In Group 3 (n = 12), which consisted of patients already receiving biologic therapy, six patients each were on omalizumab and mepolizumab. The proportion of eosinophilia was higher in Groups 2 and 3 than in Group 1 (P = 0.003). Although NAE was higher in Groups 2 and 3 (n = 14, 60.9% and n = 7, 58.3%, respectively), almost half of Group 1 was NANE (n = 7, 43.8%) (P = 0.002). Group 2 had the highest number of asthma exacerbations (P = 0.041). Minimum FEV1 was lower in Group 3 than in Groups 1 and 2 (1.04 ± 0.34 L vs 1.32 ± 0.50 L and 1.58 ± 0.59 L, respectively) (P = 0.018). Similarly, the maximum FEV1 measurement was lowest in Group 3 compared to Groups 1 and 2 (1.56 ± 0.59 L vs 1.64 ± 0.53 L and 2.14 ± 0.69 L, respectively) (P = 0.014). Refer Table 4.

Finally, biologic treatment began before tiotropium in 12 (23.4%) patients with add-on tiotropium in Step 5 treatment (group 3); 117 (76.0%) patients using Step 5 medication without tiotropium were receiving biologic treatment (P < 0.001). As stated before, patients in Group 2 (n = 23) at Step 5 were those who were started on biologic treatment after tiotropium due to asthma exacerbations.

Discussion

The results of our study indicate that tiotropium was initiated as an add-on therapy independent of demographic characteristics and asthma phenotype at both Steps 4 and 5 in our center. However, we tended to initiate tiotropium for patients with low pulmonary functions. Asthma control seemed to increase with the addition of tiotropium in patients using Step 4 medication. In Step 5 treatment, regardless of the stage at which tiotropium was started, asthma control was worse, and asthma exacerbations were more frequent in patients with add-on tiotropium than in those without.

The fact that there was no difference in terms of demographic and clinical characteristics of the patients between the groups using and not using tiotropium in our study suggested that it is not crucial to consider age, sex, asthma phenotype, existence of obesity, asthma onset, and smoking status when starting tiotropium. This finding is also compatible with the recommendations of existing guidelines.[1] Consequently, no certain phenotypic or endotypic feature related to the effectiveness of add-on LAMA was detected in the studies that provided the rationale for this recommendation.[5,11,13,15]

Since the first studies investigating the place of LAMAs in asthma treatment, many studies have shown that add-on LAMA increased peak and trough FEV1 values.[4,5,13,16,17] Therefore, although add-on LAMA is recommended in the treatment of asthma regardless of the basal FEV1 value, as well as the baseline inflammatory phenotype,[17,18] it has been preferred in our patients with asthma with low FEV1 in both Steps 4 and 5.

In our study, add-on tiotropium seemed to facilitate achieving overall asthma control in Step 4 according to our composite control assessment including symptom control, exacerbations, and FEV1. In the randomized-control trial evaluating the efficacy of single-inhaler triple therapy in asthma, in one of the two parallel groups including adult patients with uncontrolled asthma previously treated with medium-dose ICS and LABA, the rate of moderate and severe exacerbations decreased significantly accompanied by an increased FEV1 with the addition of LAMA.[12] In the study assessing the efficacy of add-on LAMA (glycopyrronium) to medium-dose ICS and LABA in Step 4, medium-dose ICS/LABA/LAMA increased lung function and reduced asthma exacerbations more than high-dose ICS/LABA.[19] These studies suggest that adding LAMA may be a better option in Step 4 rather than increasing the ICS dose. The finding that tiotropium was started in Step 4 at a significantly higher rate in our clinic and that control was better in patients with add-on tiotropium was compatible with this result.

In contrast to the current GINA recommendation related to adding LAMA before biologic treatment in Step 5, the rate of receiving biologic treatment without tiotropium in Step 5 was higher in our study population. We believe that this is because our center is an allergy-immunology clinic with a high number of patients referred to biologic therapy, and has a high number of patients included in clinical phase trials[20-23] and real-life studies.[24-27] In parallel to our result, in a study with a large population of moderate-to-severe asthmatics assessing the use of LAMA or biologic treatment as an add-on treatment, pulmonologists were more likely to initiate LAMA, whereas allergists tended to initiate biologic treatments.[28] The other explanation for the imbalance of initial rates could be that our patients were being followed for a long time and only recently was add-on LAMA treatment placed before phenotyping for biologics in the guidelines. Therefore, although symptom control was similar in both groups, the control status in the previous year was worse in patients with tiotropium than in those without add-on tiotropium. In other words, poor control in patients with add-on tiotropium at Step 5 may be explained by the fact that they were not under biological treatment.

We believe that this study will make a valuable contribution to the data gap on the use of LAMA in patients with asthma because we know it is the first study from our

Table 3 Comparison of the features of patients with and without add-on tiotropium in Step 5 (n = 205).

