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Inhaled long-acting muscarinic antagonists in asthma – A narrative review

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ABSTRACT

Long-acting muscarinic antagonists (LAMAs) have a recognised role in the management of chronic obstructive pulmonary disease. In asthma, muscarinic antagonists (both short- and long-acting) were historically considered less effective than β_2-agonists; only relatively recently have studies been conducted to evaluate the efficacy of LAMAs, as add-on to either inhaled corticosteroid (ICS) monotherapy or ICS/long-acting β_2-agonist (LABA) combinations. These studies led to the approval of the first LAMA, tiotropium, as an add-on therapy in patients with poorly controlled asthma. Subsequently, a number of single-inhaler ICS/LABA/LAMA triple therapies have been approved or are in clinical development for the management of asthma. There is now substantial evidence of the efficacy and safety of LAMAs in asthma that is uncontrolled despite treatment with an ICS/LABA combination. This regimen is recommended by GINA as an optimisation step for patients with severe asthma before any biologic or systemic corticosteroid treatment is initiated.

This narrative review summarises the potential mechanisms of action of LAMAs in asthma, together with the initial clinical evidence supporting this use. We also discuss the studies that led to the approval of tiotropium for asthma and the data evaluating the efficacy and safety of the various triple therapies, before considering other potential uses for triple therapy.

Introduction

The efficacy of muscarinic antagonists in asthma has been known since the early 1800s when inhalation of smoke from burning *Datura stramonium* leaves and roots became widespread in Britain as a treatment for obstructive airway disease (reviewed by Mansfield and Bernstein [1]). Once identified as the active agent, subsequent clinical studies were conducted with atropine [2], in turn replaced by the short-acting muscarinic antagonist (SAMA) ipratropium bromide due to better efficacy and lower systemic effects [3].

Muscarinic antagonists were considered effective only for chronic obstructive pulmonary disease (COPD) and not for asthma, as cholinergic (vagal) tone was believed to be the only reversible component of the disease [4]. In asthma, muscarinic antagonists were considered less effective as bronchodilators than β_2-agonists, as the cholinergic component of bronchoconstriction was believed to be small compared to the direct constrictor effects of inflammatory mediators or leukotrienes [4]. However, studies comparing the long-acting muscarinic antagonist (LAMA) tiotropium with the long-acting β_2-agonist (LABA) salmeterol in patients with asthma have clearly shown that LAMAs are as effective as LABAs, in terms of bronchodilation, patient-reported outcomes and exacerbations [5–7]. However, tiotropium was initially developed and then approved only for the maintenance treatment of COPD [8], despite strong evidence of its efficacy in asthma already being available [9].

Recently, LAMAs, initially tiotropium, later glycopyrronium and umeclidinium, have been studied as add-on therapy in patients with asthma, and particularly in patients who have persistent asthma symptoms or exacerbations despite optimised inhaled corticosteroid (ICS)/LABA treatment [7]. Indeed, both the Global Initiative for Asthma (GINA) strategy document and the National Asthma Education and Prevention Program guideline position tiotropium before biologic drugs or oral corticosteroids (OCS) [10,11]. In addition, the European

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Respiratory Society (ERS)/American Thoracic Society (ATS) Severe Asthma Task Force recommends tiotropium as an add-on to ICS/LABA in patients with severe asthma regardless of phenotype [12]. A number of LAMAs are now approved or are in clinical development for the management of asthma as a single-inhaler triple combination with a LABA and ICS [7]. In addition, although only one randomised controlled trial (RCT) has been conducted in patients with concomitant asthma and COPD [13], it is likely that LAMAs will be increasingly used also in these patients [14].

This review discusses the scientific rationale for the use of LAMAs in asthma, and critically appraises evidence on the clinical effects of LAMAs in asthma (including from studies with a LAMA used in a separate inhaler or as part of single-inhaler triple combination treatment). The future use of LAMAs in clinical practice is also considered.

Potential mechanisms of action of LAMAs in asthma

The contractile tone of the airways is controlled primarily by the vagus nerve, being generally increased in asthma (Figure 1) [15,16]. The contraction of airway smooth muscle (ASM), due to the neurotransmitter acetylcholine (ACh), occurs through stimulation of M3 muscarinic ACh receptors (mAChR), which are expressed throughout the whole bronchial tree including the central and peripheral (small) airways, even if vagal innervation at the peripheral level is limited or absent. ACh is also produced by the airway epithelium and by non-neuronal cells such as inflammatory cells, acting as a paracrine or autocrine hormone: so-called 'non-neurogenic ACh' [17]. In contrast, activation of postsynaptic M2 mAChRs counteracts the relaxation mediated by β-adrenoceptors on the ASM, while the expression on presynaptic parasympathetic neurons limits the release of ACh by acting as an autoreceptor [15].

