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REVIEW

Barriers to achieving asthma control in adults: evidence for the role of tiotropium in current management strategies

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Abstract: Despite the availability of a range of treatment options and management guidelines, a high proportion of adults with asthma remain uncontrolled. The challenge of managing uncontrolled asthma includes providing efficacious treatment while limiting side effects, recognizing situations when a change in asthma therapy is required, and considering patient preferences and satisfaction. In line with the Global Initiative for Asthma report, asthma management is based on a backbone of inhaled corticosteroid (ICS) therapy and use of add-on therapies to achieve disease control. This review considers whether add-on options could be better utilized in clinical practice. A number of long-acting muscarinic antagonists are in development, but tiotropium is the most widely studied for use in asthma. Evidence demonstrating the efficacy of tiotropium as an add-on therapy to at least ICS in adults with symptomatic mild, moderate, and severe asthma is presented from randomized controlled trials and real-world evidence. In addition, the benefit of tiotropium therapy in a wide range of patient phenotypes and disease severities without the need for biomarker assessment is discussed. Additional strategies that complement this approach, such as recognizing and overcoming barriers to adherence, ensuring optimal device use, and education and support to enhance patient–physician communication, are discussed. Physician education can also help raise awareness that additional management options are available for patients with moderate-to-severe asthma who remain uncontrolled on ICS/long-acting β_2-agonist treatment.

Keywords: asthma, long-acting muscarinic antagonists, tiotropium, adults

Video abstract

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Introduction

Despite the availability of a range of treatment options and management guidelines, an unacceptably high proportion of adults with asthma remain poorly controlled.[1] Reflective of the situation in a number of countries,[2] findings from a web-based survey conducted in over 2,500 Australian adults with asthma indicate poor self-rated symptom control in almost half of the participants, with an urgent need for asthma-related health care in the previous year reported by almost one-third of the participants.[3]

There remains a gap in asthma care worldwide, and effective clinical application of guideline recommendations is lacking.[3] The goals of asthma management are to achieve control, minimize the future risk of exacerbations, and reduce fixed airflow limitation, while minimizing treatment side effects.[4] In clinical practice, the challenge of managing uncontrolled asthma and achieving these goals should involve the principles outlined in the Global Initiative for Asthma (GINA) global strategy report, namely, a continuous cycle consisting of regular patient assessment, treatment adjustment, and review of the patient response to facilitate treatment decisions (Figure 1). As part of this cycle, issues that characteristically impact treatment should be addressed, including

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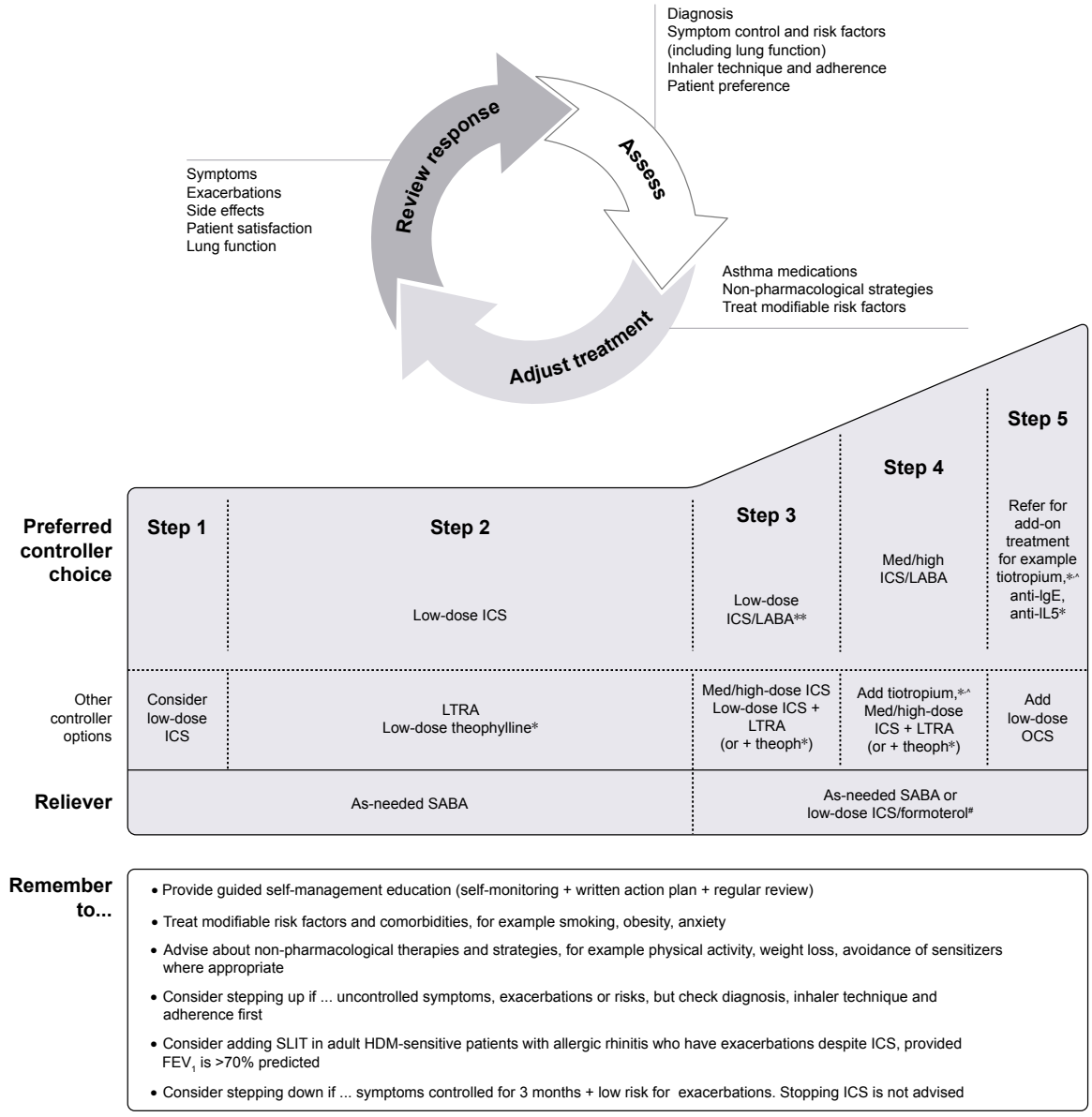

