Drugs (2016) 76:999–1013
DOI 10.1007/s40265-016-0599-7

LEADING ARTICLE

Long-Acting Muscarinic Antagonists for Difficult-to-Treat Asthma: Emerging Evidence and Future Directions

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Published online: 11 June 2016

Abstract Asthma is a complex disease where many patients remain symptomatic despite guideline-directed therapy. This suggests an unmet need for alternative treatment approaches. Understanding the physiological role of muscarinic receptors and the parasympathetic nervous system in the respiratory tract will provide a foundation of alternative therapeutics in asthma. Currently, several long-acting muscarinic antagonists (LAMAs) are on the market for the treatment of respiratory diseases. Many studies have shown the effectiveness of tiotropium, a LAMA, as add-on therapy in uncontrolled asthma. These studies led to FDA approval for tiotropium use in asthma. In this review, we discuss how the neurotransmitter acetylcholine itself contributes to inflammation, bronchoconstriction, and remodeling in asthma. We further describe the current clinical studies evaluating LAMAs in adult and adolescent patients with asthma, providing a comprehensive review of the current known physiological benefits of LAMAs in respiratory disease.

Key Points

Uncontrolled asthma carries a significant financial and health burden on healthcare systems.

Advances in our knowledge of the role of the parasympathetic nervous system within the respiratory tract has resulted in more interest in the utility of long-acting muscarinic antagonists for patients with moderate to severe persistent asthma.

Approval of tiotropium as add-on therapy for patients with uncontrolled asthma brought a needed choice for healthcare providers.

1 Introduction

In the United States, asthma affects approximately 17.7 million adults and 6.3 million children with approximately 3500 deaths per year [1]. In 2011, an estimated 1.8 million visits to the emergency room were reported with asthma as the primary diagnosis. During 2010, 439,000 hospital discharges were due to asthma, with an average length of stay of 3.6 days. In 2013, asthma accounted for an estimated 13.8 million lost school days in children and 10.1 million lost work days in adults [2]. On average, 38.4 % of children and 50 % of adults with current asthma had uncontrolled symptoms between the years of 2006–2010 [2]. Asthma ranks within the top ten prevalent conditions causing limitation of activity and costs the US about $19.7 billion in healthcare dollars annually [3]. In order to grasp a better understanding as to why this disease has such healthcare

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implications, we need to pursue a better understanding of the disease and therapeutics available to clinicians.

Asthma is defined as an airway disease with airway inflammation, reversible obstruction, and airway hyperresponsiveness [3]. It is the underlying pathophysiology with dynamic interplay of cells that contributes to the phenotypic and endotypic heterogeneity associated with this disease. At the molecular level, asthma has been broken down into two major endotypes: type 2 high and type 2 low. Type 2 high individuals tend to have airway (and systemic) eosinophilia and usually respond to glucocorticoids or anti-eosinophilic therapies [4]. These patients tend to have a predominance of CD4+ cells, whereas in many patients with chronic obstructive pulmonary disease (COPD), CD8+ cells predominate [4]. Type 2 low asthmatics typically do not respond well to glucocorticoids and have either neutrophilic inflammation or paucigranulocytic findings. Recent attention has focused on the role of chronic inflammation and cytokine release from local inflammatory cells, with little emphasis on the role of neurogenic pathways and neurotransmitters. We know that both type 2 high and low patients respond to bronchodilators, including β-agonists and anticholinergics. This review will focus on the role of cholinergic pathways, acetylcholine, and muscarinic receptors on airway smooth muscle tone and inflammation and the importance of anticholinergics in the treatment of asthma.

For many centuries, *Atropa belladonna* and *Dutura Stramonium* were recommended for treatment of asthma by Ayurvedic medicine [5]. Atropine itself was used in either powder form or smoked as a cigarette or cigar to treat respiratory disease [6]. Atropine crosses the blood–brain barrier and has equal affinity to the three major muscarinic receptors, leading to its relatively high side-effect profile, especially when not inhaled. The development of quaternary agents that allow for targeted therapy in the lung with a limited side-effect profile has been important in the clinical utility of anticholinergics for asthma. Understanding the innervation of the lung and how these compounds impact airway tone, inflammation, and remodeling is essential to appropriately using these agents for asthma.

2 The Role of Acetylcholine and Muscarinic Receptors in the Airways

The parasympathetic nervous system in the lungs contributes to increased mucus production, inflammation, and smooth muscle contraction (Fig. 1) [7, 8]. In the airways, acetylcholine is the primary parasympathetic neurotransmitter. Increase in parasympathetic nervous system basal tone in the airway has been attributed to the development of airway hyperresponsiveness (AHR) seen in patients with asthma. Neuronal acetylcholine is under the effect of both afferent and efferent nerves interacting with surrounding cells. Ganglionic release of acetylcholine is enhanced by local inflammation of the airway epithelium due to local damage and inflammatory mediators that can directly cause or augment acetylcholine release. In the presence of viral

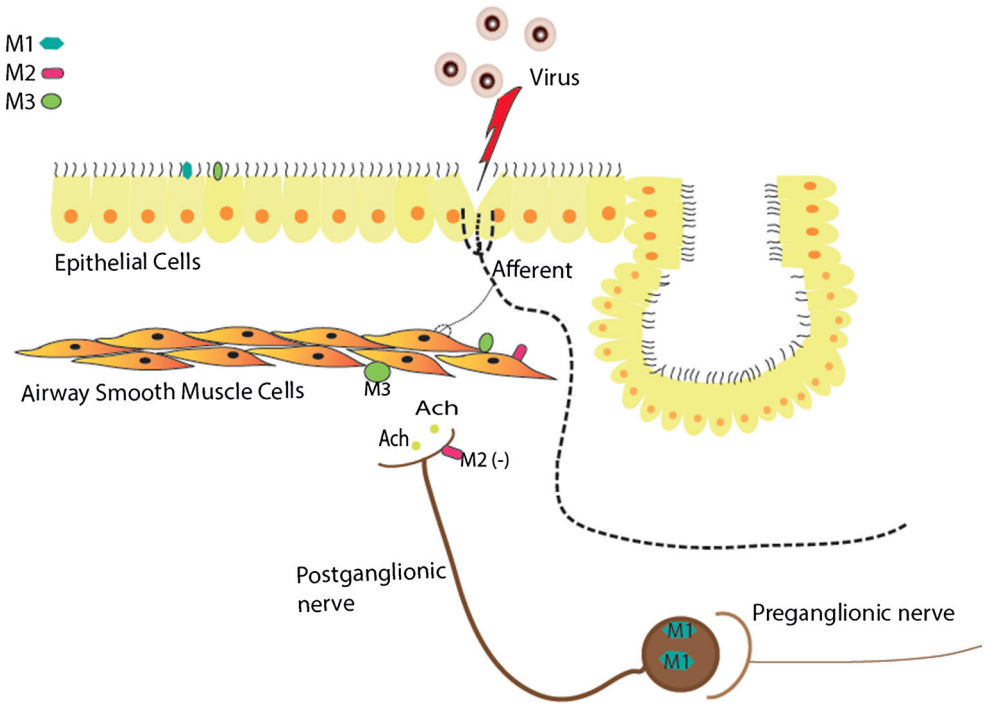

Fig. 1 Depicts the role of muscarinic receptors in the airways. M_1, M_2, M_3 are differentially distributed among local cells. M_1 facilitates neuronal release of acetylcholine (*Ach*). M_2 located in the presynaptic region of the postganglionic nerve acts as an auto-receptor with inhibitory properties. Once neuronal Ach is released, it directly acts upon the M_3 receptors on airway smooth muscle cells leading to increase in intracellular Ca^{2+} and subsequent contraction. The afferent fibers act as autonomic reflex where local inflammation or damage to epithelial cells cause an increase in cholinergic tone