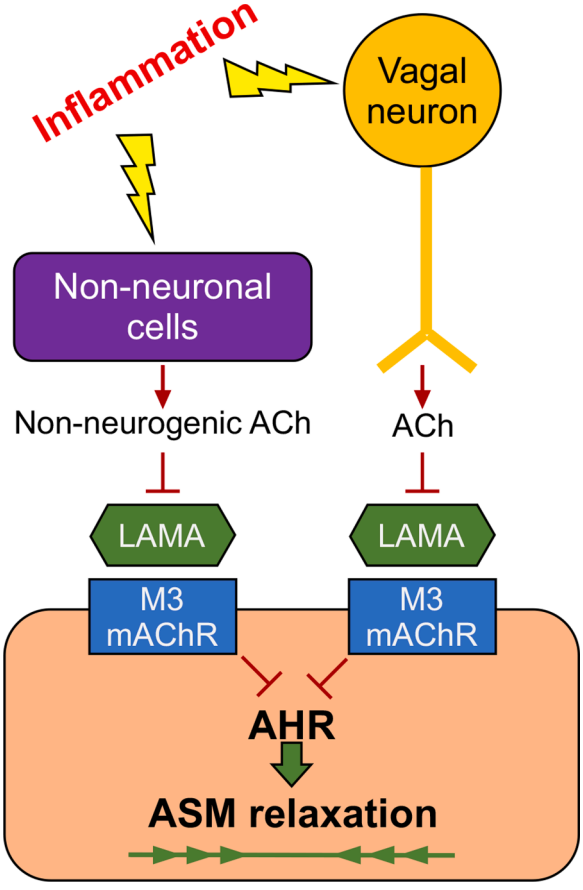

Figure 1. Mechanisms of action of LAMAs. ACh, acetylcholine; LAMA, long-acting muscarinic antagonist; mAChR, muscarinic ACh receptor; AHR, airways hyperresponsiveness; ASM, airway smooth muscle.

Airway inflammation caused by environmental or infectious factors, together with inflammation-induced epithelial damage, increases exposure of sensory nerve endings, stimulation of sensory nerves, release of ganglionic and postganglionic ACh by inflammatory mediators, and attenuation of the function of the self-inhibiting M2 mAChR [18]. The increased tone of the ASM generated by ACh increases contractility in response to further contractile stimuli, suggesting that the bronchoconstriction itself enhances the reaction to further (hyperresponsive) triggers [19]. Studies in antigen-challenge animal models demonstrate that airway hyperresponsiveness (AHR) is mediated by increased release of ACh from the vagus nerves [20]. Immunoglobulin E also appears to amplify airway contraction by facilitating ACh release from the cholinergic nerves, perhaps due to a dysfunction of M2 mAChR at the nerve endings [21].

Increased ACh receptor signalling (M1, M2 and M3 mAChRs) may play a role not only on increased bronchoconstriction but also on mucus secretion, inflammation, and airway remodelling [22]. Indeed, both neurogenic and non-neurogenic ACh contribute to inflammation and remodelling of the respiratory tract [17]. When cholinergic tone is increased, mAChR antagonists reduce ASM contraction due to cholinergic activation [15]. As demonstrated in both animal models and humans, increased contractile activity translates into AHR [23,24], and so LAMAs may block ACh signalling and may prevent increased ASM contractility induced by cholinergic tone and reduced AHR.

LABAs and LAMAs modulate bronchial tone through different pathways. The interactions between these pathways are not fully understood, yet there is cross-talk at many levels in ASM cells regulated by the activity of calcium-dependent potassium channels and by the proteins tyrosine kinase [25], in addition to the inhibition of epithelial release of non-neuronal ACh [26].

The use of LAMAs in asthma is supported by evidence of the drug interactions between LAMAs and ICSs and/or LABAs. In-vitro corticosteroid treatment reduces ASM sensitivity to ACh [27], and levels of pre-functional self-inhibiting M2 mAChR on parasympathetic airway neurons increase, reducing ACh release and increasing degradation of ACh by cholinesterases, thereby decreasing both M2 and M3 mAChR activity in ASM [28,29]. The co-administration of beclometasone and glycopyrronium showed a significant relaxation of passively sensitised human ASM pre-contracted by histamine, causing submaximal/maximal inhibition of contractile tone in medium bronchi and small airways [30]. The ICS/LAMA combination synergistically improved relaxation only of passively sensitised medium and small bronchi, associated with increased cAMP synthesis [30]. This evidence on sensitised airways suggests the potential therapeutic role of ICS/LAMA combinations, although few clinical studies have evaluated such combinations [30]. Further, in an ex-vivo experimental setting the triple ICS/LABA/LAMA combination of beclometasone dipropionate, formoterol fumarate and glycopyrronium (BDP/FF/G) synergistically relaxed both medium and small airways; in particular, the 100:6:10 concentration ratio resulted in a very strong synergistic bronchorelaxant effect. Such a synergistic interaction was related to the activation of intracellular glucocorticoid receptors and the Gsα subunit G protein of β_2-adrenoceptors, leading to modulation of the protein kinase A pathway dependent on cyclic adenosine monophosphate [31].

Overall, information from pharmacological investigations have demonstrated the potential for cross-talk between LAMAs and both ICSs and LABAs, which may result in synergistic interactions. These mechanisms may contribute to the clinical findings, reviewed later in this article, of the superiority of ICS/LABA/LAMA over ICS/LABA therapy on clinical outcomes in patients with asthma [32].

Initial clinical evidence for LAMAs in asthma

Studies conducted 45 years ago demonstrated the bronchodilator efficacy of ipratropium bromide in both asthma and COPD [33].

Ipratropium bromide was less effective than the short-acting β_2-agonist (SABA) salbutamol in asthma, although both drugs were similarly effective in COPD [33]. This, together with a slower onset of action, resulted in SAMAs becoming second choice as reliever medication, or used in acute exacerbations only [10]. Nevertheless, the principle of ameliorating cholinergic tone by muscarinic antagonists has been applied for decades in asthma [3], especially in patients with nocturnal asthma, since cholinergic mechanisms contribute to the diurnal variation of vagal tone [9]. Indeed, a mechanistic study by O'Connor and colleagues in 1996 showed that tiotropium improved lung function and protected against methacholine-induced bronchoconstriction in patients with mild atopic asthma [9]. The same effects were shown for glycopyrrolate by Hansel and colleagues 10 years later [34]. Both studies provided mechanistic evidence that long-acting muscarinic antagonism could be of potential clinical benefit in patients with asthma. However, LAMAs were initially developed with a focus on COPD [35].