Figure 1 Asthma management based on a continuous cycle of patient assessment, treatment, and review.
Notes: Treatment should be adjusted to achieve asthma control. *Not for children <12 years. **For children 6–11 years, the preferred Step 3 treatment is medium dose ICS. #Low dose ICS/formoterol is the reliever medication for patients prescribed low dose budesonide/formoterol or low dose beclometasone/formoterol maintenance and reliever therapy. ^Tiotropium by mist inhaler is an add-on treatment for patients with a history of exacerbations; it is not indicated in children <12 years. Copyright ©2018. Reproduced from Global Initiative for Asthma. GINA report: global strategy for asthma management and prevention.[4]
Abbreviations: HDM, house dust mite; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL5, interleukin-5; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids; SABA, short-acting beta$_2$-agonist; SLIT, sublingual immunotherapy.

consideration of whether the diagnosis is correct and an assessment of comorbidities, risk factors, inhaler technique, and adherence. Furthermore, the cycle of management and stepwise approach to care allows for providing treatment that is efficacious and safe according to individual patient needs, recognizing situations when a change in asthma therapy is required, while considering patient preferences and satisfaction.[4]

Scope

In this review, the evidence for asthma management in adults will be discussed in the context of clinical challenges and the GINA management cycle, with consideration of whether add-on options could be better utilized in clinical practice. In particular, this review focuses on the evidence for tiotropium as an add-on to inhaled corticosteroid (ICS) for the treatment of asthma.

Current asthma management strategies

In line with the GINA global strategy report, management of adults with asthma is based on a preferred backbone of ICS therapy and use of add-on therapies, starting with long-acting β_2-agonists (LABAs) and stepping up management based on patient needs in order to achieve disease control.[4] The GINA report proposes several options for add-on therapy in patients who are uncontrolled despite medium- to high-dose ICS with or without other controllers at GINA Step 4, including tiotropium for individuals with a history of severe exacerbations, or leukotriene receptor antagonists (LTRAs) or theophylline added to high-dose ICS. At GINA Step 5, it recommends that patients with severe asthma are offered add-on treatment with tiotropium and escalation to biologic therapies, such as anti-immunoglobulin E (IgE), anti-interleukin-5 (anti-IL-5), or low-dose oral corticosteroids (Figure 1).[4]

Anticholinergics, both long-acting and short-acting, have been used in the management of respiratory disease, particularly COPD, for many years. The short-acting anticholinergic ipratropium bromide is a well-established bronchodilator treatment for managing acute exacerbations of asthma in clinical practice.[5] Several long-acting muscarinic antagonist (LAMA) treatments are in clinical development and are reviewed elsewhere.[6–10] Tiotropium is the most widely studied LAMA and the only one licensed for use in asthma. In addition to a growing body of evidence for use in asthma, tiotropium has the benefit of over 10 years of clinical experience in COPD.[11] Anticholinergics are muscarinic (M) receptor antagonists; in the airways, tiotropium binds equally well to M receptors (M_1, M_2, and M_3), but dissociates slowly from the M_1 and M_3 anticholinergic receptors, resulting in the long duration of bronchodilator effect.[12–14] In animal models and in vitro, tiotropium also has effects on inflammation and airway remodeling, although the clinical significance of this is uncertain.[15,16] Tiotropium Respimat® is approved in patients with asthma aged 18 years and over in Australia and Singapore, 15 years and over in Japan, and 6 years and over in the US and the European Union. As the recommended dose and specific indication can vary, it is recommended that the indication/label in each country is checked.