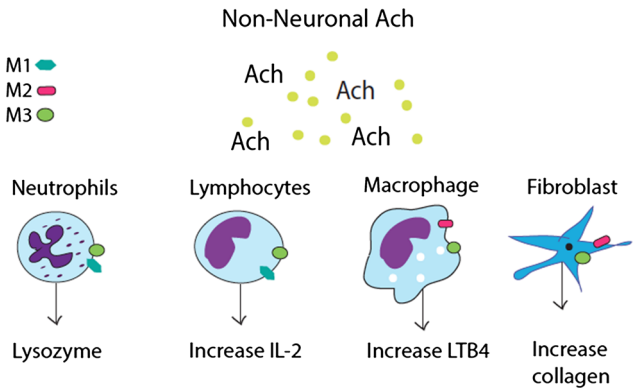

Fig. 2 Acetylcholine (*Ach*) itself has inflammatory properties. It is secreted in a paracrine/autocrine fashion by a multitude of cells in the bronchial airways including: epithelial cells, neutrophils, lymphocytes, macrophages, and fibroblasts. These cells also have muscarinic receptors. *IL-2* interlukin-2, *LTB4* leukotriene B4 Modified from Wessler and Kirkpatrick [11]

infections or allergen-induced release of mediators, the M_2 autoinhibitory receptor is down regulated allowing for further release of acetylcholine [9]. This contributes to increasing cholinergic tone (Fig. 2) [10].

It is important to note that acetylcholine can be secreted from non-neural components in the airway. The airway epithelial cells, smooth muscle cells, lymphocytes, mast cells, eosinophils, and neutrophils all express the enzyme choline acetyltransferase, which allows the synthesis of choline and acetyle-CoA forming acetylcholine (Fig. 2) [11]. Acetylcholine in itself has inflammatory properties, possibly contributing to the underlying inflammation or remodeling in asthma [10], although it is unclear to date if non-neuronal acetylcholine has a direct role in bronchoconstriction. Acetylcholine acts upon both nicotinic and muscarinic receptors. We will focus on the role of muscarinic receptors for the purpose of this review.

Muscarinic receptors are found on the cholinergic nervous system, airway smooth muscle cells, epithelial cells, mucous cells, macrophages, neutrophils, and lymphocytes. The predominant muscarinic receptor directly involved in bronchoconstriction is M_3 [7]. In proximal airway tissue, the M_3 receptors are typically under cholinergic tone; however, in the peripheral airways they are typically activated by acetylcholine released from epithelial cells [12]. These G_q-coupled protein receptors, once stimulated, cause activation of phospholipase C (PLC) leading to hydrolysis of phosphatidylinositol 4.5-bisphosphate (PIP_2) forming diacylglycerol (DAG) and 1,4,5-trisphosphate (IP_3) [13]. IP_3 causes mobilization of Ca^{2+} from the endoplasmic reticulum leading to increased intracellular Ca^{2+} [10] and muscle contraction [9]. M_1 receptors are expressed on postganglionic nerves facilitating acetylcholine transmission [14]. M_1 receptors are also found on epithelial cells, stimulating water and electrolyte secretion. M_3 receptors primarily regulate smooth muscle contraction and mucus secretion by the sub-mucosal glands [10]. M_2 receptors are G_i-coupled protein receptors that act as autoreceptors at the presynaptic junction, inhibiting the release of acetylcholine [7]. M_2 receptors are also directly found on airway smooth muscle cells and display a small contribution to smooth muscle relaxation [15]. In animal models, decreased expression of M_2 receptors induced an increase in acetylcholine from the vagal nerve, enhancing the cholinergic tone as seen in asthmatics [6, 10]. It has also been found that major basic protein secreted from eosinophils binds to the M_2 receptor, eliminating the negative feedback mechanism which allows for increase in tone as well [10, 15]. Thus, airway inflammation can cause increased production and release of acetylcholine in patients with asthma.

Remodeling (manifested by increased airway smooth muscle, mucous metaplasia, collagen deposition, and inflammatory changes) is a major component of chronic asthma. Mucus secretion is stimulated by cholinergic pathways, and this contributes to airway obstruction [16]. In smokers with COPD and asthma, the overproduction of mucus has been attributed to MUC5AC overexpression in airway epithelial cells [16]. In vitro studies have illustrated a decrease in expression of MUC5A/C in bronchial tissue exposed to aclidinium or atropine [16, 17]. Arai et al. found that tiotropium inhibited the metaplasia of goblet cells [18]. Similar findings were seen in guinea pigs where a reduction in mucous gland hypertrophy was seen with the presence of tiotropium [16, 19]. Acetylcholine also increases the production of profibrotic cytokines including transforming growth factor (TGF)-β. In murine models, anticholinergics were found to inhibit the expression of these profibrotic cytokines [20]. Therefore, acetylcholine acting via muscarinic receptors can contribute to the inflammatory and remodeling changes seen in asthma, suggesting the importance of anticholinergics as therapeutic agents.

3 Crosstalk Between Muscarinic Receptors and Other Receptors in the Human Airway: Therapeutic Implications in Asthma

The crosstalk between the M_2 and M_3 receptors and the β_2 adrenoceptors at the presynaptic and postsynaptic level is important and has potential therapeutic implications. The combination of long-acting antimuscarinics (LAMAs) and long-acting β_2 agonists (LABAs) has been shown to have synergist effects for bronchodilation (Fig. 3) [7]. In guinea pig models, the addition of tiotropium to carmoterol (LABA) significantly enhanced bronchodilation [7, 21]. Also, improvements in lung function were noted after the addition of tiotropium to patients with asthma on LABA/inhaled corticosteroid [22]. At the postsynaptic level, the

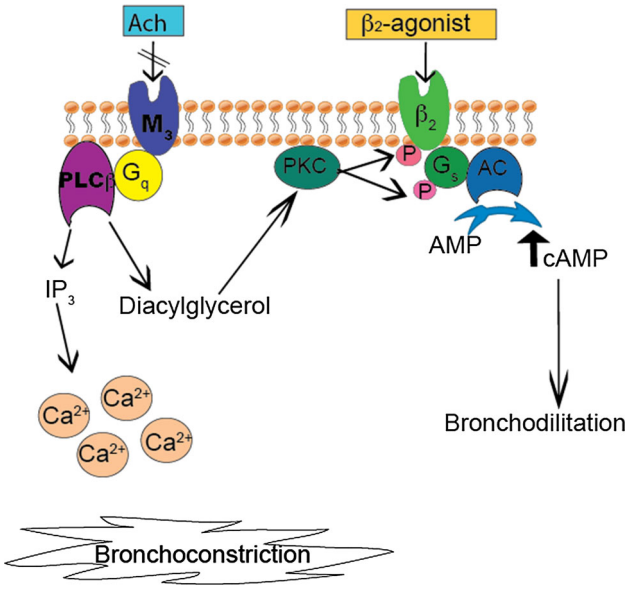

Fig. 3 Schematic of proposed synergistic effect of long-acting muscarinic antagonist to β_2-adrenoceptors. The interaction of M_3 receptor in the presence of acetylcholine causes intracellular increase in calcium and subsequent bronchoconstriction. The diacylglycerol causes the activation of protein kinase C and the deactivation of the downstream components of the β_2-adrenoceptors. The inhibition of the M_3 receptor with anticholinergics contributes to an increase in cAMP and subsequent bronchodilation. *Ach* acetylcholine, *AMP* adenosine monophosphate, *cAMP* cyclic AMP, *IP3* 1,4,5-trisphosphate, *PKC* protein kinase C, *PLC* phospholipase C