In 2008, the effects of tiotropium in 472 patients with COPD and concomitant asthma were investigated [13]. Eligible patients had a physician diagnosis of asthma before the age of 30 years, a current diagnosis of COPD with fixed airflow obstruction and a smoking history of at least 10 pack-years, were receiving ICS for ≥1 year prior to study entry, and had a documented bronchodilator response of ≥200 mL and ≥12% improvement in forced expiratory volume in 1 second (FEV_1) [13]. Improvements in lung function and reductions in salbutamol use with tiotropium in that study were consistent with reported changes in patients with COPD and no asthma.

A smaller study examined the effects of tiotropium on short-term lung function improvements in patients with severe asthma that was uncontrolled despite medium- to high-dose ICS and at least one other controller medication, which included OCS in about 25% of the recruited population [36]. After four weeks treatment, tiotropium was most effective in patients with lower sputum eosinophil levels. Similarly, Kapoor and colleagues described a patient with severe OCS-dependent asthma, in whom the OCS dose could be substantially reduced following the initiation of tiotropium [37].

In 2010 Peters and colleagues published the results of a study funded by the National Heart, Lung, and Blood Institute to evaluate the role of tiotropium as step-up therapy in patients with mild-to-moderate asthma, whose disease was uncontrolled despite low-dose ICS (80 μg beclometasone twice daily) [38]. In this placebo-controlled, double-dummy, three-way cross-over study 210 patients were treated with: a double dose of ICS (i.e. 160 μg beclometasone twice daily); ICS (80 μg beclometasone twice daily) plus LABA (50 μg salmeterol twice daily); and ICS (80 μg beclometasone twice daily) plus tiotropium (18 μg one daily), for 14 weeks each with a 2-week washout between treatments. Adding tiotropium was superior to doubling the ICS dose in terms of morning and evening peak flow, pre-dose FEV_1, and proportion of asthma-control days (Figure 2). Furthermore, tiotropium was non-inferior to salmeterol on all asthma outcomes with a significantly better improvement in pre-dose FEV_1. Even though this study did not evaluate the role of LAMA as add-on treatment to medium- or high-dose ICS/LABA in severe asthma, it provided strong evidence of a potential role of LAMA in a population with a high unmet medical need.

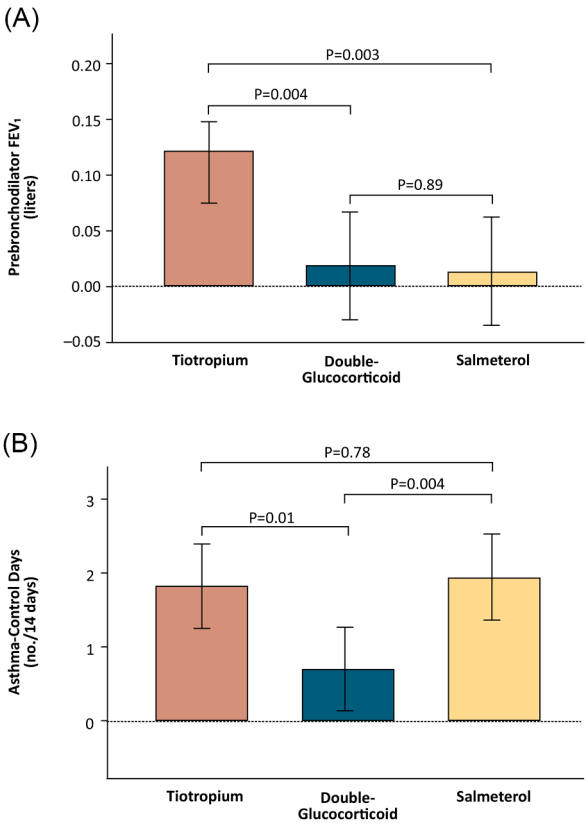

Figure 2. Shown are the mean differences among patients receiving tiotropium, those receiving double-glucocorticoid, and those receiving salmeterol with respect to the prebronchodilator forced expiratory volume in 1 second (FEV_1) (Panel A), and the proportion of asthma-control days per 14-day period (Panel B). The I bars indicate 95% confidence intervals. From Peters et al. N Engl J Med 2010;363:1715–26 [38]. Copyright © 2010 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Tiotropium in asthma: the UniTinA programme

To subsequently test the efficacy of tiotropium in asthma, a large clinical trial programme (UniTina-asthma) was conducted in over 6000 adults, adolescents and children [39]. This programme included patients with mild, moderate and severe asthma, with tiotropium administered in the Respimat formulation, always in addition to ICS via a separate inhaler, with or without a LABA depending on disease severity.

The PrimoTina studies were two identical 48 week, randomised, placebo-controlled, double-blind trials in 912 adults with severe asthma, who were symptomatic despite moderate-to-high dose ICS (≥800 μg budesonide or equivalent) and LABA [40]. Eligible patients had post-bronchodilator FEV_1 ≤80% predicted and FEV_1 to forced vital capacity (FVC) ratio ≤70%, were lifelong non-smokers or had a smoking history <10 pack-years with no smoking in the year before enrolment, and ≥1 exacerbation in the previous year leading to systemic corticosteroid use. Patients with COPD were excluded. During a four-week screening period and throughout the trial, patients continued their own ICS/LABA, and were then randomised to tiotropium 5 μg or placebo via Respimat once daily in the morning. Three co-primary endpoints were defined in hierarchical sequence: peak and trough FEV_1 response at 24 weeks, and time to first exacerbation necessitating systemic corticosteroids over the full trial period.