Practical considerations for the management of patients with asthma

Each stage of the GINA control-based management strategy (assessment, adjustment, review) involves key principles for clinicians who care for patients with asthma.[4] These principles include the importance of recognizing patient preferences and satisfaction, offering support to overcome any barriers to adherence, assessing inhaler use, providing a written asthma action plan, and scheduling regular asthma reviews to optimize control and ensure that ineffective or poorly tolerated treatments are reviewed. A Cochrane review reported that education in asthma self-management, involving self-monitoring by either peak expiratory flow or symptoms, together with regular medical review and a written action plan, led to an improvement in several health outcomes for adults with asthma.[17] Regular clinical review can help health care professionals identify a need for a therapeutic change and recognize when an add-on option might be more appropriate than increasing ICS dose, and helps patients understand the important components to achieving good asthma control. Disease education empowers patients; hence, supporting patients to self-monitor symptoms and recognize triggers and disease worsening are valuable aspects of care.[18] Regular review opens communication channels between the patient and the health care professional, providing benefits on both sides, both clinically and with respect to patient satisfaction. Review is essential to assess recent asthma control and the benefit of treatment, check inhaler technique, and educate patients in self-management.[18] In accordance with the GINA cycle of asthma management, every treatment change should be followed by a scheduled asthma review after at least 2–3 months to assess and optimize control, and to ensure that ineffective or poorly tolerated treatments are reviewed.[4]

Treatment adherence is a well-known challenge in asthma management. Effective communication regarding asthma management may help increase patients' adherence, but, in addition to the challenges of time constraints, health care professionals may not be skilled in providing effective adherence assessment and advice. In one study, primary care physicians were provided with 2 hours' training in delivering brief, motivational, interview-based adherence counseling with asthma-specific counseling support tools.[19] Almost all participants found the training very or extremely useful, leading to increased confidence and satisfaction with the quality of their consultations. Continuing to keep abreast of the evolving clinical evidence, new devices and treatment combinations, and support strategies for the care of patients with asthma is also important. It is becoming clear that asthma is a highly heterogeneous disease, and that ascertaining asthma phenotype may also guide therapeutic decisions in suboptimally controlled asthma.[20] However, there are very

few clinical trials apart from those of targeted monoclonal therapies that examine treatment response in relation to phenotype. At present, monoclonal therapies are expensive, and it behooves clinicians to address all treatable traits – of which adherence is one, before embarking on long-term expensive therapies.

Optimally, health care professionals may look to continually evolve and refine the softer skills required for effective patient care. Participation in communication skills training can improve patient adherence, with the odds of patient adherence being 1.62 times higher than when a physician receives no training.[21] This meta-analysis reported a 19% higher risk of nonadherence among patients when their physician communicated poorly than among those who experienced effective physician communication.[21] Continuing professional development can also help enhance awareness of the alternative management options available for patients who remain uncontrolled on ICS with or without other controllers.

Counseling and training are also required, so that patients better understand their condition and how to use their inhaler, as even the most user-friendly devices require education and a demonstration.[22] In a study by Jahedi et al,[23] a total of 87.5% of patients were not able to demonstrate the correct inhaler technique and the majority of patients did not have any degree of involvement with decision-making regarding treatment. This was the case despite a body of evidence across many disease areas (including asthma) demonstrating that shared decision-making and effective patient–physician communication is of benefit to patients.[23] Routine checking of inhaler technique and asking patients to demonstrate use is important,[24] as patients can revert to an incorrect technique just after a short period.[25] Crane et al[26] reported that use of tailored education that included observation, verbal instruction, and device demonstration led to a significant improvement in device technique that was sustained at 12 months, while no significant improvement was recorded in those who only received written instructions.[26] A physical demonstration of inhaler technique and patient retraining at follow-up appointments is recommended in the GINA report,[4] as many studies show a rapid loss of technique after a single demonstration.[27,28] A wide range of drug and inhaler device combinations are available; the most commonly used devices include pressurized metered-dose inhalers, dry powder inhalers, and soft mist inhalers.[25,29] The soft mist inhaler, of which the Respimat® Soft Mist™ Inhaler (Boehringer Ingelheim, Ingelheim, Germany) for the delivery of tiotropium is an example, was developed to help overcome the limitations of other devices, which include aerosol velocity, limited drug deposition in the lung, and adequate patient coordination for inhalation.[29] Use of a number of separate inhalers requiring different inhalation techniques can be confusing for patients with asthma, but training and education can ensure that the benefit of additional controller medication is achieved. Of note, patient preference is recognized as a key factor in device selection, successful drug delivery, and adherence.[30]

In summary, a number of strategies can be employed to help overcome perceived barriers to good asthma outcomes by offering individualized education and support.

Therapeutic strategies: tiotropium as an add-on therapy to at least ICS

The efficacy and safety of treatment with tiotropium as an add-on to standard ICS maintenance treatment, with or without a LABA, has been demonstrated in a large clinical study program comprising 18 trials with over 6,000 patients aged 1–75 years with symptomatic mild, moderate, or severe asthma.[31–40] Six Phase III, double-blind, placebo-controlled, parallel-group trials have been conducted in adults with symptomatic asthma.[31–34] The broad-based inclusion criteria required patients to have a documented history of poorly controlled asthma (defined by the seven-question Asthma Control Questionnaire [ACQ-7] score ≥1.5). Those with a significant disease other than asthma were excluded. Patients were also either lifelong nonsmokers or had a smoking history of fewer than 10 pack-years, with no smoking in the year before the study.

