REVIEW ARTICLE

Current role of anticholinergic drugs in the treatment of asthma

Key messages for clinical practice

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KEY WORDS

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ABSTRACT

Anticholinergic bronchodilators such as tiotropium, a potent long-acting drug, are central to the symptomatic treatment of chronic obstructive pulmonary disease. Its role in asthma treatment has been recently investigated. This review critically evaluates documented evidence of clinical trials and assesses the therapeutic implications of anticholinergic drugs in asthma management.

So far, the results of 10 Phases II and III randomized controlled trials evaluating the effect of adding tiotropium to the treatment of mild-to-moderate or severe asthma have been published. These trials had a duration of 4 to 52 weeks and involved 3368 subjects with mild-to-moderate asthma and 1019 subjects with severe asthma. Also, 1 systematic review and 6 meta-analyses have appraised the results of published and unpublished trials investigating the role of tiotropium in asthma. The results of the trials in mild to moderate asthma showed that adding tiotropium to inhaled corticosteroids (ICSs) was not inferior to adding long-acting β_2-agonists (LABAs). In addition, the safety and efficacy of tiotropium were similar to those of salmeterol. The results of studies on severe asthma showed that adding tiotropium to a treatment with high doses of an ICS plus LABA results in further improvement in lung function, increases the time to the first severe exacerbation of asthma and to worsening of asthma, and improves asthma control. Except for dry mouth, the safety profile of tiotropium was similar to placebo both in moderate and in severe asthma.

Adding tiotropium to an ICS or ICS plus LABA improves lung function, symptoms, and asthma control, and in severe asthma, it increases the time to exacerbations, with good safety profile. The effect seems independent of baseline characteristics such as age, level of bronchial obstruction, smoking status, allergic status, and bronchial reversibility.

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Introduction Asthma is one of the most common chronic noncommunicable respiratory diseases worldwide. The disease imposes great personal and social burden and currently ranks No. 15 of the global top 25 causes of years lived in disability.[1] Although characteristically asthma is a disease of children and young adults,[2] it affects all age groups, and late-onset asthma in adults and elderly individuals is not uncommon.[3] Currently, asthma is defined as a heterogeneous disease, usually characterized by chronic airway inflammation and clinically expressed by a history of variable respiratory symptoms (wheeze, shortness of breath, chest tightness, and cough) and variable airflow limitation.[4]

It is now commonly recognized that the main objective of asthma treatment is to achieve and maintain asthma control and to prevent future risks including worsening, exacerbations, accelerated loss of lung function, and side effects of treatment.[4] Despite remarkable recent advances in the understanding of asthma epidemiology, physiopathology, and management, current evidence suggests that asthma control is still

suboptimal in many patients, especially in those with more severe asthma.[5] Poor adherence, incorrect use of inhaler devices, misdiagnosis, occupational or environmental exposures, and comorbidities may account for a great part of inadequate asthma control.

In a stepwise manner, the Global Initiative for Asthma[4] recommends starting with short-acting β_2-agonists, quickly followed by inhaled corticosteroids (ICSs) in patients with symptoms occurring every week or more often. However, if the disease remains uncontrolled even after correcting for all the above factors and optimizing asthma treatment at least with an ICS, a step-up in treatment is required.[6] This step-up routinely consists of long-acting β_2-agonists (LABAs), but control remains poor in many patients. Moreover, some patients cannot tolerate LABAs.

An alternative mode of bronchodilation is antagonizing the cholinergic system. In asthma, the use of short-acting anticholinergics is advocated for exacerbations of asthma in the hospital, but administering these drugs in stable asthma is not generally advocated.[4] It is notable that tiotropium, a potent long-acting selective anticholinergic bronchodilator, approved for use in chronic obstructive pulmonary disease (COPD) for more than a decade, only recently has been investigated as a controller treatment in asthma.[14-24] The role of tiotropium in asthma management has generated great interest as shown by the recent publication of 1 systematic review[7] and 6 meta-analyses.[8-13] This interest is not unforeseen, as most of the studies investigating the effect of adding tiotropium to asthma treatment were conducted in patients with moderate[14-16,18-22] and with severe asthma,[23,24] those with the greatest burden of asthma, significant impact on the quality of life,[25] and those that would benefit most from alternative or additional treatments.

This review will critically evaluate the documented evidence of the clinical trials conducted to date and will subsequently assess the therapeutic implications of anticholinergic drugs in the treatment of asthma.