potential hypothesis for this interaction is that the M_2 receptor-coupled activation of G_i, in the presence of inflammatory cytokines such as IL-1β, tumor necrosis factor (TNF-α)- and IL-13, may attenuate β_2 adrenoceptor-mediated airway smooth muscle relaxation. In addition, multiple animal models have illustrated the functional antagonism of β_2 agonist-induced relaxation by muscarinic receptor stimulation [9]. Muscarinic antagonists target the postsynaptic G_i-coupled M_2 receptor leading to stabilization of adenylyl cyclase activity and airway smooth muscle relaxation induced by β_2-agonist [23]. Furthermore, these agents can counteract the potassium calcium channels modulated by β_2 adrenoceptors via the Gβγ protein of the M_2 receptor [23]. Through M_3 receptor stimulation, protein kinase C is formed which phosphorylates β_2 adrenoceptor G_s causing uncoupling of the receptor. This downstream regulation contributes to the functional antagonism of β_2-agonist-induced relaxation (Fig. 3). Therefore, the concomitant use of LAMAs and LABAs for obstructive airway diseases such as asthma has a sound pharmacological basis.

In patients with asthma, a clinical benefit is observed with the addition of LAMAs to inhaled corticosteroids as well. A recent publication by Cazzola et al. described the possible pharmacological benefit and the synergistic activity of adding glycopyrronium to beclomethasone [24]. They found that in sensitized bronchi, the glycopyrronium/beclomethasone combination synergistically enhanced the relaxation of medium and small airways. This effect was attributed to higher concentrations of cyclic adenosine monophosphate (cAMP). This synergistic interaction was not noted in non-sensitized bronchi [24]. In summary, understanding the interaction of LAMAs, LABAs, and corticosteroids provides a basis for the appropriate use of these agents in patients with asthma.

4 Pharmacology of Short- and Long-Acting Antimuscarinics

Current muscarinic antagonists include the short-acting ipratropium and oxitropium, and the long-acting agents including tiotropium, glycopyrronium, aclidinium, and umeclidinium (Table 1). Currently published data for LAMAs in asthma include studies with tiotropium, unceclidinium, and aclidinium. As described above, muscarinic receptors are abundant throughout the airways with M_2 receptors having a bronchoprotective role and M_1 and predominantly M_3 receptors having bronchoconstrictive roles [10]. A common characteristic of LAMAs is that they all have longer residence time at the M_3 receptor and shorter residence time at the M_2 receptor compared with the short-acting muscarinic antagonists, which have nonselective binding characteristics [25]. The longer residence time is consistent with longer duration of action of LAMAs. As seen in Table 1, tiotropium has a very prolonged dissociation time from M_3 receptors. It is important to note that glycopyrronium dissociates from M_3 faster than aclidinium; however, it is still also efficacious at once per day. This is suggestive that within the actual respiratory tract other underlying processes might be contributing. Most of this data is obtained with respect to patients with COPD. We will next discuss the current evidence on using LAMAs in asthma with a focus on tiotropium as the majority of published data is with this medication.

5 Asthma Studies Supporting the Use of Long-Acting Antimuscarinics

5.1 Tiotropium Bromide

Tiotropium is the most studied LAMA medication in asthma and has strong evidence of its effectiveness in COPD [26, 27]. Early evidence supporting tiotropium use in asthma came from a study by O'Connor et al. [28]. Subjects were treated with either tiotropium or placebo and subsequently underwent a methacholine challenge. Three doses of tiotropium (10, 40, and 80 μg) were used. Each dose of tiotropium produced mild

Table 1 Comparison of current muscarinic antagonists

Medication	Receptor targets	M_2 $t_{½}$ (h) receptor residence time	M_3 $t_{½}$ (h) receptor residence time	Indication	Distinguishing feature	Formulations	References
Ipratropium	Non-selectively M_1, M_2, M_3	0.08 ± 0.01	0.47 ± 0.02	Approved for COPD maintenance therapy and asthma exacerbation moderate to severe	Short-acting muscarinic agonists. Only one approved in the US market	Nebulized treatment every 6–8 h	[46, 47]
Aclidinium bromide	Selective antagonism with very slow dissociation time from M_3 receptors and shorter residence time at M_2 receptors	4.69 ± 0.29	29.24 ± 0.6	Approved as monotherapy and combination therapy with LABA for COPD	Low systemic bioavailability and less propensity to induce cardiac arrhythmias	Multiple dose device inhaled twice daily	[25, 46, 47]
Glycopyrronium bromide	High non-selective affinity for all five muscarinic receptor subtypes with a greater kinetic selectivity for M_3 over M_2	1.07 ± 0.20	8.10 ± 0.45	Approved as monotherapy and combination therapy with LABA for COPD	Shorter residence time at M3 compared with tiotropium and aclidinium; however, found to be efficacious	Dry powder inhaler for oral inhalation Used once per day	[25, 47, 48]
Tiotropium bromide	Kinetic selectivity for M_1 and M_3 receptors over M_2 receptor. Very slow dissociation from M3 accounting for its prolonged duration of action	3.6 ± 0.5	34.7 ± 2.96	Approved as monotherapy and combination with LABA for COPD Approved as add-on therapy for asthma	Only LAMA approved for asthma	Powder device and propellant-free inhaler with slow-moving mist of aerosolized solution used once per day	[47]
Umeclidinium bromide	High affinity for M3 receptors and long duration of action	9.4 ± 0.5 (min)	82.2 ± 0.0012 (min)	Approved as monotherapy and combination therapy with LABA for COPD	It has comparable duration of action compared with tiotropium in isolated bronchial strips	Dry powder inhaler for oral inhalation used once per day	[49–51]

COPD chronic obstructive disease, *LABA* long-acting β agonist, *LAMA* long-acting muscarinic agonists, $t_{½}$ dissociation half life

bronchodilation as measured by an increase in the forced expiratory volume in 1 s (FEV_1) sustained for 24 h, and the effects were dose-dependent. The authors reported the prolonged bronchodilator response and protection against methacholine challenge were suggestive of the usefulness of tiotropium in asthma. Later, Magnussen et al. in a double-blinded, placebo-controlled randomized trial of COPD patients with concomitant asthma further demonstrated the efficacy of tiotropium. They illustrated improvement in spirometric parameters as well as symptomatic benefit by reduction of need for rescue medications [29].