After 24 weeks, mean treatment differences were 120 mL in peak FEV_1 and 99 mL in trough FEV_1 [40]. Since these differences were highly significant in both trials individually, the third co-primary endpoint in this pooled analysis could also be tested: there was an increase of 56 days in time to first severe exacerbation, hazard ratio 0.79, p=0.03 (Figure 3A). Among the secondary endpoints, there were large improvements in Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ) scores in both arms, with only small differences between treatments, although tiotropium reached significance in one trial. Adverse event incidence was similar in both arms; the percentage of patients reporting dry mouth (1.8% with tiotropium and 0.7% with placebo) was lower than reported in most COPD trials.

The addition of tiotropium to ICS in 2103 patients with moderate asthma was tested in the MezzoTinA studies, two replicate placebo- and active-controlled, double-blind, double-dummy, 24 week trials [41]. Patients were randomised equally to one of four arms: tiotropium

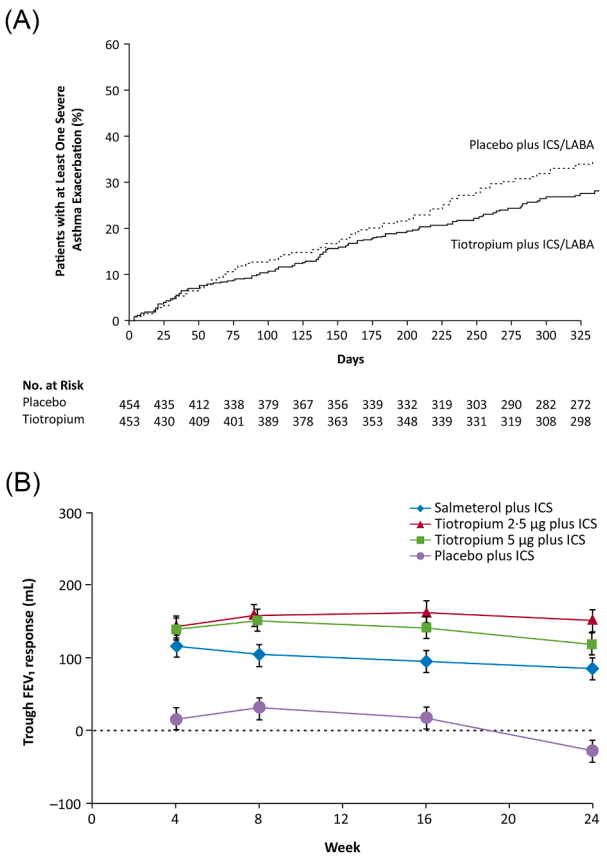

Figure 3. A. Cumulative number of severe exacerbations, with a risk reduction of 21% (hazard ratio, 0.79; p=0.03 in pooled analysis) in PrimoTinA study. From Kerstjens et al. N Engl J Med 2012;367:1198–207 [40]. Copyright © 2010 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. B. Adjusted mean trough FEV_1 over 24 weeks response in MezzoTinA studies, pooled analysis. Error bars show SEs. All p values were <0.0001 for active drug versus placebo, except salmeterol at week 16 (p=0.0002). FEV_1, forced expiratory volume in 1 s. Reprinted from Kerstjens et al. Lancet Respir Med 2015;3:367–76 [41], Copyright © 2015, with permission from Elsevier.

Respimat 2.5 or 5 µg once daily in the evening, salmeterol 50 µg via pressurised metered dose inhaler (pMDI) twice daily, or matched placebos. Moderate asthma was defined as an ICS dose of 400–800 µg budesonide or equivalent, which was continued throughout the study using the patient's own device. Eligible patients were symptomatic (ACQ ≥1.5), with pre-bronchodilator FEV_1 60–90% predicted, significant bronchodilator response to salbutamol, and the same smoking restrictions as above. There were no exacerbation history requirements. Three co-primary endpoints were defined in hierarchical sequence: peak and trough FEV_1 response at 24 weeks in the separate trials, and ACQ-7 responder rates in the pooled analysis. Peak and trough FEV_1 responses were significantly greater with tiotropium and salmeterol than with placebo in both studies [41]. The pooled difference versus placebo in peak FEV_1 was 185 mL with tiotropium 5 µg, 223 mL with tiotropium 2.5 µg, and 196 mL with salmeterol (all p<0.0001); the differences in trough FEV_1 were 146, 180, and 114 mL, respectively (Figure 3B). There were more ACQ-7 responders with tiotropium 5 µg (OR 1.32, p=0.035) and 2.5 µg (1.33, p=0.031), and with salmeterol (1.46, p=0.0039), than placebo. No safety signals were identified.

Pre-specified subgroup analyses were performed on the two sets of studies; the effects of tiotropium 2.5 and 5 µg were independent of age, sex, baseline FEV_1, bronchodilator response, smoking history, prior exacerbation rate, and allergic status in moderate or severe disease [42,43]. The improvements in FEV_1 and exacerbation rates were also independent of blood eosinophils and other markers of T2 phenotype [44].