In the replicate PrimoTinA-asthma® 1 and 2 studies, tiotropium (5 µg) or placebo was added to high-dose ICS (≥800 µg budesonide or equivalent per day) plus LABA once daily for 48 weeks in 912 patients with symptomatic severe asthma (Table 1).[31] In patients with uncontrolled asthma despite treatment with ICS/LABA, the use of tiotropium add-on therapy significantly increased the time to first exacerbation and provided a modest sustained bronchodilation.[31] At 24 weeks, change in peak forced expiratory volume in 1 s (FEV_1) within 3 hours post-dose ($FEV_{1(0–3h)}$) from baseline was significantly greater with tiotropium in both trials compared with placebo (mean difference in the two studies: 86 mL [95% CI: 20–152 mL; $P<0.05$] and 154 mL [95% CI: 91–217 mL; $P<0.001$]). Findings were also significant for trough FEV_1 with tiotropium compared with placebo (adjusted mean difference: 88 mL [95% CI: 27–149 mL; $P<0.01$] and 111 mL [95% CI: 53–169 mL; $P<0.001$]). Time to the first severe exacerbation was increased in patients treated with tiotropium add-on therapy vs placebo (282

Table 1 Summary of clinical trials and real-world evidence with tio add-on therapy in adult patients with asthma

Clinical trial	Study design	Duration	Patient population	Treatment arms[a]	Key endpoints	Summary of findings
Phase III trials						
PrimoTinA-asthma® 1 and 2 (NCT00772538/NCT00776984) Kerstjens et al (2012)[31]	Two double-blind, randomized, placebo-controlled, parallel group, replicate studies	48 weeks	Adults (18–75 years old) with symptomatic severe asthma receiving high-dose ICS and LABA	• Tio 5 µg (n=456) • Pbo (n=456)	• Peak $FEV_{1(0–3h)}$ • Trough FEV_1 • Time to first severe exacerbation • Asthma control • Safety	• Tio added on to ICS/LABA improves lung function and reduces severe exacerbations and episodes of disease worsening • Improvements in asthma control scores were observed with tio vs placebo, but did not achieve the MCID • Safety and tolerability were comparable with pbo
MezzoTinA-asthma® 1 and 2 (NCT01172808/NCT01172821) Kerstjens et al (2015)[32]	Two double-blind, randomized, double-dummy, placebo-controlled, parallel-group, replicate studies	24 weeks	Adults (18–75 years old) with symptomatic moderate asthma receiving medium-dose ICS±LABA	• Tio 5 µg (n=517) • Tio 2.5 µg (n=519) • Salmeterol 50 µg twice daily (n=541) • Pbo (n=523)	• Peak $FEV_{1(0–3h)}$ • Trough FEV_1 • Time to first severe exacerbation • Asthma control • Safety	• Tio add-on treatment significantly improved lung function and asthma control compared with pbo, with similar efficacy and tolerability to the LABA salmeterol • Safety and tolerability were comparable with pbo
GraziaTinA-asthma® (NCT01316380) Paggiaro et al (2016)[33]	Placebo-controlled, randomized, parallel-group study	12 weeks	Adults (18–75 years old) with symptomatic mild-to-moderate asthma receiving low- to medium-dose ICS	• Tio 5 µg (n=155) • Tio 2.5 µg (n=154) • Pbo (n=155)	• Peak $FEV_{1(0–3h)}$ • Trough FEV_1 • Asthma control • Safety	• Tio add-on therapy was an efficacious bronchodilator • Safety and tolerability were comparable with placebo • No difference in the reduction of ACQ-7 score between tio and pbo groups
CadenTinA-asthma® (NCT01340209) Ohta et al (2015)[34]	Double-blind, randomized, placebo-controlled, parallel-group study	52 weeks	Adults (18–75 years old) from Japan with symptomatic moderate-to-severe asthma receiving medium-dose ICS±LABA	• Tio 5 µg (n=114) • Tio 2.5 µg (n=114) • Pbo (n=57)	• Safety • Trough FEV_1 • Asthma control	• No significant difference in adverse events between treatment groups • Tio 5 µg added to ICS±LABA significantly improved lung function (trough FEV_1) vs pbo • At Week 52, ACQ-7 responder rates were similar across treatment groups

(*Continued*)

Table 1 (*Continued*)