5.1.1 *Safety and Efficacy of Different Doses of Tiotropium in Addition to Inhaled Corticosteroid (ICS)*

Beeh et al. evaluated tiotropium respimat in multiple doses as add-on to an inhaled corticosteroid (ICS) in symptomatic moderate persistent asthma subjects [30]. In their 4-way crossover, randomized, double-blind, placebo-controlled study, 5, 2.5 or 1.25 μg of tiotropium respimat or placebo were examined for 4 weeks each. Analysis of peak $FEV_{1\ (0–3h)}$ change from baseline at the end of each 4-week period demonstrated significant improvements across all tiotropium respimat doses compared with placebo (all $p < 0.0001$) with the greatest adjusted mean difference between tiotropium respimat 5 μg and placebo. All secondary endpoints including trough FEV_1, FEV_1 area under the curve $(AUC)_{(0–3h)}$, peak forced vital capacity $(FVC)_{(0–3h)}$, trough FVC, FVC $AUC_{(0–3h)}$, peak expiratory flow $(PEF)_{AM/PM}$, and Asthma Control Questionnaire-7 (ACQ-7) score had significant improvements with all doses of tiotropium respimat except for trough FVC in the 1.25-μg group. Further analysis of the response difference among tiotropium doses showed the 5-μg dose to be somewhat better. Incidence of adverse events was comparable between placebo and all tiotropium respimat groups with no drug-related serious adverse events.

In an effort to demonstrate the best timing and frequency of tiotropium use, Timmer et al. assessed the efficacy and safety of once-daily tiotropium respimat 5 μg in comparison with 2.5 μg twice daily as add-on to medium dose ICS in asthmatic patients [31]. In this randomized, double-blind, placebo-controlled, crossover study, 4-week treatment periods of tiotropium 5 μg daily, 2.5 μg twice daily and placebo were examined. FEV_1 $AUC_{(0–24h)}$ at the end of each treatment period was the primary end point. Peak $FEV_{1\ (0–24h)}$, trough FEV_1, $PEF_{AM/PM}$ and pharmacokinetic assessments were secondary points. Both tiotropium dosing regimens significantly improved FEV_1 $AUC_{(0–24h)}$ response (once-daily 5 μg 158 ± 24 mL; twice-daily 2.5 μg 149 ± 24 mL and $p < 0.01$ for both) compared with placebo. There was no significant difference among both verum dosing regimens. There were prominent improvements ($p < 0.01$) in peak $FEV_{1\ (0–24h)}$ (5 μg 131 ± 24 mL; 2.5 μg 132 ± 24 mL), trough FEV_1 (5 μg 133 ± 29 mL; 2.5 μg 111 ± 30 mL), and pre-dose $PEF_{AM/PM}$ with both dosing regimens versus placebo. No statistical difference was observed among the tiotropium treatment regimens. Total systemic exposure and tolerability were comparable between treatment regimens. The mean ACQ-7 score showed a statistically significant improvement ($p < 0.01$) for both tiotropium dosing regimens when compared with placebo (once-daily 5 μg 0.274; twice-daily 2.5 μg 0.190). The authors concluded that tiotropium as add-on to medium-dose ICS has sustained and similar lung function improvement as once-daily 5 μg and twice-daily 2.5 μg in patients with symptomatic moderate asthma. It is likely that once-daily dosing would promote better patient adherence.

5.1.2 *Safety and Efficacy of Tiotropium with ICS ± Long-Acting β_2 Agonist (LABA) Compared with Placebo*

Kerstjens et al. looked at the safety and efficacy of tiotropium respimat in asthma as add-on therapy to ICS ± LABA comparing two different doses (5 and 10 μg daily) with placebo in severe uncontrolled asthmatics [32]. After 8-week treatment periods in a crossover fashion, a significant difference in peak FEV_1 was found among the tiotropium respimat 5- and 10-μg treatments compared with placebo. However, there was no significant difference between the tiotropium doses. Secondary endpoints FEV_1 trough and daily home PEF rates were also significantly different compared with placebo. There were no noticeable differences in asthma-related health status or symptoms. Adverse reactions were balanced except for some anticholinergic effects at the higher dose of tiotropium. The authors concluded using tiotropium daily along with high-dose ICS plus LABA in severe uncontrolled asthmatics would significantly improve lung function. Subsequently, two replicate, randomized controlled trials (PrimoTinA-asthma 1 and PrimoTinA-asthma 2) involving 912 poorly controlled asthmatics were conducted [22]. After 24 weeks of tiotropium use, the mean peak FEV_1 change from baseline was significantly greater in treated groups compared with placebo in both trials ($p < 0.01$ and $p < 0.001$, respectively). Also, trough FEV_1 improved in the tiotropium arm compared with placebo ($p < 0.01$ and $p < 0.001$, respectively). Furthermore, the days to first exacerbation increased: 282 days compared with 226 days, and there was a 21 % overall reduction in the risk of a severe exacerbation (hazard ratio [HR] 0.79; $p < 0.03$) with tiotropium versus placebo. The adverse reactions reported were predominately anticholinergic in nature with dry mouth the most commonly reported. Drug-related

cardiac events were reported in two patients (0.4 %) in the tiotropium group and one patient (0.2 %) in the placebo group. In a similar fashion, Paggiaro et al. evaluated the efficacy and safety of tiotropium as add-on to ICS in mild to moderate symptomatic asthma patients [33]. A phase III, double-blind, placebo-controlled trial of 464 mild to moderate asthmatics was conducted. After 12 weeks of receiving tiotropium respimat 5 or 2.5 μg, or placebo, there was a higher difference of peak $FEV_{1\ (0–3h)}$ response among tiotropium groups compared with placebo (adjusted mean difference from placebo: 5 μg, 128 mL; 2.5 μg, 159 mL; both $p < 0.001$). Other studied parameters including trough FEV_1, FEV_1 $AUC_{(0–3h)}$, and $PEF_{AM/PM}$ also showed statistically significant improvements in comparison with placebo. Reported adverse events were similar across the treatment groups.

5.1.3 *Effect of Tiotropium in Addition to ICS Compared with LABA plus ICS*

In a three-way, double-blind, triple-dummy crossover trial, Peters et al. evaluated the addition of tiotropium bromide to ICS, as compared with doubling of ICS dose or the addition of LABA to ICS [34]. Two hundred and ten asthmatic subjects were enrolled in this trial. Tiotropium 18 μg once daily plus belcomethasone 80 μg twice daily versus belcomethasone 160 μg twice daily versus salmeterol plus belcomethasone 80 μg twice daily were used in this trial. The mean difference of 25.8 L/min ($p < 0.001$) in the PEF_{AM} established the superiority of tiotropium use with ICS, as compared with a doubling of the dose of ICS. Additionally, PEF_{PM} difference of 35.3 L/min ($p < 0.001$); the proportion of asthma-control days difference of 0.079 ($p < 0.01$); FEV_1 before bronchodilation difference of 0.10 L ($p < 0.004$); and daily symptom scores difference of −0.11 points ($p < 0.001$) all supported the advantage of adding tiotropium to ICS. Moreover, the addition of tiotropium to ICS was not inferior to the LABA/ICS combination for all assessed outcomes. In fact, the tiotropium/ICS combination increased the prebronchodilator FEV_1 more than did LABA, with a difference of 0.11 L ($p < 0.003$). Recently, Kerstjens and colleague studied effectiveness of tiotropium as add-on to moderate asthma therapy in comparison with LABA [35]. In 24-week, replicate, double-blind, placebo-controlled, parallel group studies (MezzoTinA-asthma®), the peak $FEV_{1\ (0–3)}$ and trough FEV_1 responses and responder rate by ACQ-7 were the primary endpoints. There were statically significant improvements in peak FEV_1 and trough FEV_1 with tiotropium and salmeterol versus placebo (Fig. 4). Moreover, a significant improvement in ACQ-7 responder rate was noticed with tiotropium 5 μg (odds ratio [OR] 1.32; 95 % CI 1.02–1.71; $p < 0.035$), 2.5 μg (OR 1.33; 95 % CI 1.03–1.72; $p < 0.031$), and salmeterol (OR 1.46; 95 % CI 1.13–1.89; $p < 0.0039$) compared with placebo (Fig. 5). However, this mean increase in ACQ-7 score did not reach the minimal clinical important difference for either drug. These findings supported the use of tiotropium as add-on to ICS in moderately severe adult asthmatics. Population-specific effects were evaluated in the BELT (Blacks and Exacerbations on LABA vs Tiotropium) trial. Wechsler et al. examined the superiority of LABAs in combination with ICS against tiotropium in combination with ICS in a Black moderate to severe asthmatic population and assessed any associated variation among genetic Arg16Gly alleles of the β2-adrenergic receptor (*ADRB2*) gene [36]. In this multicenter, randomized, open-label, and parallel-group study, the time to first asthma exacerbation was the primary outcome. Secondary outcomes included ACQ, Asthma Symptom Utility Index, and Asthma Symptom-