For more than two decades, the preferred long-acting bronchodilator added to ICS in asthma has been a LABA, and most clinicians have the impression of a larger effect of the LABA compared to LAMA. This could be due to the studies of adding the LAMA were mainly performed in severe symptomatic asthma, on top of ICS+LABA. At least three studies have performed a head-to-head comparison of the relative efficacy of adding a LABA or LAMA, in (mild to) moderate asthma [6,38,41]. In the TALC study in patients with mild to moderate asthma, the addition of tiotropium (via HandiHaler) was noninferior to the addition of salmeterol for all assessed outcomes and increased the prebronchodilator FEV_1 more than did salmeterol (difference 0.11 L; p=0.003) [38]. In a study of patients with moderate persistent asthma and B16-Arg/Arg, tiotropium was also non-inferior to salmeterol [6]. Finally, in the MezzoTinA studies, the effect of both tiotropium doses on trough FEV_1 was slightly greater than salmeterol (Figure 3B) [41]. Overall, therefore, the effect on lung function of adding tiotropium seems at least as good as salmeterol. The results from RCTs show that tiotropium is effective in adults across the ranges of asthma severity from GINA Step 2 to Step 5 [45], and is effective and well tolerated in adolescents and children with moderate to severe asthma [46].

The positive efficacy results of the UniTina-asthma programme coupled with the good safety profile led to the approval of tiotropium as the first LAMA for the management of asthma in adults and children.

Triple ICS/LABA/LAMA combinations in a single inhaler in asthma

The efficacy and safety of single inhaler triple therapy with extrafine BDP/FF/G (100/6/10 µg or 200/6/10 µg, two inhalations twice daily via pMDI) was compared to the corresponding doses of ICS/LABA (BDP/FF via pMDI) in patients with uncontrolled asthma in the TRIMARAN (medium-dose ICS; N=1155) and TRIGGER (high-dose ICS; N=1437) Phase III clinical trials (Table 1) [47]. The key inclusion criteria were pre-bronchodilator FEV_1 <80% predicted with reversibility >12% and >200 mL after inhaled salbutamol, uncontrolled asthma (ACQ-7 ≥1.5) and ≥1 exacerbation in the previous year (requiring treatment with systemic corticosteroids or an emergency department visit or hospital admission). The co-primary endpoints for both studies were morning pre-dose FEV_1 at Week 26 and rate of moderate and severe exacerbations over 52 weeks. A severe exacerbation was defined as asthma worsening needing systemic corticosteroids while a moderate exacerbation was defined by various criteria, including nocturnal awakening, increased reliever use and PEF decrease. Triple therapy had a greater effect on (a) change in pre-dose FEV_1 from baseline to Week 26 (57 mL in TRIMARAN, p=0.0080; 73 mL in TRIGGER, p=0.0025; Figure 4A) and (b) the rate of moderate and severe exacerbations (15% lower in TRIMARAN, p=0.033; 12% lower in TRIGGER, p=0.11; Figure 4B). A pre-specified pooled analysis (a key secondary endpoint) reported a 23% reduction in the severe exacerbation rate in favour of BDP/FF/G (p=0.008), leading to a reasonable interpretation that the overall pattern of results supports a greater benefit of BDP/FF/G on exacerbations compared to BDP/FF. There were no differences between treatments for change in ACQ-7 total score or rescue medication use. The TRIGGER study also showed that BDP/FF/G was similar to BDP/FF plus tiotropium for lung function and exacerbations.

Additional benefits with triple therapy were observed for lung function and exacerbations, but there appeared to be no treatment difference for symptoms. This may reflect insensitivity of the instrument (ACQ-7) to detect treatment differences.

The IRIDIUM Phase III, 52 week study (N=3092) investigated the effects of the once-daily, single-inhaler triple therapy mometasone furoate (MF) / indacaterol acetate (IND) / glycopyrronium bromide (GLY) compared to the ICS/LABA combinations MF/IND (once daily) and fluticasone/salmeterol (500/50 µg, twice daily) in patients with

Table 1
Summary of the designs of key single-inhaler triple therapy studies in patients with asthma.

Study	Single-inhaler triple therapy	Comparator(s)	Population	Primary endpoint(s)	Key secondary endpoint(s)
TRIMARAN and TRIGGER (Virchow et al) [47]	BDP/FF/G (TRIMARAN 100/6/10 μg; TRIGGER 200/6/10 μg, both 2 inhalations BID)	TRIMARAN: BDP/FF 100/6 μg, 2 inhalations BID TRIGGER: BDP/FF 200/6 μg, 2 inhalations BID, and BDP/FF 200/6 μg, 2 inhalations BID plus tiotropium 2.5 μg, 2 inhalations OD	Pre-bronchodilator FEV_1 <80% predicted; reversibility >12% and >200 mL; ACQ-7 ≥1.5; ≥1 exacerbation in the previous year; stable dose of ICS/LABA for ≥4 weeks before study entry (TRIMARAN medium ICS dose; TRIGGER high ICS dose)	Morning pre-dose FEV_1 at Week 26 and rate of moderate and severe exacerbations over 52 weeks	Peak FEV_1 at Week 26 and average morning PEF over the first 26 weeks in each study, and the rate of severe exacerbations using data pooled from the two studies.
IRIDIUM (Kerstjens et al) [48]	MF/IND/GLY 80/150/50 and 160/150/50 μg, both 1 inhalation OD	MF/IND 160/150 and 320/150 μg 1 inhalation OD; FLU/SAL 500/50 μg 1 inhalation BID	Pre-bronchodilator FEV_1 <80% predicted; reversibility ≥12% and ≥200 mL; ACQ-7 ≥1.5; ≥1 exacerbation in the previous year; medium/high-dose ICS/LABA for ≥3 months, stable for ≥1 month before study entry	Trough FEV_1 at Week 26	ACQ-7 at Week 26
ARGON (Gessner et al) [49]	MF/IND/GLY 80/150/50 and 160/150/50 μg OD	FLU/SAL 500/50 μg BID + tiotropium 5 μg OD	Pre-bronchodilator FEV_1 <85% predicted; reversibility ≥12% and ≥200 mL; ACQ-7 ≥1.5; ≥1 exacerbation in the previous year; stable medium/high-dose ICS/LABA	AQLQ at Week 24 (non-inferiority)	Not applicable
CAPTAIN (Lee et al) [50]	FluF/UMEC/VI 100/31.25/25, 100/62.5/25, 200/31.25/25, and 200/62.5/25 μg, 1 inhalation OD	FluF/VI 100/25, 200/25 μg, 1 inhalation OD	Pre-bronchodilator FEV_1 30–80% predicted; reversibility ≥12% and ≥200 mL; ACQ-6 ≥1.5; ≥1 healthcare contact or change in therapy for acute asthma symptoms in the previous year; medium/high-dose ICS/LABA for ≥12 weeks, stable for ≥6 weeks	Trough FEV_1 at Week 24	Annualised rate of moderate and/or severe exacerbations