Tiotropium bromide Long-acting β_2-bronchodilators in combination with an ICS are the preferred option in the management of asthma when the use of an ICS alone does not allow to achieve sufficient disease control.[4] Short-acting anticholinergics (ipratropium bromide) alone or in combination with a short-acting β_2-agonist have long been used as a reliever medication in asthma. Tiotropium bromide is a potent long-acting selective inhaled muscarinic antagonist with bronchodilator effect sustained for 24 hours. It is extensively used as maintenance therapy in moderate--to-severe COPD.[26] These bronchodilatory properties, the putative additional effects of tiotropium decreasing mucus production[26] and possibly modulating airway inflammation,[27,28] make this an attractive therapeutic option for the management of asthma.

The innervation of the human airways is based predominantly on the cholinergic parasympathetic system, and consequently, the tone of the airways is predominantly controlled by the vagus nerve. The nerve releases acetylcholine, which in turn activates muscarinic receptors on smooth muscle and submucosal gland cells, resulting in bronchoconstriction and mucus secretion, respectively.[29] There are 5 types of muscarinic receptors (M1–M5), of which 4 (M1–M4) are active and expressed in the majority of airway cells and lung tissue.[30,31] In humans, the M1 receptors are located in the periphery of the lungs and airway nodes, whereas the M2 and M3 receptors are located more centrally in the airways and lungs.[29,30] In human lungs, acetylcholine-induced bronchoconstriction results from the stimulation of M3 receptors on smooth muscle cells.[32]

The prolonged pharmacologic activity of tiotropium bromide is the result of its slow dissociation from M1 receptors (expressed particularly in the small airways and believed to facilitate cholinergic traffic through peribronchial ganglia) and M3 receptors (which promote smooth muscle constriction in the airways and increased mucous secretion) and quick dissociation from M2 receptors (which inhibit the further release of acetylcholine from postganglionic nerves and are believed to inhibit smooth muscle relaxation).[29,30,32,33] In asthma, the dysfunction of airway muscarinic receptors has been related to airway hyperresponsiveness, particularly to neuronal M2 receptors, which are susceptible to products released from eosinophils and to viral infection.[26,33,34]

The mechanism of action of anticholinergic bronchodilators either in asthma or COPD is believed to be related to a reduction in the basal level of bronchomotor tone in the small airways. However, the extent to which the cholinergic tone contributes to the narrowing of the airways in asthma is unclear.[35] Nevertheless, the fact that airway hyperresponsiveness can persist in asthmatic patients, even in the absence of airway inflammation following the long-term use of an ICS,[36] suggests that other factors, such as increased cholinergic and smooth muscle tone, have a role in asthma.[37] Also, there is increasing evidence that cells outside the cholinergic neuronal network, such as airway epithelial cells, synthesize, contain, and release acetylcholine.[28,38] Thus, acetylcholine is both a neurotransmitter and a local signaling molecule produced by nonneuronal cells. Regardless of the mechanism, the raised parasympathetic tone[39] is sufficient to provide a rationale for the use of tiotropium in asthma.

Clinical insights from tiotropium trials in asthma Despite current effective treatments, suboptimal control of asthma occurs in at least 40% of patients.[40,41] The current guidelines[4] recommend stepwise management to obtain and maintain control, in which the clinical definition of control is the absence of daytime symptoms or their presence less than twice a week, no need for reliever

medication or less than twice a week, no limitations of activity, and no nocturnal awakenings from asthma symptoms.

Tiotropium has been investigated in mild-to--moderate and in severe asthma, which will be discussed separately.

Tiotropium in mild-to-moderate asthma The role of tiotropium in mild-to-moderate asthma or in moderate asthma has been investigated in various randomized, double-blind, placebo-controlled clinical trials (RCTs)[15-22] with a duration that ranged from 4 to 52 weeks (TABLE 1), and reviewed in a recent meta-analysis.[13] The TALC trial[16] was the only published study to investigate the role of tiotropium in mild-to-moderate asthma, though an additional trial has been presented as an abstract.[17] In the other studies,[15-19] the severity of asthma was moderate. The primary outcome was morning peak expiratory flow (PEF) in 2 studies,[15,16] peak forced expiratory volume in 1 second (FEV_1) in 2 studies,[17,18] and peak FEV_1 area under the curve from zero to 24 hours in 1 study.[19] In another manuscript, which comprised of 2 replicate RCTs, prespecified coprimary endpoints were peak and trough FEV_1 and asthma control.[20]