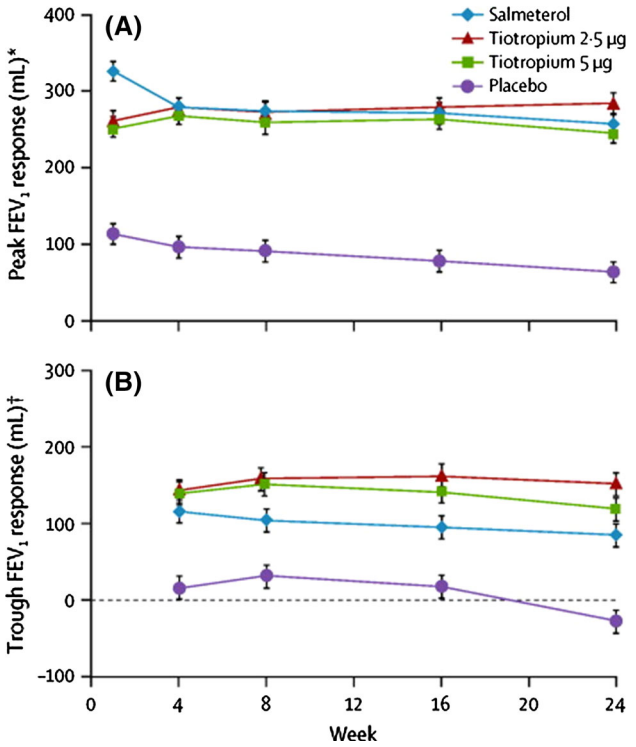

Fig. 4 Effectiveness of tiotropium as add-on to ICS in moderate asthma in comparison with LABA and placebo. Adjusted mean FEV_1 over 24 weeks for peak (**a**) and trough (**b**) responses in the full analysis set (pooled data). For peak FEV_1, all p values were <0.0001 for active drug versus placebo; for trough responses, all drugs were $p < 0.0001$ except salmeterol at week 16 ($p = 0.0002$). *FEV_1* forced expiratory volume in 1 s, *ICS* inhaled corticosteroid, *LABA* long-acting β-agonist. *Asterisk* measured within the first 3 h after evening dosing. *Dagger* 0 h denotes the trough FEV_1 value taken 10 min before inhalation of study drug, between 1800 and 2000 h Adapted from Kerstjens et al. [35], with permission

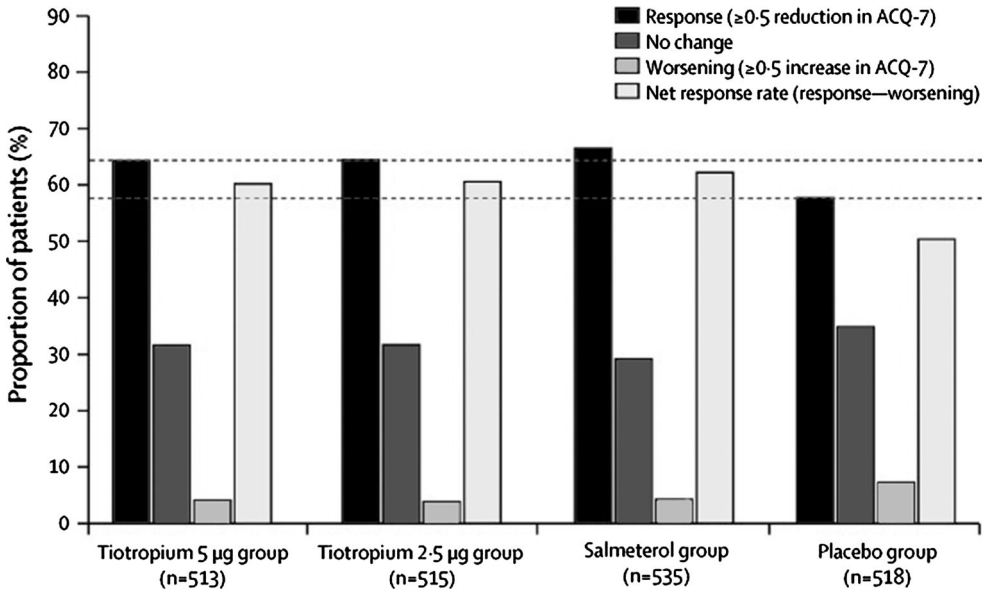

Fig. 5 Effectiveness of tiotropium as add-on to ICS in moderate asthma in comparison with LABA and placebo. ACQ-7 responder rate at Week 24 in the full analysis set (pooled data). Mean ACQ-7 at baseline was 2.21 (SD 0.49) in the tiotropium 5-µg group, 2.17 (0.49) in the tiotropium 2.·5-µg group, 2.15 (0.47) in the salmeterol group, and 2.18 (0.50) in the placebo group. Adjusted mean ACQ-7 score responses versus placebo were −0.12 (SD 0.04; $p = 0.0084$) in the tiotropium 5-µg group, −0.16 (0.04; $p = 0.0002$) in the tiotropium 2.5-µg group, and −0.20 (0.04; $p < 0.0001$) in the salmeterol group. Dashed lines show the difference in responder rate (tiotropium vs -placebo). *ACQ-7* seven-question Asthma Control Questionnaire, *ICS* inhaled corticosteroid, *LABA* long-acting β-agonist Adapted from Kerstjens et al. [35] with permission

Free Days questionnaire; FEV_1; rescue medication use; asthma deteriorations; and adverse events. There was no difference between LABA/ICS versus tiotropium/ICS in time to first exacerbation (mean number of exacerbations/person-year 0.42 versus 0.37 [95 % CI 0.73–1.11]), change in FEV_1 at 12 months and 18 months, ACQ score, and other patient-reported outcomes. No detected difference was found in the responses to tiotropium/ICS and LABA/ICS among the *ADRB2* Arg16Gly allelic groups. With all these findings they concluded that combination therapy of LABA/ICS is not superior to tiotropium/ICS in Black asthmatic patients.