BDP, beclometasone dipropionate; FF, formoterol fumarate; G, glycopyrronium; BID, twice daily; OD, once daily; FEV_1, forced expiratory volume in 1 second; ACQ, Asthma Control Questionnaire; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; PEF, peak expiratory flow; MF, mometasone furoate; IND, indacaterol acetate; GLY, glycopyrronium bromide; FLU, fluticasone; SAL, salmeterol; AQLQ, Asthma Quality of Life Questionnaire; FluF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol.

poorly controlled asthma (Table 1) [48]. Medium and high doses of MF/IND/GLY (80/150/50 and 160/150/50 μg respectively) were compared to medium and high doses of MF/IND (160/150 μg and 320/150 μg respectively), with the higher MF dose in the ICS/LABA arm necessitated by an increase in MF fine particle mass (and therefore lung deposition) when formulated as triple therapy compared to ICS/LABA. The main inclusion criteria were similar to the TRIMARAN and TRIGGER studies, with patients required to meet similar criteria for FEV_1, reversibility, ACQ-7 and exacerbation history at study entry while taking medium- or high-dose ICS/LABA. The primary endpoint was trough FEV_1 change from baseline at Week 26; medium- and high-dose MF/IND/GLY had greater effects compared to the respective MF/IND treatments (mean differences 76 mL, $p<0.001$ and 65 mL, $p<0.001$, respectively; Figure 4A). Medium- and high-dose MF/IND/GLY were also superior to fluticasone–salmeterol (mean differences 99 mL, $p<0.001$, and 119 mL, $p<0.001$, respectively; Figure 4A). A key secondary endpoint was change from baseline in ACQ-7 score; no difference were observed for either dose of MF/IND/GLY versus corresponding MF/IND doses, although MF/IND/GLY was superior to fluticasone/-salmeterol. Similarly, MF/IND/GLY had no significant effect on moderate to severe exacerbations compared to MF/IND, but significantly fewer events were observed for medium and high dose MF/IND/GLY versus fluticasone/salmeterol (mean differences 19%, $p=0.041$ and 36%, $p<0.001$, respectively; Figure 4B). The rate of moderate to severe exacerbations was lower in this study than in the BDP/FF/G studies, probably due to a more stringent definition in IRIDIUM, where two criteria needed to be met for moderate exacerbations. Overall, the effects of MF/IND/GLY on the primary endpoint analysis (compared to MF/IND) were clearly met, but these lung function differences were not accompanied by benefits on symptoms or exacerbations. The ACQ-7 result may have been impacted by a high response to ICS/LABA treatment. Nevertheless, MF/IND/GLY demonstrated benefits on these secondary endpoints versus the commonly used ICS/LABA fluticasone/salmeterol, suggesting potential utility for this triple therapy as a step-up option in clinical practice. Furthermore, the ARGON study, a Phase III study in patients with uncontrolled asthma, demonstrated non-inferiority for medium- and high-dose MF/IND/GLY compared to fluticasone/salmeterol plus tiotropium across a range of endpoints, while high dose MF/IND/GLY had a greater effect on lung function and asthma control (Table 1) [49]. These results demonstrate similar or improved asthma outcomes for MF/IND/GLY compared to triple therapy using separate inhalers.

The CAPTAIN Phase III, 24–52-week study (N=2439) compared fluticasone furoate / umeclidinium / vilanterol (FluF/UMEC/VI) with ICS/LABA (FluF/VI) in patients with uncontrolled moderate/severe asthma (Table 1) [50]. The treatment arms were FluF/UMEC/VI (100/31.25/25, 100/62.5/25, 200/31.25/25 and 200/62.5/25 μg) and FluF/VI (100/25 and 200/25 μg), delivered once a day using a multi-dose dry-powder inhaler. While triple therapy showed greater effects on the primary outcome measure of change from baseline in FEV_1 at Week 24, there was no significant difference in exacerbations (Figure 4A and B). Interestingly, in a *post-hoc* analysis that compared pooled data from all FluF 100 μg-containing treatment groups with the pooled FluF 200 μg-containing treatment groups, the higher dose had a greater effect than the lower dose on moderate/severe exacerbation prevention in patients with greater type-2 airway inflammation measured by blood eosinophil counts and exhaled nitric oxide.