		With add-on tiotropium (n = 51)	Without add-on tiotropium (n = 154)	P
Age (mean ± SD)		52.16 ± 12.18	49.74 ± 12.80	0.239
Female % (n)		68.6 (35)	73.4 (113)	0.634
Allergy % (n)	Allergic	39.2 (20)	52.6 (81)	0.135
	Nonallergic	60.8 (31)	47.4 (73)	
Blood eosinophilia % (n)	Eosinophilic (≥ 300cells/μL)	78.4 (40)	75.3 (116)	0.794
	Noneosinophilic (<300 cells/μL)	21.6 (11)	24.7 (38)	
Phenotype %(n)	AE	29.4 (15)	37.0 (57)	0.374
	ANE	9.8 (5)	15.6 (24)	
	NAE	47.1 (24)	38.3 (59)	
	NANE	13.7 (7)	9.1 (14)	
Obesity % (n)	Obese (BMI ≥ 30)	43.1 (22)	42.9 (66)	0.126
	Overweight (BMI = 25–29.9)	41.2 (21)	27.9 (43)	
	Normal (BMI <25)	15.7 (8)	29.2 (45)	
BMI		29.59 ± 5.76	29.07 ± 6.24	0.605
The onset age of asthma (mean ± SD)		35.27 ± 12.68	33.94 ± 12.21	0.504
Asthma onset % (n)	Early onset	9.8 (5)	10.4 (16)	0.826
	Adult onset	51.0 (26)	55.2 (85)	
	Late onset	39.2 (20)	34.4 (53)	
History of smoke % (n)	Nonsmoker	68.6 (35)	81.2 (125)	0.169
	Smoker	2.0 (1)	1.9 (3)	
	Ex-smoker	29.4 (15)	16.9 (26)	
Asthma control % (n)	Well	34.0 (17)[a]	55.2 (85)[b]	<0.001[#]
	Partial	34.0 (17)[a]	7.1 (11)[b]	
	Uncontrolled	32.0 (16)[a]	37.7 (58)[a]	
ACT (mean ± SD)		21.33 ± 4.72	21.95 ± 3.96	0.362
Number of visits per year median (min–max)		6 (2–15)	8.5 (0–24)	0.111
Number of asthma exacerbations median (min–max)		1 (0–6)	0 (0–5)	<0.001
Pulmonary function tests (mean ± SD)	FEV1 min %	56.49 ± 20.52	75.69 ± 18.31	<0.001
	FEV1 min mL	1.38 ± 0.55	1.99 ± 0.75	<0.001
	FEV1/FVC min	64.17 ± 12.23	72.45 ± 9.02	<0.001
	FEV1 max %	72.55 ± 25.52	93.81 ± 18.40	<0.001
	FEV1 max mL	1.85 ± 0.67	2.48 ± 0.86	<0.001
	FEV1/FVC max	68.56 ± 12.19	76.69 ± 7.60	<0.001

ACT, asthma control test; AE, allergic eosinophilic; ANE, allergic non-eosinophilic; BMI, body mass index; FEV1, forced expiratory volume in 1 s; FVC: forced vital capacity; NAE, nonallergic eosinophilic; NANE, nonallergic non-eosinophilic; SD, standard deviation.
*Different letter indices indicate significance.
[#]The results of the pairwise comparisons as follows: partial vs well-controlled: P < 0.001, partial versus uncontrolled: P < 0.001, well-controlled versus uncontrolled: P = 0.525.

country and one of the limited real-life studies in world literature. However, the study also has some limitations. First, because of being a cross-sectional study, no direct results demonstrating the effect of add-on tiotropium on asthma outcomes could be obtained. In addition, due to the nature of the study, data on follow-up could not be provided. Another limitation is that only the data of patients receiving tiotropium are presented in our study because the triple treatment option in a single device is very recent in our country and our patients have been followed for many years.

Conclusion

In the present study, individuals with asthma using Step 4 medication with add-on tiotropium showed improved

Table 4 Comparison of the features of the patients with add-on tiotropium in Step 5 (n = 51).