5.1.4 Long-Term Safety of Tiotropium Use

Most of the previous efficacy studies showed comparable adverse effects between tiotropium and LABA as short-term therapy. Ohta et al. studied the safety of tiotropium use long term in a double-blind, randomized, placebo-controlled trial. They assessed the safety and efficacy of tiotropium in 285 moderate to severe asthmatics for 52 weeks [37]. They found the incidence of adverse events was similar across all the groups (5, 2.5 µg, and placebo). The most commonly reported adverse events were nasopharyngitis, asthma worsening, bronchitis, decreased PEF, pharyngitis, and gastroenteritis. Rates of drug-related adverse events were similar in the placebo and tiotropium 2.5-µg groups at 5.3 % versus tiotropium 5 µg at 8.8 % of subjects. Four percent of tiotropium 5-µg subjects had mild cardiac adverse events that were attributed to the medication. One subject each in the tiotropium 2.5- and 5-µg groups had worsening asthma symptoms which were documented as a serious adverse event. No deaths or life-threatening conditions were reported. The long-term efficacy at week 52 revealed a significantly higher difference in the mean trough FEV_1 response of 112 mL (95 % CI 18–207; $p < 0.0203$) with tiotropium respimat 5 µg compared with placebo. Not much change was noted with tiotropium respimat 2.5 µg compared with placebo at week 52 with trough FEV_1 change of 12 mL (95 % CI −82 to 106; $p < 0.7971$). Adjusted mean trough PEF response was significantly higher with tiotropium respimat 5 µg than with placebo but not with tiotropium respimat 2.5 µg. ACQ-7 responder rates were similar across treatment groups at Week 52.

5.1.5 Safety and Efficacy of Tiotropium in Children

In a shift in the population being studied, Vogelberg et al. studied tiotropium in adolescents with asthma. A randomized, double-blind, placebo-controlled, incomplete crossover, phase II trial was conducted in adolescents with

moderate persistent asthma taking a moderate dose of ICS [38]. Subjects were assigned to different doses of tiotropium respimat of 5, 2.5, 1.25 μg, and placebo for 4 weeks each (total of 12 weeks). Noticeably, LABA was discontinued for each subject that was on it during the run-in period. They noted significant improvements in FEV_1 3 h after using tiotropium respimat 5 μg and in trough FEV_1 compared with placebo. This improvement was not seen in tiotropium respimat 2.5 and 1.25 μg. Morning PEF response for all three tiotropium respimat groups was superior compared with placebo. ACQ-7 scores improved during treatment to the same degree in all three groups of tiotropium and placebo. These findings suggest that tiotropium respimat 5 μg might be the most efficacious dose in an adolescent population. In a similar study design, Vogelberg et al. studied tiotropium in children aged 6–11 years old [39]. There was a statistically significant difference in peak $FEV_{1\ (0–3h)}$ response across the tiotropium respimat dose group (5, 2.5 and 1.25 μg) versus placebo after 4 weeks of treatment. Furthermore, there was no dose-dependent response in patients treated with tiotropium respimat. The group treated with tiotropium respimat also showed improvements in trough FEV_1 response, FEV_1 $AUC_{(0–3h)}$ response, FEV_1 response over 3 h after dosing, and morning PEF. There were positive trends in ACQ-7 and Pediatric Asthma Quality of Life Questionnaire (PAQLQ) scores, but these were not statistically significant. The safety and tolerability of tiotropium respimat groups were comparable with the placebo group.

5.1.6 Real-Life Trials

Although collective evidence from all the trials discussed here shows benefits of adding tiotropium in adult and pediatric populations (Table 2), these studies were more controlled and perhaps not indicative of actual asthma patients seen in clinic. Price et al. recently examined the effectiveness of LAMAs as add-on therapy in real-life asthma care [40]. Records of over 2000 asthmatics on ICS ± LABA (COPD excluded) were evaluated before (baseline) and after (outcome) starting tiotropium. They found a significant decrease in occurrence of acute exacerbations, oral corticosteroid use, and acute respiratory events that required antibiotics along with significant increases in the rate of asthma control (all $p < 0.001$). However, there was a significant increase in short-acting β_2 agonist use and there were no significant changes in PEF, FEV_1, or FEV_1/FVC ratio. Despite some limitations in this real-life study, its findings were consistent with well controlled and randomized trials discussed above.

5.2 Umeclidinium

Although umeclidinium (UMEC) is approved for COPD as maintenance therapy in the US and EU, it is not approved for asthma. There are only a few small studies suggesting its effectiveness in asthma. Lee et al. evaluated the dose response, efficacy, and safety of UMEC in adults with asthma [41]. A randomized, double-blind, placebo-controlled, three-period crossover incomplete block study involved 350 steroid-naïve asthmatic subjects. A sequence of three of eight potential treatments (UMEC 15.6, 31.25, 62.5, 125, or 250 μg once daily, UMEC 15.6 or 31.25 μg twice daily, or placebo) were used. Trough $FEV_{1\ 0–24h}$, weighted mean (WM) FEV1, and safety were assessed. Significant improvements in change from baseline trough FEV_1 were observed for UMEC 15.6 μg once daily (0.066 L; $p = 0.036$) and UMEC 125 μg once daily (0.088 L; $p = 0.005$) versus placebo, but not other once-daily or twice daily doses. UMEC increased 0–24 h WM FEV_1 versus placebo (0.068–0.121 L, $p = 0.017$) with no clear dose response. The incidence of adverse events was 9.21 % for UMEC and 12 % for placebo. There were no treatment-related effects on laboratory parameters. The authors concluded that, despite the modest trough FEV_1 improvements, there was no therapeutic benefit of UMEC in non-ICS-treated patients with asthma. Lee et al. also studied the dose-response effect of UMEC in combination with fluticasone furoate (FF) in asthmatic subjects [42]. In their double-blind, three-period crossover study, 421 symptomatic asthma subjects were enrolled. A sequence of three of seven treatments (FF 100 μg alone, FF 100 μg combined with UMEC (15.6, 31.25, 62.5, 125, or 250 μg), or vilanterol [LABA] 25 μg) was inhaled once daily for 14 days. Trough FEV_1, PEF, and safety were assessed. The researchers faced issues with carryover effect between treatment periods. Despite that, the trough FEV_1 improved with FF/UMEC 125 and 250 μg versus FF (treatment difference 0.055 L [both doses]; $p = 0.018$). FF/UMEC increased morning (15.9–22.9 L/min) and evening (16.2–28.8 L/min) PEF versus FF. However, due to the carryover effect, a post hoc Period 1 data analysis was performed. This demonstrated significant increases in trough FEV_1 with FF/UMEC 31.25, 62.5, and 250 μg versus FF. Interestingly, trough FEV_1 improvements with FF/UMEC were higher in subjects with fixed (0.095–0.304 L) versus non-fixed (0.084–0.041 L) obstruction. Again, no treatment-related effects on laboratory parameters were found. The incidence of adverse events was 13–25 % across groups. Although there were clear carryover effects, ICS + UMEC may be an option for patients with symptomatic asthma, especially with fixed

Table 2 Key efficacy and safety studies for long-acting muscarinic antagonists in asthma