Perhaps one of the most intriguing aspects of the role of muscarinic antagonists in asthma is the hypothesis that their effectiveness might be confined or more marked in specific phenotypes or endotypes of asthma. Interestingly, the addition of a LAMA in a single-inhaler triple therapy, e.g., glycopyrronium [47,51,52] or umeclidinium [50], is more effective

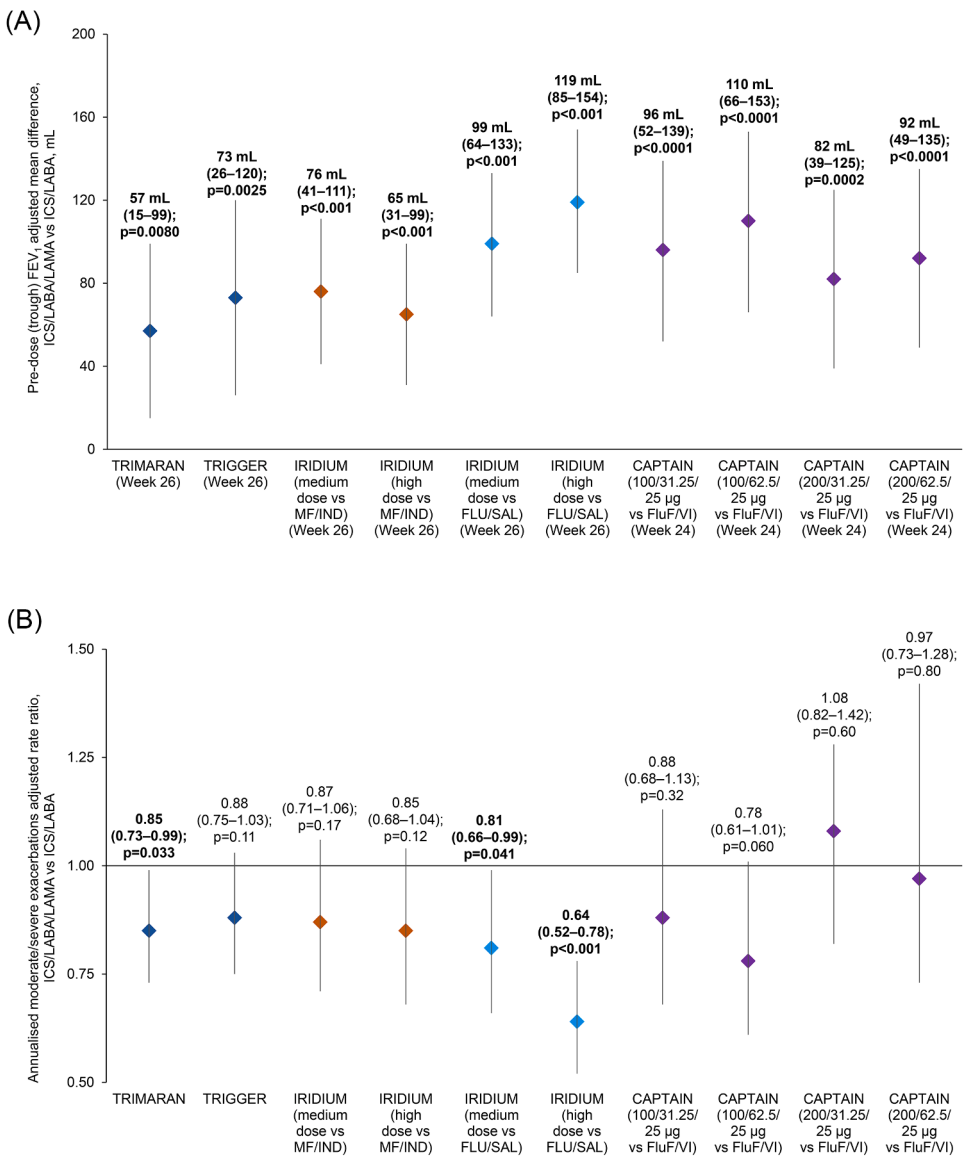

Figure 4. Single-inhaler triple therapy vs ICS/LABA differences from three clinical studies [47,48,50]. A) Adjusted mean differences (and 95% confidence intervals) in pre-dose or trough FEV_1 at Week 24 or 26. B) Adjusted rate ratios (and 95% confidence intervals) for annualised moderate and severe exacerbation rate. FEV_1, forced expiratory volume in 1 sec; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; MF, mometasone furoate; IND, indacaterol acetate; FLU, fluticasone; SAL, salmeterol; FluF, fluticasone furoate; VI, vilanterol.

on symptoms, quality of life and/or lung function in subjects with baseline persistent airflow limitation or greater bronchodilator reversibility. A post-hoc analysis of TRIMARAN and TRIGGER focused on the subgroup with persistent airflow limitation (defined as FEV_1/FVC ratio ≤ 0.7); the effects of extrafine BDP/FF/G on lung function and exacerbations appeared to be greater in this subgroup than in the overall population [51]. Furthermore, in an analysis of determinants of response, although the relative efficacy of BDP/FF/G versus BDP/FF was not influenced by a range of clinical characteristics, for exacerbations the relative efficacy of BDP/FF/G was greater in patients with greater lung function reversibility [52]. In the tiotropium studies, there was no dependency of exacerbation or lung function response on baseline factors [42].

The effect of single-inhaler triple therapy vs the same ICS/LABA on severe exacerbations was significant in the pooled analyses of TRIMARAN/TRIGGER [47], with efficacy not impacted by baseline blood eosinophil levels [52]. Furthermore, in CAPTAIN, the addition of UMEC to FluF/VI resulted in small, dose-related improvements in lung function, irrespective of baseline blood eosinophil levels [50]. Similarly, the effects of triple therapy containing tiotropium were independent of T2 phenotype including blood eosinophils [44]. By contrast, the effect of increasing FluF dose on annualised moderate and/or severe exacerbation rate was related to baseline blood eosinophil and fractional exhaled nitric oxide (FENO) levels [50]. These results support the need to further identify clinical characteristics that may alter treatment responses. For example, in patients with moderate-to-severe asthma that is not controlled by ICS/LABA, the addition of a LAMA should be considered preferentially for patients with persistent airflow limitation and bronchodilator reversibility, independent of blood eosinophil and/or FENO levels, whereas the step-up to triple with high-dose ICS should be considered particularly in patients with increased eosinophil and/or FENO levels.