		Group 1 (n = 16)	Group 2 (n = 23)	Group 3 (n = 12)	P
Age (mean ± SD)		54.31 ± 10.73	49.65 ± 13.33	54.92 ± 11.79	0.369
Female % (n)		75.0 (12)	65.2 (15)	66.7 (8)	0.795
Allergy % (n)	Allergic	37.5 (6)	39.1 (9)	41.7 (5)	0.975
	Nonallergic	62.5 (10)	60.9 (14)	58.3 (7)	
Blood eosinophilia	Eosinophilic (≥300 cells/μL)	50.0 (8)[a]	95.7 (22)[b]	83.3 (10)[a,b]	0.003[§]
% (n)	Noneosinophilic (<300 cells/μL)	50.0 (8)[a]	4.3 (1)[b]	16.7 (2)[a,b]	
Phenotype % (n)	AE	15.4 (4)[a]	35.7 (8)[a]	25.0 (3)[a]	0.001[†]
	ANE	12.5 (2)[a]	4.3 (1)[a]	16.7 (2)[a]	
	NAE	18.8 (3)[a]	60.9 (14)[b]	58.3 (7)[a,b]	
	NANE	43.8 (7)[a]	00.0 (0)[b]	00.0 (0)[b]	
Obesity % (n)	Obese (BMI ≥ 30)	56.3 (9)	30.4 (7)	41.7 (5)	0.492
	Overweight (BMI = 25–29.9)	37.5 (6)	47.8 (11)	41.7 (5)	
	Normal (BMI <25)	6.3 (1)	21.7 (5)	16.7 (2)	
BMI		31.85 ± 7.02	28.34 ± 4.57	29.13 ± 5.97	0.174
The onset age of asthma (mean ± SD)		35.31 ± 11.25	32.21 ± 11.96	34.41 ± 11.28	0.761
Asthma onset %(n)	Early onset	0.0 (0)	17.4 (4)	8.3 (1)	0.243
	Adult onset	56.3 (9)	52.2 (12)	41.7 (5)	
	Late-onset	43.8 (7)	30.4 (7)	50.0 (6)	
History of smoke %(n)	Nonsmoker	62.5 (10)	73.9 (17)	66.7 (8)	0.614
	Smoker	0.0 (0)	4.3 (1)	0.0 (0)	
	Ex-smoker	37.5 (6)	21.7 (5)	33.3 (4)	
Asthma control	Controlled	52.5 (10)	73.9 (17)	66.7 (8)	0.385
	Uncontrolled	37.5 (6)	26.1 (6)	33.3 (4)	
ACT (mean ± SD)		21.94 ± 3.90	20.00 ± 5.83	22.33 ± 3.39	0.298
Number of asthma exacerbations median (min-max)		1 (0-2)	1 (0-6)	1 (0-2)	0.041[#]
Pulmonary function tests	FEV1 min %	57.56 ± 19.72	59.56 ± 17.42	47.16 ± 23.97	0.210
(mean ± SD)	FEV1 min mL	1.32 ± 0.50	1.58 ± 0.59	1.04 ± 0.34	0.018[ß]
	FEV1/FVC min	63.81 ± 12.35	66.43 ± 11.96	60.00 ± 11.80	0.331
	FEV1 max %	70.50 ± 20.18	76.71 ± 25.47	69.00 ± 33.59	0.643
	FEV1 max mL	1.64 ± 0.53	2.14 ± 0.69	1.56 ± 0.59	0.014[ŧ]
	FEV1/FVC max	67.18 ± 11.13	72.43 ± 11.69	62.91 ± 12.63	0.074

ACT, asthma control test; AE, allergic eosinophilic; ANE, allergic non-eosinophilic; BMI, body mass index; FEV1, forced expiratory volume in 1 s; FVC: forced vital capacity; NAE, nonallergic eosinophilic; NANE, nonallergic non-eosinophilic; SD, standard deviation.

*Different letter indices indicate significance.

Group 1: Add-on tiotropium to high-dose ICS-LABA, **Group 2:** Add-on tiotropium to high-dose ICS-LABA ± low-dose OCS and added-on biologic therapy during follow-up, **Group 3:** Add-on tiotropium to high-dose ICS-LABA+biologic therapy ± low-dose OCS.

A post-hoc test was performed to identify exactly which groups differed from each other.

[§]Group 1 vs Group 2: P = 0.001; Group 1 vs Group 3: P = 0.114; and Group 2 vs Group 3: P = 0.266

[†]Group 1 vs Group 2: P < 0.001; Group 1 vs Group 3: P = 0.012; and Group 2 vs Group 3: P = 0.458

[#]Group 1 vs Group 2: P = 0.028; Group 1 vs Group 3: P = 0.999; and Group 2 vs Group 3: P = 0.032

[ß]Group 1 vs Group 2: P = 0.375; Group 1 vs Group 3: P = 0.508; and Group 2 vs Group 3: P = 0.016

[ŧ]Group 1 vs Group 2: P = 0.052; Group 1 vs Group 3: P = 0.999; and Group 2 vs Group 3: P = 0.037

asthma control compared with those without add-on tiotropium independent of baseline characteristics and asthma phenotype. Our results showed that we preferred biologic treatment before add-on tiotropium, especially in type-2 dominant individuals in Step 5. Taken together, these findings will help to encourage starting LAMA in patients using Steps 4 and 5 medication before biologics. Future follow-up real-life studies should focus on investigating the effectiveness of add-on LAMA in patients with various phenotypes and distinct features.

Statement of Ethics

The local ethics committee of Ankara University, School of Medicine, approved the study (Approval no: 2023/137). The

authors declare that they have followed the protocols of their work center on the publication of patient data and that the patients included in the study received sufficient information and gave their informed consent in writing to participate in this study. The study was conducted under the Declaration of Helsinki.

Artificial Intelligence Disclosure Statement

No artificial intelligence (AI) tools or techniques were employed in the creation or analysis of this paper.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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