Study	Study type	Medication formula and dosage	Asthma population	Primary outcome	Secondary outcome	Outcome
Tiotropium initial trials						
O'Connor et al. [28]	RDBPC, crossover study	Tiotropium 10, 40, or 80 μg	Adult with mild asthma	FEV_1 changes after methacholine-induced bronchoconstriction	None	FEV_1 increased between 5.5 and 11.1 % from baseline and sustained for 24 h. There was a dose-dependent effect
Magnussen et al. [29]	RDBPC, parallel-group trial	Inhaled powder 18 μg tiotropium	Concomitant asthma with COPD	FEV_1 $AUC_{(0–6h)}$ (over 6 h)	FVC, FVC $AUC_{(0–6h)}$, weekly mean $PEF_{AM/PM}$, weekly mean SABA use, and adverse events	Improvement of FEV_1 $AUC_{0–6h}$ (difference = 186 ± 24 mL, $p < 0.001$), morning pre-dose FEV_1 ($p < 0.001$), FVC ($p < 0.001$) and FVC $AUC_{0–6h}$ ($p < 0.001$). Reduction of the mean weekly puffs of SABA as needed by 0.05 ± 0.12 puffs/day ($p < 0.05$)
Different doses of tiotropium plus ICS						
Beeh et al. [30]	RDBPC, crossover study	Tiotropium respimat 5, 2.5 or 1.25 μg	Adult with moderate persistent asthma	Peak $FEV_{1\ (0–3h)}$	Trough FEV_1, FEV_1 $AUC_{(0–3h)}$, peak $FVC_{(0–3h)}$, trough FVC, FVC $AUC_{(0–3h)}$, $PEF_{AM/PM}$ and ACQ-7 score	Significant improvements in peak $FEV_{1\ (0–3h)}$ response in tiotropium vs placebo (all $p < 0.0001$). Trough FEV_1 and FEV_1 $AUC_{(0–3h)}$ responses were greater with tiotropium ($p < 0.0001$). $FVC_{(0–3h)}$, trough FVC, and FVC $AUC_{(0–3h)}$ responses vs placebo, were greatest with tiotropium. Adverse events were comparable for all groups
Timmer et al. [31]	RDBPC, crossover study	Tiotropium respimat 5 or 2.5 μg	Adult with moderate asthma	FEV_1 $AUC_{(0–24h)}$	Peak $FEV_{1\ (0–24h)}$, trough FEV_1, $PEF_{AM/PM}$ and pharmacokinetic assessments	FEV_1 $AUC_{(0–24h)}$ response was significantly greater with both tiotropium dosing regimens (once-daily 5 μg: 158 ± 24 mL; twice-daily 2.5 μg; 149 ± 24 mL; both $p < 0.01$). Improvements in peak $FEV_{1(0–24h)}$, trough $FEV_{1,}$, and pre-dose $PEF_{AM/PM}$ with both dosing regimens vs placebo were statistically significant (all $p < 0.01$). No significant differences between the tiotropium treatment regimens

Table 2 continued

Study	Study type	Medication formula and dosage	Asthma population	Primary outcome	Secondary outcome	Outcome
Tiotropium plus ICS ± LABA versus placebo						
Kerstjens et al. [32]	RDBPC, crossover study	Tiotropium respimat inhaler 5 or 10 μg	Adult with severe persistent asthma	Peak FEV_1 (within 3 h after dosing)	Trough FEV_1 and peak and trough FVC, FEV_1 $AUC_{(0–3h)}$ and FVC $AUC_{(0–3h)}$, pre-dose $PEF_{AM/PM}$, asthma symptoms, use of rescue medication, asthma symptom-free days, and MiniAQLQ	Significantly greater peak FEV_1 mean with 5 μg (difference, 139 mL) and 10 μg (difference, 170 mL) (both $p < 0.0001$). No significant difference between the active doses. Trough FEV_1 (5 μg: 86 mL) (10 μg: 113 mL) (both $p < 0.0004$). PEF measurements higher with both tiotropium doses. There were no significant differences in asthma-related health status or symptoms. Adverse events were balanced across groups
Kerstjens et al. [22]	Two replicate RDBPC, parallel-group trials	Tiotropium respimat 5 μg	Adult with moderate to severe asthma	Peak $FEV_{1\ (0–3h)}$, trough FEV_1, and the time to the first severe asthma exacerbation	FEV_1 and FVC $AUC_{(0–3h)}$, the time to the first worsening of asthma, peak $PEF_{AM/PM}$, asthma symptoms (ACQ-7 and AQLQ), and adverse events	Mean FEV_1 was greater with tiotropium vs placebo (86 ± 34 mL in trial 1 ($p = 0.01$) and 154 ± 32 mL in trial 2 ($p < 0.001$). Trough FEV_1 improved in both trials (88 ± 31 mL ($p = 0.01$) and 111 ± 30 mL ($p < 0.001$), respectively. Adding tiotropium increased the time to the first severe exacerbation with an overall reduction of 21 % (HR 0.79; $p = 0.03$). Adverse events were similar in the two groups
Paggiaro et al. [33]	Phase III, RDBPC trial	Tiotropium respimat 5 or 2.5 μg	Adult with mild to moderate asthma	Peak $FEV_{1\ (0–3h)}$	Trough FEV_1, $FEV_{1\ (0–3h)}$ AUC responses, PEF_{AM} and PEF_{PM} and adverse effect	Significant greater peak FEV_1 mean with tiotropium (mean difference 5 μg, 128 mL; 2.5 μg, 159 mL; both $p < 0.001$). Also significant response to mean trough FEV_1 and FEV_1 $AUC_{(0–3h)}$ responses, and morning and evening PEF. Adverse events were comparable across the groups
Tiotropium plus ICS versus ICS plus LABA						
Peters et al. [34]	Three-way, RDBPC, triple-dummy crossover trial	Inhaled powder 18 μg tiotropium	Adult with mild to moderate asthma	The morning PEF	The FEV_1 before bronchodilation, the number of asthma-control days, asthma symptoms, rescue-bronchodilator use, asthma exacerbations, use of healthcare services, biomarkers of airway inflammation, ACQ-7, the Asthma Symptom Utility Index, and AQLQ	Significant improvement in morning PEF (mean difference of 25.8 L/min [$p < 0.001$]). Superiority in evening PEF (mean 35.3 L/min [$p < 0.001$]); asthma-control days of 7.9 % ($p = 0.01$); the FEV_1 prior to bronchodilation (0.10 L ($p = 0.004$); and daily symptom scores, with a difference of −0.11 points ($p < 0.001$). Addition of tiotropium was noninferior to the addition of salmeterol for all assessed outcomes