In the investigator-initiated TALC trial (tiotropium as an alternative to increase the dose of an ICS in patients inadequately controlled on a lower dose of an ICS), a 3-way randomized, double--blind, triple-dummy crossover study of 14 weeks of duration, 210 subjects were included and 174 completed all the study arms.[15] The primary outcome measure was the morning PEF and secondary outcomes included prebronchodilator FEV_1, the number of asthma-control days (defined as days without symptoms and without the use of a rescue bronchodilator), asthma symptoms, the Asthma Control Questionnaire (ACQ),[42] and the Asthma Quality-of-Life Questionnaire (AQLQ),[43] among others. This is the only study in this review performed with the dry-powder formulation of tiotropium. It demonstrated that treatment with tiotropium (18 μg) via HandiHaler plus beclomethasone (2 puffs of 40 μg twice daily) resulted in greater improvements in PEF compared with doubling the dose of an ICS (160 μg, 2 puffs of 80 μg twice daily of beclomethasone) and similar to adding salmeterol (50 μg) twice daily. Also, treatment with added tiotropium was associated with improvements in spirometry, asthma control, and provided symptomatic benefit that was greater than doubling the dose of an ICS, and either noninferior to or better than salmeterol.

In another study, with a similar design, Bateman et al,[16] based on the concerns regarding the safety of LABAs in asthmatic patients with the B16-Arg/Arg genotype, investigated the role of tiotropium as add-on treatment in patients with this genotype and moderate asthma not controlled by an ICS alone (budesonide, 400–1000 μg/d, or equivalent). This study provided evidence that tiotropium (5 μg) was not inferior to salmeterol treatment in maintaining the lung function improvement achieved with salmeterol and was superior to placebo. Improvements in symptoms were comparable between tiotropium and salmeterol and better than placebo. In addition, the results suggested that tiotropium might be an alternative add-on treatment for asthmatics with the B16-Arg/Arg genotype requiring treatment with an ICS plus a second controller drug to achieve and maintain asthma control.

Two phase II studies[18,19] investigated the effect of different doses of tiotropium on symptomatic asthma despite medium doses of ICS alone or associated with a second controller drug. In a dose-ranging, double-blind, placebo-controlled crossover study published by Beeh et al,[18] 174 adults with moderate asthma not fully controlled on an ICS alone (budesonide, 400–800 μg/d, or equivalent) or in a fixed-dose combination with a LABA or short-acting β_2-agonist were randomized to receive tiotropium delivered via a Respimat inhaler (5, 2.5, or 1.25 μg once daily) or placebo, while discontinuing the LABA medication. Peak FEV_1, the primary endpoint, was significantly higher with a dose of 5 μg when compared with placebo (by 188 ml), and to 2.5 μg (60 ml), and to 1.125 μg (49 ml). Tiotropium respimat (5 μg) was found to be the most effective and consistent dose, with a safety profile comparable to that of placebo. The second dose-ranging phase II study was published by Vogelberg et al.[19] This study differed from the one performed by Beeh et al[18] by including only adolescents aged from 12 to 17 years and by an incomplete crossover design. Tiotropium respimat (5 μg) was the only dose that was significantly better than placebo in both peak and trough FEV_1. There were no safety issues.

However, the above studies[15,18,19] were relatively small. Recently, Kerstjens et al[21] published the results of the first large trials in adults with moderate symptomatic asthma (N = 2103). This consisted of 2 replicate randomized, double-blind, placebo-controlled, parallel-group studies, with an active comparator and 24-week follow-up. Eligible patients were aged from 18 to 75 years with symptomatic asthma and a prebronchodilator FEV_1 of 60% to 90% predicted despite the use of a medium dose of an ICS. They were nonsmokers or ex-smokers for 1 year or more with 10 pack--years or less. Patients randomly received tiotropium (5 μg or 2.5 μg once daily), salmeterol (50 μg twice daily), or placebo, while maintaining ICSs. Primary endpoints were peak and trough FEV_1, and asthma control assessed as ACQ responder rates. Once-daily tiotropium as add-on treatment to a medium-dose ICS resulted in significant improvements in lung function and asthma control compared with placebo, and which were similar to those recorded for twice-daily salmeterol. There was no significant difference between the 2 doses of tiotropium. In addition, the safety of tiotropium was similar to that of salmeterol.[21]