Clinical trial	Study design	Duration	Patient population	Treatment arms[a]	Key endpoints	Summary of findings
Independent study						
TALC study (NCT00565266) Peters et al (2010)[45]	Three-way, double-blind, triple-dummy, crossover study	52 weeks (each treatment 14 weeks)	Adults with inadequately controlled asthma (FEV_1 <70% predicted normal) receiving BDA 80 μg twice daily	• BDA 80 μg twice daily+tio 18 μg+salmeterol pbo twice daily • BDA 80 μg twice daily+salmeterol 50 μg twice daily+tio pbo • BDA 160 μg twice daily+tio pbo+salmeterol pbo twice daily	• Morning PEF	• Tio 18 μg is superior to doubling the ICS dose and non-inferior to salmeterol in patients with uncontrolled asthma
Real-life evidence						
Abadoglu and Berk (2016)[46]	Retrospective analysis of medical records	2003–2011	Patients with uncontrolled asthma (GINA Step 4/5) with irreversible airway obstruction	High-dose ICS and LABA combination and/or daily oral prednisone, LTRA, and sustained theophylline at least for 1 year	• Lung function • Asthma control	Tio use showed an improvement in lung function and asthma control, and decreased the number of ED visits and hospitalizations
Price et al (2015)[47]	Retrospective analysis of medical records	2001–2013	A recorded diagnosis of asthma	At least one prescription for tio	• Exacerbations • Acute respiratory events • Lung function	A significant decrease in the incidence of exacerbations and antibiotic prescriptions for lower respiratory tract infections in the year following the addition of tio

Notes: [a]Treated population; tio 5 or 2.5 μg was delivered as two puffs once daily via the Respimat®.

Abbreviations: ACQ-7, seven-question Asthma Control Questionnaire; BDA, beclomethasone dipropionate aerosol; ED, emergency department; $FEV_{1(0-3h)}$, FEV_1 within 3 hours post-dose; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; MCID, minimal clinically important difference; pbo, placebo; PEF, peak expiratory flow; TALC, Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid study; tio, tiotropium.

vs 226 days), with a 21% reduction in the risk of a severe exacerbation (P=0.03). Improvements in asthma control and quality of life were observed in both trials between the tiotropium group and the placebo group. At Week 24, the mean difference in ACQ-7 and Asthma Quality of Life Questionnaire scores between groups was significantly improved for tiotropium-treated patients vs placebo in trial 2, but did not achieve the minimal clinically important differences (0.5 units for each questionnaire). The proportion of patients reporting adverse events (AEs) was comparable between placebo and tiotropium (Table 2).[31]

MezzoTinA-asthma® 1 and 2, conducted in 2,103 adult patients with symptomatic moderate asthma, also comprised two replicate, randomized, double-blind, placebo-controlled trials. Once-daily tiotropium (5 or 2.5 µg), twice-daily salmeterol 50 µg, or placebo was added to medium-dose ICS (400–800 µg budesonide or equivalent per day) for 24 weeks (Table 1).[32] Data from the two studies were pooled. Tiotropium 5 and 2.5 µg add-on therapy led to a significant improvement in lung function compared with placebo (peak FEV_1: 185 mL [95% CI: 146–223 mL; $P<0.0001$] with tiotropium 5 µg; 223 mL [95% CI: 185–262 mL; $P<0.0001$] with tiotropium 2.5 µg). Both doses of tiotropium significantly improved trough FEV_1, and results were also numerically higher for tiotropium 2.5 µg. A significant reduction in the risk of first severe exacerbation and of first asthma worsening was reported for tiotropium 2.5 µg. There were also more ACQ-7 responders with tiotropium (5 and 2.5 µg), and salmeterol, compared with placebo (all $P<0.05$). The proportion of patients reporting AEs was similar across all treatment groups (Table 2). Overall, tiotropium added to medium-dose ICS provided significant improvements in lung function and asthma control that were similar to those of salmeterol; as such, it was concluded that tiotropium is a safe and effective bronchodilator and a potential alternative to salmeterol for use as an add-on therapy in this patient population.[32]

In the GraziaTinA-asthma® study, 464 adults with symptomatic mild-to-moderate asthma received tiotropium (5 or 2.5 µg) or placebo added to low- to medium-dose ICS (200–400 µg budesonide or equivalent per day), as shown in Table 1.[33] Findings showed that once-daily tiotropium was an efficacious bronchodilator, and that safety and tolerability were comparable with placebo.[33] After 12 weeks, lung function was significantly improved with both doses of tiotropium compared with placebo (peak $FEV_{1(0–3h)}$: 128 mL [95% CI: 57–199 mL] with tiotropium 5 µg; 159 mL [95% CI: 88–230 mL] with tiotropium 2.5 µg; both $P<0.001$). Trough FEV_1 was also significantly improved with both doses of tiotropium compared with placebo. This study was not designed to evaluate the effect of tiotropium on asthma exacerbations. Numerical improvements in the adjusted mean ACQ-7 total score were observed across all treatment groups after 12 weeks. The differences between each dose of tiotropium vs placebo were not statistically significant. The proportion of patients reporting AEs was similar across all treatment groups (Table 2).[33]