Overall, these studies show consistent efficacy for single-inhaler triple therapies over ICS/LABA on pulmonary function, while the benefit on exacerbations was less consistent, although it was observed in two studies. Furthermore, the effects of single-inhaler triple therapies were comparable to ICS/LABA and LAMA in separate inhalers, supporting the use of single-inhaler triple therapies in clinical practice. Although one may speculate that, in patients with asthma, triple therapy in a single inhaler should improve compliance and adherence as compared to triple therapy in separate inhalers, thus potentially providing better efficacy and safety, this has not yet been demonstrated. Interestingly, in patients with COPD while single-inhaler triple therapy was non-inferior to multiple-inhaler triple therapy [53,54], in a

'real-life' setting single-inhaler triple therapy provided superior effectiveness to multiple-inhaler triple therapy [55,56], suggesting that the same superiority might be observed in asthma.

Safety profile of LAMAs in asthma

Overall, the use of LAMAs for the maintenance treatment of asthma is well tolerated. The asthma trials in which LAMAs were used 1) did not report any drug-related fatal adverse events, and 2) LAMAs were not associated with adverse events dissimilar to those already reported in patients with other chronic respiratory diseases [40,41,47–50]. Upper respiratory tract infections were the most frequently reported adverse events; side effects typically associated with anticholinergic drugs, i.e., dry mouth and urinary retention, were infrequent. Importantly, in elderly patients a similar proportion reported adverse events and serious adverse events in those who received tiotropium versus those who received placebo [57].

Other possible future uses of LAMAs in asthma

Asthma can be associated with COPD as concomitant disease, with real-world studies in patients with COPD suggesting that a history of asthma is associated with an increased risk of exacerbations [58]. Although many RCTs in COPD exclude patients with active asthma, patients with a history of asthma were included in two of the largest [59,60]; these RCTs demonstrated for the first time that triple therapy with ICS/LABA/LAMA reduces mortality in COPD [59,60]. The benefit of ICS/LABA/LAMA combination treatment on mortality in patients with COPD is likely to be related to the beneficial effects of each component, i.e. LABA [61], LAMA [62], and ICS [59,60,63,64], which may possibly linked to the increased efficacy of specific components in specific phenotypes. Whether COPD associated with history of asthma is one of these phenotypes remains to be studied [65].

Given the interest in personalised treatment of asthma and COPD [66], with the concept that specific phenotypes and endotypes should be treated with different agents or combination of agents to target individual traits of the disease [67], an important avenue to be explored is asthma with concomitant COPD, although unfortunately this has been studied in only one properly designed RCT [13].

Finally, a large RCT showed that tiotropium is as effective as the ICS mometasone in patients with asthma who have low sputum eosinophil levels, contradicting the principle that asthma should never be treated with a long-acting bronchodilator alone [68]. It should be noted that the use of tiotropium is not approved in this context.

Discussion

Overall, the use of LAMAs in asthma is supported from a mechanistic perspective, with evidence from a series of animal and human studies [15–17]. Furthermore, drug interaction studies suggest synergy of effect between LAMAs and ICSs and/or LABAs [25–30], including within triple combination ICS/LABA/LAMA [32] – although such data are from ex-vivo analyses. Early clinical data demonstrated that short-acting muscarinic antagonist treatment was effective in patients with asthma [33], yet although early data also suggested that LAMAs had efficacy in asthma [9,34], LAMAs were initially developed with a focus on COPD. Only some decades later were studies conducted of LAMAs in asthma [36,37]. Subsequent studies demonstrated the benefits of tiotropium as add-on to ICS or ICS/LABA – with tiotropium at least as effective as salmeterol when added-on to ICS [38–41].

The most recent development has been the use of single-inhaler triple ICS/LABA/LAMA therapy in patients with asthma that is uncontrolled by ICS/LABA [47–50]. Importantly, the use of LAMAs for the maintenance treatment of asthma is well tolerated, with no reports in studies of drug-related fatal adverse events, and with adverse events similar to those already reported in patients with other chronic respiratory diseases [40,41,47–50].

In conclusion, there is now substantial evidence of the efficacy and safety of LAMAs in asthma that is uncontrolled despite treatment with ICS/LABA combinations. This regimen is recommended by GINA as an optimisation step for patients with severe asthma before any biologic or systemic corticosteroid treatment is initiated, with a number of single-inhaler triple therapies now available or in clinical development. Whether LAMAs are more efficacious in asthma patients with specific clinical/biologic characteristics (phenotypes) needs to be explored in suitably designed trials.

Declaration of Competing Interest

AP reports grants, personal fees, non-financial support and payment for advisory board membership, consultancy, payment for lectures, grants for research, and travel expenses reimbursement from Chiesi, AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Mundipharma and TEVA, and personal fees and non-financial support from Menarini, Novartis, Zambon and Sanofi.

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HAMK has received fees for participation in advisory boards from Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Chiesi. All above was paid to his institution. His institution has also received unrestricted research and educational grants from Boehringer Ingelheim, Novartis and GlaxoSmithKline.

PR participated as a lecturer and advisor in scientific meetings and courses under the sponsorship of Almirall, AstraZeneca, Biofutura, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Menarini Group, Mundipharma, Novartis, Recipharm and her department was funded by Almirall, Boehringer Ingelheim, Chiesi, Novartis and Zambon.

HW reports personal fees from Chiesi during the conduct of the study. Outside the submitted work, Dr Watz reports personal fees from AstraZeneca, Bayer, BerlinChemie, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, and Roche.

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