Tiotropium in severe asthma The role of tiotropium in severe asthma was examined in 3 clinical

TABLE 1 Clinical trials of tiotropium in moderate asthma (continued on page 863)

Study ref.	Design/duration	Intervention	Subjects (n) /age/ FEV_1	Key inclusion criteria	Outcomes
Peters et al[15]	RCT: 3-way, DB, triple-dummy, crossover study 14 weeks	double ICS dose (to medium dose) vs ICS low dose + TIO HandiHaler® 18 µg OD vs ICS low dose + SALM 50 µg BID	randomized: 210 completed: 174 mean age: 42.2 y mean pre-BD baseline FEV_1: 71.5% predicted	• age: >18–75 y • asthmatics with mild-to-moderate disease not fully controlled on a low-dose ICS (160 µg BDP BID) • FEV_1 >40% predicted • never smokers or ex-smokers[a]	primary outcome: • morning PEF secondary outcomes: • mean weekly PEF • proportion of control days • AQLQ • pre-BD FEV_1
Bateman et al[16]	RCT: DB, double-dummy, PC, parallel-group study 16 weeks	ICS moderate-to-high dose + TIO 5 µg OD vs ICS moderate-to-high dose + SALM 25 µg BID vs ICS moderate-to-high dose + placebo	randomized: 388 completed: 367 mean age: 43 y mean pre-BD baseline FEV_1: 75% predicted	• age: >18–67 y • asthmatics, B16-Arg/Arg genotype, with moderate disease not fully controlled on a medium-dose ICS (400–1000 µg BUD OD) alone or + SALM • pre-BD FEV_1 <90% predicted for those on ICS alone and <80% for those on ICS + LABA • never smokers or ex-smokers[a]	primary outcome: • mean morning PEF at the end of treatment secondary outcomes: • other weekly PEF parameters • proportion of control days • AQLQ • pre-BD FEV_1
Beeh et al[18]	RCT: phase II, DB, PC, dose-ranging, 4-way crossover study four 4-week periods	ICS + TIO 5.0 µg OD vs ICS + TIO 2.5 µg vs ICS + TIO 1.25 µg vs ICS+ placebo	randomized: 149 completed: 141 mean age: 49.3 y mean pre-BD baseline FEV_1: 71.5%	• age: >18–75 y • asthmatics with moderate disease not fully controlled with an ICS (BUD, 400–800 µg, or equivalent) alone or + LABA • pre-BD FEV_1 ≥60% and ≤90% predicted • never smokers or ex-smokers[a] • ACQ ≥1.5	primary outcome: • peak FEV_1 secondary outcomes: • trough FEV_1 • peak FVC • trough FVC • ACQ score • safety
Vogelberg et al[19]	RCT: Phase II, DB, PC, 4-way, incomplete crossover study three 4-week periods	ICS + TIO 5.0 µg OD vs ICS + TIO 2.5 µg vs ICS + TIO 1.25 µg vs ICS+ placebo	randomized: 139 completed: 97 mean age: 14.0 y mean pre-BD baseline FEV_1: 71.5% predicted	• age: 12–17 y • asthmatics with moderate disease on a medium dose of an ICS alone or + LABA; LABA was discontinued • pre-BD FEV_1 ≥60% and ≤90% predicted • never smokers or ex-smokers[a] • ACQ ≥ 1.5	primary outcome: • peak FEV_1 secondary outcomes • FEV_1 peak and area under the curve • PEF • ACQ score • safety
Timmer et al[20]	RCT: phase II, DB, PC, crossover study three 4-week periods and 21-day follow-up	ICS medium dose + TIO 5.0 µg OD (evening) vs ICS medium dose + TIO 2.5 µg BID	randomized: 94 completed: 89 mean age: 44.3 y mean pre-BD baseline FEV_1: 73.4% predicted	• age: >18–75 y • asthmatics with moderate disease not fully controlled with a medium dose of an ICS alone or + LABA • pre-BD FEV_1 ≥60% and ≤90% predicted • never smokers or ex-smokers[a]	primary outcome: • FEV_1 area under the curve from 0 to 24 h at the end of each treatment period secondary outcomes: • peak and trough FEV_1 • PEF
Kerstjens et al[21]	RCT: DB, PC, 2 replicate parallel-group trials 24 weeks	ICS medium dose + TIO 5.0 µg OD vs ICS medium dose + TIO 2.5 µg OD vs ICS medium dose + SALM 50 µg BID vs ICS medium dose + placebo	randomized: trial 1, 1071 trial 2, 1032 completed: trial 1, 998 trial 2, 974 mean age: 43.1 y mean pre-BD baseline FEV_1: 72.7% predicted	• age: >18–75 y • symptomatic asthmatics on a medium dose of an ICS • pre-BD FEV_1: 60%–90% predicted • never smokers or ex-smokers[a]	primary outcome: • peak and trough FEV_1 • ACQ score secondary outcomes: • peak and trough FVC • mean weekly PEF • safety