In addition to the safety findings reported with the use of tiotropium add-on therapy in the Phase III studies described, a Japanese study randomized 285 patients to receive tiotropium (5 or 2.5 µg) or placebo as an add-on therapy to ICS/LABA for 52 weeks.[34] At Week 52, the proportion of patients reporting AEs with tiotropium 5 µg, 2.5 µg, and placebo were 88.6%, 86.8%, and 89.5%, respectively. No significant difference in the percentage of patients reporting AEs was observed between the groups (Table 2). Dahl et al[41] conducted a pooled safety analysis of seven Phase II and III, randomized, double-blind, parallel-group trials of 12–52 weeks' treatment duration, which investigated once-daily tiotropium add-on therapy vs placebo in adult patients across a range of asthma severities. The proportion of patients with AEs was comparable between treatment groups (tiotropium 5 µg vs placebo 5 µg pool: 60.8% vs 62.5%; tiotropium 2.5 µg vs placebo 2.5 µg pool: 57.1% vs 55.1%). Patients were most commonly reported with asthma, decreased peak expiratory flow rate, and nasopharyngitis. A low proportion of patients reported AEs of special interest, including dry mouth (1.0% and 0.5% with tiotropium 5 µg and placebo, respectively) or cardiac AEs (1.4% with both tiotropium 5 µg and placebo).[41]

Overall, these studies demonstrate the efficacy and safety of tiotropium in adults with a range of asthma severities. Furthermore, systematic reviews have concluded that a LAMA, such as tiotropium, serves as an effective bronchodilator across varying severities of asthma in patients who remain symptomatic on at least ICS, and particularly as an add-on to ICS/LABA therapy.[42–44] In addition, findings from an independent study by Peters et al[45] support the use of tiotropium for the treatment of asthma in patients with asthma uncontrolled by ICS alone, demonstrating that the use of tiotropium was superior to doubling the ICS dose, with improvements in symptoms and lung function; tiotropium was also shown to be non-inferior to salmeterol (Table 1).

To date, a limited number of real-life studies have investigated the impact of incorporation of add-on tiotropium into clinical practice. A retrospective analysis was conducted of

Table 2 Summary of adverse events in Phase III clinical trials of tio in adults (18–75 years old) with mild, moderate, or severe asthma

Clinical trial	Treatment arm[a]	Patients with any AE, n (%)	Patients with SAEs,[b] n (%)	Patients with investigator-defined treatment-related AEs, n (%)	Patients with AEs leading to discontinuation, n (%)
PrimoTinA-asthma® 1 and 2 (pooled) (NCT00772538/NCT00776984) Kerstjens et al (2012)[31]	Tio 5 µg (n=456)	335 (73.5)	37 (8.1)	26 (5.7)	8 (1.8)
	Pbo (n=456)	366 (80.3)	40 (8.8)	21 (4.6)	14 (3.1)
MezzoTinA-asthma® 1 and 2 (pooled) (NCT01172808/NCT01172821) Kerstjens et al (2015)[32]	Tio 5 µg (n=517)	296 (57.3)	11 (2.1)	38 (7.4)	9 (1.7)
	Tio 2.5 µg (n=519)	302 (58.2)	12 (2.3)	36 (6.9)	6 (1.2)
	Salmeterol 50 µg twice daily (n=541)	294 (54.3)	11 (2.0)	28 (5.2)	10 (1.8)
	Pbo (n=523)	309 (59.1)	14 (2.7)	28 (5.4)	13 (2.5)
GraziaTinA-asthma® (NCT01316380) Paggiaro et al (2016)[33]	Tio 5 µg (n=155)	50 (32.3)	1 (0.6)	2 (1.3)	1 (0.6)
	Tio 2.5 µg (n=154)	48 (31.2)	0	2 (1.3)	2 (1.3)
	Pbo (n=155)	45 (29.0)	1 (0.6)	2 (1.3)	0
CadenTinA-asthma® (NCT01340209) Ohta et al (2015)[34]	Tio 5 µg (n=114)	101 (88.6)	4 (3.5)	10 (8.8)	2 (1.8)
	Tio 2.5 µg (n=114)	99 (86.8)	4 (3.5)	6 (5.3)	1 (0.9)
	Pbo (n=57)	51 (89.5)	9 (15.8)	3 (5.3)	1 (1.8)

Notes: Data are presented as n (%). [a]Treated population; tio 5 or 2.5 µg was delivered as two puffs once daily via the Respimat®. [b]SAE was defined as any AE that resulted in death, was immediately life-threatening, resulted in persistent or significant disability/incapacity, required or prolonged patient hospitalization, was a congenital anomaly/birth defect, or was to be deemed serious for any other reason that might have jeopardized the patient and might have required medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Abbreviations: AE, adverse event; pbo, placebo; SAE, serious adverse event; tio, tiotropium.

medical records from 633 adult patients with asthma who were admitted to an immunology and allergy diseases clinic between 2003 and 2011.[46] A total of 64 patients with severe asthma were followed for at least 1 year and treated with add-on tiotropium for at least 3 months. The mean time for onset of add-on tiotropium treatment was 5.5 months after admission to the outpatient clinic. The authors reported that tiotropium as an add-on to high-dose ICS and LABA therapy resulted in a number of improved endpoints compared with baseline (Table 1). These included lung function with a mean FEV_1 of 57.5%±1.9% at baseline increasing to 65.5%±1.9% after 12 months of treatment with tiotropium add-on, and improved asthma control, according to GINA-based control assessment (based on daytime symptoms, night waking, need for reliever, and activity limitations), in 42.2% of cases with tiotropium add-on. Furthermore, with tiotropium add-on therapy compared with baseline, there was a reduction in the number of emergency department visits and hospitalizations in 46.9% and 50.0% of patients with severe asthma, respectively (all $P<0.05$).