Table 2 continued

Study	Study type	Medication formula and dosage	Asthma population	Primary outcome	Secondary outcome	Outcome
Kerstjens et al. [35]	Two replicate, RDBPC, parallel group studies	Tiotropium respimat 5 or 2.5 μg	Adult with moderate asthma	The peak $FEV_{1\ (0–3h)}$, trough FEV_1 response and responder rate by ACQ-7	Peak $FVC_{(0–3h)}$, trough FVC, mean $PEF_{AM/PM}$, AQLQ score response, and times to first severe asthma exacerbation	Significant greater peak FEV_1 mean with tiotropium (mean difference 185 mL in 5 μg, 223 mL in 2.5 μg) and salmeterol (196 mL) (all $p < 0.0001$) and trough FEV_1 mean difference 146, 180, and 114 mL (all $p < 0{\cdot}0001$), respectively. Greater ACQ-7 responders in the tiotropium 5 μg (OR 1.32; $p = 0{\cdot}035$) and 2.5 μg (1.33; $p = 0{\cdot}031$) groups, and the salmeterol (1.46; $p = 0{\cdot}0039$). Non-treatment serious adverse events occurred in 2 %
Wechsler et al. [36]	RDBPC, parallel-group study	Inhaled powder 18 μg tiotropium	Black adult with moderate to severe asthma	First asthma exacerbation	ACQ-7, Asthma Symptom Utility Index, and Asthma Symptom-Free Days questionnaire, FEV_1, rescue medication use, asthma deteriorations, and adverse events	No difference between LABA/ICS vs tiotropium/ICS in time to first exacerbation (RR 0.90 [95 % CI 0.73–1.11]; $p = 0.31$). There was no difference in change in FEV_1 at 12 months (difference 0.020 [95 % CI −0.021 to 0.061], $p = 0.33$) and at 18 months (difference 0.025 [95 % CI −0.045 to 0.095], $p = 0.49$). There were no differences in ACQ-7 score at 18 mo (difference 0.04 [95 % CI, −0.18 to 0.27], $p = 0.70$)
Long-term safety of tiotropium use						
Ohta et al. [37]	RDBPC trial	Tiotropium respimat 5 or 2.5 μg	Adult with mild to moderate asthma	Adverse-event rates (the long-term safety over 52 weeks)	Trough FEV_1 and FVC; PEF response; and ACQ-7	Adverse-event rates with tiotropium 5 μg, 2.5 μg, and placebo were 88.6, 86.8, and 89.5 %, respectively. Adjusted mean trough FEV_1 and trough PEF responses were significantly higher with tiotropium 5 μg (but not 2.5 μg) vs placebo. ACQ-7 responder rates were higher with both
Tiotropium in children						
Vogelberg et al. [38]	Phase II, RDBPC, incomplete crossover trial	Tiotropium respimat of 5, 2.5, or 1.25 μg	Adolescents with moderate persistent asthma	Peak $FEV_{1\ (0–3h)}$	Trough FEV_1, FEV_1 $AUC_{(0–3h)}$, $PEF_{AM/PM}$, and ACQ-7	Peak $FEV_{1\ (0–3h)}$ mean response with tiotropium 5 μg was significantly greater than placebo ($p = 0.0043$). No significance with other doses. Trough FEV_1 responses were significantly greater for all doses ($p = 0.0001$–0.0975). FEV_1 $AUC_{(0–3h)}$ responses were significant for all doses ($p = 0.0001$–0.0398). Overall incidence of adverse events was balanced across groups

Table 2 continued

Study	Study type	Medication formula and dosage	Asthma population	Primary outcome	Secondary outcome	Outcome
Vogelberg et al. [39]	Phase II, RDBPC, incomplete crossover trial	Tiotropium respimat of 5, 2.5 or 1.25 μg	Children with moderate persistent asthma	Peak $FEV_{1\ (0–3h)}$	Trough FEV_1, FEV_1 $AUC_{(0–3h)}$, $PEF_{AM/PM}$ and ACQ-7	Peak $FEV_{1\ (0–3h)}$ mean responses with tiotropium doses (5, 2.5, 1.25 μg) were significantly greater than with placebo ($p = 0.0002$, $p < 0.0001$, and $p = 0.0011$, respectively). Trough FEV_1 responses were significantly greater for all doses ($p = 0.0001$–0.0023). FEV_1 $AUC_{(0–3h)}$ responses were significant for all doses ($p = 0.0001$–0.013). The safety and tolerability of all doses of tiotropium were comparable with placebo
Umeclidinium in asthma						
Lee et al. [41]	RDBPC, three-period crossover, incomplete block study	Umeclidinium 15.6, 31.25, 62.5, 125, or 250 μg daily, UMEC 15.6 or 31.25 μg twice daily	Adult with mild intermittent asthma	Trough FEV1	0–24 h WM FEV_1, and safety	Significant improvements in trough FEV_1 were observed for UMEC 15.6 μg daily (0.066 L; $p = 0.036$) and UMEC 125 μg daily (0.088 L; $p = 0.005$) vs placebo, but not other daily or twice daily doses. UMEC increased 0–24 h WM FEV1 vs placebo (0.068–0.121 L $p = 0.017$ with no clear dose-response). The incidence of on-treatment adverse events was 9–21 % for UMEC and 12 % for placebo
Lee et al. [42]	RDBPC, three-period crossover, incomplete block study	Umeclidinium 15.6, 31.25, 62.5, 125, or 250 μg	Adult with moderate persistent asthma	Trough FEV_1	$PEF_{AM/PM}$, rescue albuterol use, and safety	Trough FEV_1 improved with ICS/UMEC 125 and 250 μg vs ICS (0.055 L; $p = 0.018$). ICS/UMEC increased morning (15.9–22.9 L/min) and evening (16.2–28.8 L/min) PEF vs ICS. Trough FEV_1 improvements with ICS/UMEC were greater in subjects with fixed (0.095–0.304 L) vs non-fixed (0.084–0.041 L) obstruction. The incidence of on-treatment adverse events was 13–25 % across groups

ACQ-7 Asthma Control Questionnaire-7, *AQLQ* the Asthma Quality-of-Life Questionnaire, *FEV_1* forced expiratory volume in 1 s, *FEV_1 AUC* forced expiratory volume in 1 s area under the curve, *FVC* forced vital capacity, *FVC AUC* forced vital capacity area under the curve, *HR* hazard ratio, *ICS* inhaled corticosteroid, *LABA* long-acting β-adrenergic agonist, *MiniAQLQ* Mini-Asthma Quality of Life Questionnaire, *OR* odds ratio, *PEF* peak expiratory flow, *RDBPC* randomized, double-blind, placebo controlled, *RR* rate ratio, *SABA* short-acting beta adrenergic agonist, *UMEC* umeclidinium, *WM* weighted mean

obstruction; however, further studies with better design are needed to confirm its effectiveness.

5.3 Glycopyrronium Bromide and Aclidinium Bromide

Despite glycopyrronium showing prolonged bronchodilatation effect, especially in an acute setting [43–45], to date there are no published clinical trials supporting the effectiveness of this or aclidinium in asthma. Previous trials have demonstrated their effectiveness in COPD as add-on therapy to ICS with or without LABA. The discussion of these studies is beyond this review.

6 Conclusion

Asthma is a heterogeneous disease that has been targeted with various treatment modalities. Unfortunately, many patients still remain symptomatic. Understanding the complex neuronal involvement of bronchoconstriction and inflammation in patients with asthma has allowed us to re-evaluate the clinical utility of antimuscarinics. Cumulative data have established the effectiveness of these agents as maintenance therapy. Evidence supports prescribing LAMA as add-on therapy to ICS in symptomatic asthma regardless of the severity in both adult and pediatric populations. Currently, tiotropium is the only LAMA approved for asthma. Tiotropium has been found to benefit patients as an add-on to ICS alone or in combination with LABAs. A daily dose of tiotropium 5 μg has the most sustainable effect and safety profile. Among different available formulations for tiotropium (powder or respimat), respimat has less local side effects, probably due to the delivery method. Emerging data for other LAMAs, such as aclidinium, will likely aid in the guideline-driven placement of LAMAs for asthma.

Compliance with Ethical Standards

Conflict of interest Dr. Bulkhi and Dr. Tabatabaian have no conflicts of interest to disclose. Dr. Casale has been an investigator on grants from Boehringer Ingelheim to his University and has been on advisory boards for Boehringer Ingelheim.

Funding No sources of funding were used to support the writing of this manuscript.

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