TABLE 1 Clinical trials of tiotropium in moderate asthma (continued from page 862)

Study ref.	Design/duration	Intervention	Subjects (n) /age/ FEV_1	Key inclusion criteria	Outcomes
Otha et al[22]	RCT: DB, PC, parallel-group study 52 weeks	ICS medium dose with or without LABA + TIO 5.0 µg OD vs ICS medium dose with or without LABA + TIO 2.5 µg OD vs ICS medium dose with or without LABA + placebo	randomized: 285 completed: 264 mean age: 44.5 y mean pre-BD baseline FEV_1: 80.2% predicted	• age: >18–75 y • symptomatic asthmatics on a medium dose of an ICS (≥400 µg ≤800 µg with or without a LABA) • pre-BD FEV_1: ≥60% – ≤90% predicted • ACQ ≥1.5 • never smokers or ex-smokers[a]	primary outcome: • safety secondary outcomes: • trough FEV_1 • trough FVC • trough PEF • ACQ responder rate

a ex-smokers: individuals who had stopped smoking ≥1 years prior to enrollment and with a smoking history of <10 pack-years

All studies used a tiotropium respimat inhaler unless otherwise specified.

Abbreviations: ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality-of-Life Questionnaire; BD, bronchodilator, BUD, budesonide; DB, double-blind; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting β_2-bronchodilator; OD, once daily; PC, placebo-controlled; PEF, peak expiratory flow; TIO, tiotropium; SALM, salmeterol; RCT, randomized controlled trial

trials[23,24] (TABLE 2). In a relatively small phase II trial (n = 107), Kerstjens et al[23] compared the efficacy and safety of 2 doses of tiotropium (5 µg 10 µg daily) with placebo as add-on therapy in patients with uncontrolled severe asthma as measured by an ACQ score of 1.5 or higher while on a combination of a high-dose ICS and LABA. Adding tiotropium at a dose of 5 µg or 10 µg daily resulted in an improvement in peak FEV_1 of 139 ml and 170 ml, respectively. Morning and evening PEF was slightly but significantly higher with a dose of 10 µg compared with that of 5 µg.

The second published manuscript on severe asthma[24] reported on 2 replicate RCTs involving 912 asthmatics who were receiving a high-dose ICS plus LABA. This study compared the effect of adding tiotropium (5 µg) or placebo on lung function and exacerbations, both delivered by a Respimat inhaler once daily for 48 weeks. The improvements in peak FEV_1 were 86 ml and 154 ml in trials 1 and 2, respectively, compared with placebo, and the improvements in trough FEV_1 were 88 ml and 111 ml in trials 1 and 2, respectively, compared with placebo (all $P \leq 0.01$). Also, the addition of tiotropium significantly increased the time to the first severe exacerbation (282 days vs 226 days), with an overall reduction of 21% in the risk of a severe exacerbation. Adverse events were similar in both groups.

Safety of tiotropium in asthma The safety of tiotropium as add-on treatment was examined in 3705 patients,[18,19,21-24] either when added to a medium-dose ICS for 24 to 52 weeks[18,19,21,22] or to a high-dose ICS plus LABA for 48 weeks.[23,24] In 2 large trials with tiotropium added to a medium-dose ICS,[21] the numbers of adverse events were very similar between tiotropium at doses of 2.5 µg or 5 µg, salmeterol, and placebo. Especially cardiac adverse events were recorded in less than 2% of all patients, with no differences between the treatment groups. Dry mouth was recorded in less than 2% of subjects in any treatment group. In 2 other large trials, in which tiotropium was added to a high-dose ICS plus LABA in severe asthmatics followed for 48 weeks,[24] among the adverse events reported by at least 2% of the patients in any study group, only allergic rhinitis occurred at a significantly higher rate in the tiotropium group, and asthma events and insomnia were significantly more common in the placebo group. Again, the incidence of cardiac adverse events was less than 2%, with no difference in occurrence between the active or placebo treatment groups.[21-24] In the only study that examined tiotropium at a dose of 5 µg or 10 µg as add-on therapy to an ICS plus LABA in severe asthma, adverse events were slightly higher in subjects receiving tiotropium at a dose of 10 µg (50% vs 40% in subjects on tiotropium at a dose of 5 µg and 42% in subjects on placebo).