In a real-life study conducted by Price et al,[47] medical records of adults with asthma who were prescribed tiotropium were obtained from the United Kingdom Optimum Patient Care Research Database for the period 2001–2013. Of the 2,042 study patients, 83% and 68% were receiving an ICS or a LABA, respectively, during the baseline year; 67% of patients were receiving both. When the outcome year, defined as the year after addition of tiotropium, was compared with the baseline year, the percentage of patients having at least one exacerbation decreased from 37% to 27% ($P<0.001$) and patients experiencing at least one acute respiratory event decreased from 58% to 47% ($P<0.001$), as shown in Table 1. Few real-world studies are available, and evidence to date is consistent with the findings from randomized clinical trials of tiotropium in asthma.[46,47]

Other add-on therapies for adults with asthma uncontrolled with ICS with or without other controllers

Other add-on therapies are available for adults with asthma that is uncontrolled with ICS. Leukotrienes are lipid mediators produced by inflammatory cells of the airways, and can cause bronchoconstriction, among other pathophysiologic effects. Montelukast is an LTRA that targets an inflammatory cascade mediated by sulfidopeptide leukotrienes, which are involved in the chemoattraction of inflammatory cells

(including eosinophils) and possibly the proliferation of mucosal fibroblasts.[48] LTRAs disrupt leukotriene-mediated signaling, and can improve lung function and decrease other symptoms across a range of asthma severities in adults and children.[49] There are controversies in the clinical evidence supporting the efficacy of LTRAs, particularly in adults; for example, a meta-analysis of six clinical studies assessing montelukast as an add-on therapy in mild-to-moderate asthma showed significantly improved symptom control compared with ICS monotherapy.[50] In contrast, other studies of patients treated with ICS (mostly high-dose ICS) and additional therapy such as LABA showed the addition of montelukast produced no improvement in symptoms, lung function, or rescue medication use compared with placebo.[51,52] Furthermore, a meta-analysis showed that LABA add-on to ICS is superior to LTRA addition, in terms of risk of exacerbations requiring systemic corticosteroids, and improvements in lung function, asthma symptoms, rescue medication use, and quality of life.[53] Overall, LTRAs may be most useful in specific populations, such as asthma in obese patients, in some with exercise-induced asthma, and in viral-induced wheezing episodes with asthma.[54]

Theophylline is a non-selective phosphodiesterase inhibitor. It has relatively modest bronchodilator effects,[55,56] but does have anti-inflammatory properties.[57] There is evidence to show that the addition of theophylline to ICS is clinically equivalent to doubling the dose of ICS in terms of improvements in lung function and symptoms in patients with moderate asthma.[58] However, theophylline has a narrow therapeutic window, thereby making it less well tolerated than inhaled treatment.[57]

Biologic therapy has been the focus of more recent research. Omalizumab is a humanized anti-IgE monoclonal antibody approved as an add-on therapy for the treatment of moderate-to-severe allergic asthma inadequately controlled with high-dose ICS, with or without other controller medication.[59] Reslizumab (Teva) and mepolizumab (GlaxoSmithKline) are humanized anti-IL-5 monoclonal antibodies, and benralizumab (AstraZeneca) is an anti-IL-5 receptor α monoclonal antibody, which have all recently been approved for the treatment of severe eosinophilic asthma.[4,60,61] Dupilumab (Regeneron), which targets the receptors for both IL-4 and IL-13, has also demonstrated improved outcomes, including lung function and exacerbations, in patients with severe asthma.[62] Targeted monoclonal therapies show particular effects in reducing exacerbations in severe asthma in patients with eosinophilic inflammation, but are somewhat less effective in improving lung function and optimizing asthma control.[63] Biomarkers are usually required to identify patient populations that are most likely to benefit from the different biologic treatments (eg, peripheral eosinophil counts for anti-IL-5 therapies). This additional testing adds to an already costly therapy. Therefore, it may be most beneficial to assess the effects of biologics after the use of ICS/LABA plus additional controller medications, such as tiotropium, ensuring that more cost-effective therapeutic options have been exhausted. Currently, add-on anti-IgE and anti-IL-5 treatment form options at Step 5 of the GINA report recommendations.[4]