In a longer study, Otha et al[22] examined the tolerability profile of tiotropium as an add-on therapy in patients from Japan who had moderate-to-severe symptomatic asthma while receiving a medium-dose ICS, with or without a LABA. The safety profile of tiotropium was similar to that in previous studies.[21,24] Over 52 weeks, adverse events were generally mild and nonserious, and the overall tolerability profile of tiotropium was comparable to that of placebo.

Discussion Taken together, the results of the 10 published RCTs[15-24] demonstrated that: 1) adding tiotropium at a dose of 5 µg in patients with symptomatic asthma despite low-to-high doses of an ICS with or without LABA significantly improves FEV_1 compared with placebo; 2) adding tiotropium at a dose of 5 µg in patients with symptomatic asthma despite high-doses of an ICS and LABA significantly lengthens the time to the first severe exacerbation[24]; 3) adding tiotropium at doses of 2.5 µg and 5 µg once daily to a medium--dose ICS significantly increases asthma control expressed as ACQ responders when compared with placebo[21]; 4) adding tiotropium at a dose of 5 µg once daily to an ICS is at least comparable to adding salmeterol[15,16,21] and superior to doubling the dose of an ICS[15] in patients on a

TABLE 2 Clinical trials of tiotropium in severe asthma

Study ref.	Design/duration	Intervention	Subjects (n) / age / FEV_1	Key inclusion criteria	Outcomes
Kerstjens et al[23]	RCT: DB, PC, crossover study three 8-week periods	high-dose ICS + TIO 5.0 µg OD vs high--dose ICS + TIO 10 µg OD vs high-dose ICS + placebo	enrolled: 107 completed all arms: 103 mean age: 54.8 y mean post-BD baseline FEV_1: 65.3% predicted	• age: >18–75 y • asthma diagnosed before the age of 49 years • current diagnosis of severe asthma on a high-dose ICS (≥ BUD, 800 µg, or equivalent + LABA) • post-BD FEV_1 ≤80% and FVC ≤70% predicted • never smokers or ex-smokers[a] • ACQ ≥1.5	primary outcome: • peak FEV_1 secondary outcomes: • trough FEV_1 • peak and trough FVC area under the curve • asthma symptoms • rescue medication
Kerstjens et al[24]	RCT: DB, PC, 2 replicate parallel-group trials 48 weeks	high-dose ICS TIO 5.0 µg OD vs high--dose ICS + placebo	randomized: trial 1, 459 trial 2, 453 completed: trial 1, 413 trial 2,401 mean age: 53 y mean post-BD baseline FEV_1: 62.2% predicted	• age: >18–75 y • asthma diagnosed before the age of 45 years • current diagnosis of severe asthma on a high-dose ICS (BUD, ≥800 µg, or equivalent + LABA) • post-BD FEV_1 ≤80% predicted and FEV_1/FVC ≤70% • never smokers or ex-smokers[a] • at least 1 exacerbation in the previous year (by history) • ACQ ≥1.5	primary outcomes: • peak and trough FEV_1 • time to first severe exacerbation of asthma secondary outcomes: • peak and trough FEV_1 and FVC at each visit • time for the first worsening of asthma • ACQ score • AQLQ score • safety

a ex-smokers: individuals who had stopped smoking ≥1 years prior to enrollment and with a smoking history of <10 pack-years

Abbreviations: see TABLE 1

low--to-medium dose of an ICS; and 5) adding tiotropium at a dose of 5 µg once daily either to an ICS alone or to ICS plus LABA in these studies has a favorable safety profile similar to that of salmeterol and placebo.[21,23]

Rodrigo et al[13] have recently assessed that the major benefits of adding tiotropium were improvements in lung function and, in patients with severe asthma, the reduction of exacerbations. They calculated a reduction of 30% in asthma exacerbations with a number needed to treat of 17. These results are relevant because of the great impact of exacerbations of severe asthma and the costs of current alternatives to reduce asthma exacerbations in this particular group of asthmatics.

Furthermore, Price et al[44] examined the clinical effects of add-on therapy with tiotropium in a real-life study of a group of over 2042 asthma patients treated in primary care practice in the United Kingdom. The study patients were at least 18 years of age and had a physician-recorded diagnosis of asthma and the only exclusion criteria was a recorded diagnosis of COPD. In this study, the addition of tiotropium was associated with significant decreases in the incidence of exacerbations within the first year of treatment.

It would be useful for clinicians to predict which patients respond to tiotropium and which do not. Interestingly, none of the published studies has been able to discriminate responders from nonresponders to tiotropium respimat. Subgroup analyses showed no overall differences in improvement in lung function by the following baseline characteristics: disease duration, age class, smoking, history, sex, percent predicted prebronchodilator FEV_1 at baseline, allergic status (assessed by the concentration of immunoglobulin E [IgE], eosinophil count, or clinical judgment), region, and body-mass-index class.[21,23] This renders the addition of tiotropium at a dose of 5 µg a valuable option in a broad group of patients with symptomatic asthma while being treated by an ICS with or without LABA, and averts the need for biomarker testing before the start of treatment such as with anti-IgE or anti-interleukin-5.

Conflict of interest HAMK was principal investigator on 3 studies in this review. His institution, the University Medical Center Groningen, received grants from Boehringer Ingelheim and Pfizer. Additionally, he has served, on behalf of his institution, on advisory boards for Boehringer Ingelheim and Pfizer. In the past year, his institution has received similar funding from Almirall, AstraZeneca, Chiesi, GlaxoSmithKline, Novartis, and Takeda.

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ARTYKUŁ POGLĄDOWY

Rola leków przeciwcholinergicznych we współczesnym leczeniu astmy

Wskazówki dla praktyki klinicznej

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SŁOWA KLUCZOWE

ciężka astma, kontrola astmy, pierwszosekundowa objętość wydechowa, tiotropium, zaostrzenia

STRESZCZENIE

Leki przeciwcholinergiczne takie jak tiotropium, silnie działający lek o długim czasie działania, mają kluczowe znaczenie w objawowym leczeniu przewlekłej obturacyjnej choroby płuc. Ich rola w terapii astmy była ostatnio przedmiotem badań. W niniejszym artykule przeglądowym krytycznie oceniono dostępne wyniki badań klinicznych i zastosowanie terapeutyczne leków przeciwcholinergicznych w leczeniu astmy. Do chwili obecnej opublikowano 10 badań z randomizacją (fazy II i III), w których oceniano wpływ dołączenia tiotropium do leczenia chorych na astmę lekką lub umiarkowaną lub na astmę ciężką. Badania te trwały od 4 do 52 tyg. i objęły 3368 chorych na astmę lekką lub umiarkowaną i 1019 chorych na astmę ciężką. Ponadto wyniki opublikowanych i nie opublikowanych badań oceniających rolę tiotropium w leczeniu astmy przedstawiono w 1 przeglądzie systematycznym i 6 metaanalizach. Wyniki badań u chorych na umiarkowaną astmę wskazują, że dołączenie do tiotropium glikokortykosteroidów (GKS) wziewnych jest nie mniej skuteczne niż długo działający β_2-mimetyk (*long-acting β_2-agonist* – LABA). Ponadto skuteczność i bezpieczeństwo tiotropium są podobne jak w przypadku salmeterolu. Badania u chorych na ciężką astmę wskazują, że dołączenie tiotropium do dużej dawki GKS wziewnego i LABA powoduje dodatkową poprawę czynności płuc, wydłuża czas do pierwszego ciężkiego zaostrzenia astmy i czas do pogorszenia kontroli astmy oraz poprawia kontrolę astmy. Za wyjątkiem uczucia suchości w ustach profil bezpieczeństwa tiotropium jest podobny do placebo zarówno u chorych na astmę umiarkowaną, jak i ciężką.

Dołączenie tiotropium do GKS wziewnego albo GKS wziewnego i LABA poprawia czynność płuc i kontrolę astmy, zmniejsza nasilenie objawów, a u chorych na ciężką astmę wydłuża czas do zaostrzenia. Leczenie to jest bezpieczne. Efekty stosowania tiotropium wydają się niezależne od wyjściowej charakterystyki chorych, np. wieku, nasilenia obturacji oskrzeli, palenia tytoniu, obecności alergii i odwracalności obturacji oskrzeli.

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