Bronchial thermoplasty is a non-pharmaceutical intervention that uses thermal energy to reduce the amount of smooth muscle in the airway walls, making it less likely that the airways will become narrow in the future.[64] This option has shown improvements in quality of life and reduced exacerbations in patients with severe asthma. As it is an expensive intervention requiring several bronchoscopies, more evidence is required on the long-term efficacy and safety of the procedure to accurately assess its role and cost–benefit.[65] The GINA report recommends bronchial thermoplasty as a potential treatment option in patients with severe asthma (Step 5), but indicates that it should be performed "in adults with severe asthma only in the context of an independent Institutional Review Board-approved systematic registry or a clinical study, so that further evidence about the effectiveness and safety of the procedure can be accumulated".[4]

Incorporation of tiotropium in clinical practice

In the GINA report, tiotropium is recommended as an add-on option to ICS with or without other controller options in adult patients with a history of asthma exacerbations at Steps 4 or 5 (Figure 1),[4] with no requirement for prior phenotyping. Several studies have been conducted to investigate the efficacy and safety of tiotropium, irrespective of baseline characteristics, allergic status, and phenotypic characteristics. In an exploratory analysis from four large asthma trials, pooled data from adults with moderate-to-severe asthma who were treated with once-daily tiotropium 5 or 2.5 μg as an add-on to at least ICS were analyzed.[66] Findings suggest that the efficacy of tiotropium is not predicted by a $T2_{high}$ or $T2_{low}$ profile, defined by IgE level, eosinophil count, or clinician judgment of allergic asthma in patients with asthma. Another analysis (in adults with severe asthma) reported that tiotropium 5 μg improved lung function, reduced the risk of exacerbations (time to first severe exacerbation), and improved asthma symptom control independent of several

baseline characteristics such as IgE levels, eosinophil counts, age, gender, or baseline demographics compared with placebo.[67] Similar findings have been demonstrated in adults with symptomatic moderate asthma.[68]

Obesity is a common comorbidity in patients with asthma.[69] Obese patients have more severe and more frequent respiratory symptoms compared with non-overweight asthma patients,[70] and thus may require specific consideration during treatment selection. A post hoc analysis of patients with symptomatic mild, moderate, and severe asthma demonstrated that changes in lung function were consistent across the range of body mass index, suggesting that tiotropium is an effective add-on therapy to ICS, independent of body mass index.[71] Thus, tiotropium offers an easy option to implement in clinical practice prior to moving onto other options if necessary.

It has been reported that some African-American patients with asthma may not benefit from LABA treatment to the same degree as individuals in other population subgroups,[72] and the use of tiotropium has been investigated as an alternative to LABA add-on therapy.[73] Findings suggest that LABA plus ICS did not add any benefit compared with tiotropium plus ICS in this population group. The Arg16/Arg16 β_2-adrenergic receptor polymorphism has been reported in both African Americans and white asthma patients,[74] with an increased risk of a severe asthma exacerbation requiring hospitalization shown among patients with this polymorphism who are treated with a LABA.[74–76] As such, tiotropium may offer an alternative add-on option to LABA in patients with this genotype who are not adequately controlled on ICS alone.[77] This was evident in a post hoc analysis of African-American patients (n=155) who participated in the tiotropium clinical trial program that showed the efficacy and safety of tiotropium compared with placebo in this group.[78] The proportion of African-American patients treated with tiotropium who experienced an AE leading to discontinuation or a drug-related AE was similar to placebo and to that of the overall population treated with tiotropium.[78]

Asthma can be a costly disease due to its prevalence, long-term nature, and both direct and indirect health care costs, particularly attributable to patients with poor asthma control. The consequences of poor control, apart from the burden on the patient, include the impact on school and work attendance, work productivity, and health care services.[79] Findings from a UK-based analysis of adult patients with symptomatic severe asthma demonstrated that tiotropium Respimat® add-on therapy was a cost-effective management option when added to usual care, despite treatment with high-dose ICS/LABA therapy.[80,81] Additionally, a US-based analysis has also shown that addition of tiotropium was cost-effective compared with both standard therapy and add-on omalizumab therapy in patients with uncontrolled allergic asthma.[82] In the US analysis, omalizumab resulted in the highest improvement in quality-adjusted life years and reduction in the number of exacerbations, but this came with substantial costs. Clearly, patients need to be trialed on different therapeutic options and all avenues should be explored before stepping up treatment.

In conclusion, tiotropium is a highly effective add-on therapy to ICS/LABA in poorly controlled asthma and the only long-acting anticholinergic therapy currently approved for asthma management. Its efficacy and safety has been demonstrated in a large-scale clinical trial program conducted in adults with symptomatic mild, moderate, or severe asthma. Given that a large proportion of patients with asthma are uncontrolled, health care professionals should continually work to implement the asthma management principles described in the GINA report, which involve a cycle of assessment, treatment adjustment, and regular review. Furthermore, empowering patients to play a role in their own care using tools such as written asthma management plans, developed in collaboration with their health care provider, may help earlier identification of cases where therapy changes or the use of an add-on therapy such as tiotropium is appropriate to help optimize patient outcomes.

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Disclosure

CJ is a member of advisory boards and steering committees for Boehringer Ingelheim and for several pharmaceutical companies the drugs of which are mentioned in this review. She has received payments for travel and attending these meetings.

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