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

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A B S T R A C T

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

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.

as an autoreceptor [15].

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 β₂-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].
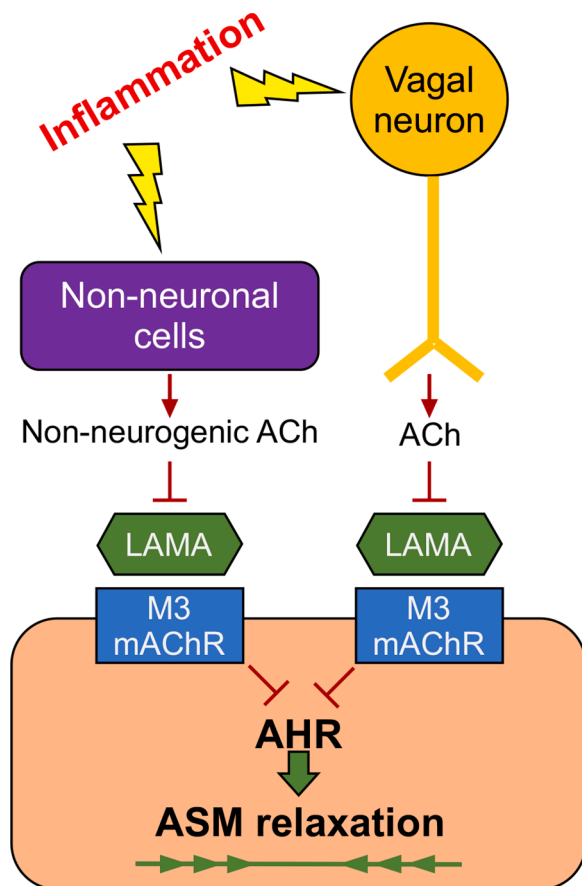
Ipratropium bromide was less effective than the short-acting β_2-agonist (SABA) salbutamol in asthma, although both drugs were similarly effective in COPD [33]. This, together with a slower onset of action, resulted in SAMAs becoming second choice as reliever medication, or used in acute exacerbations 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.

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
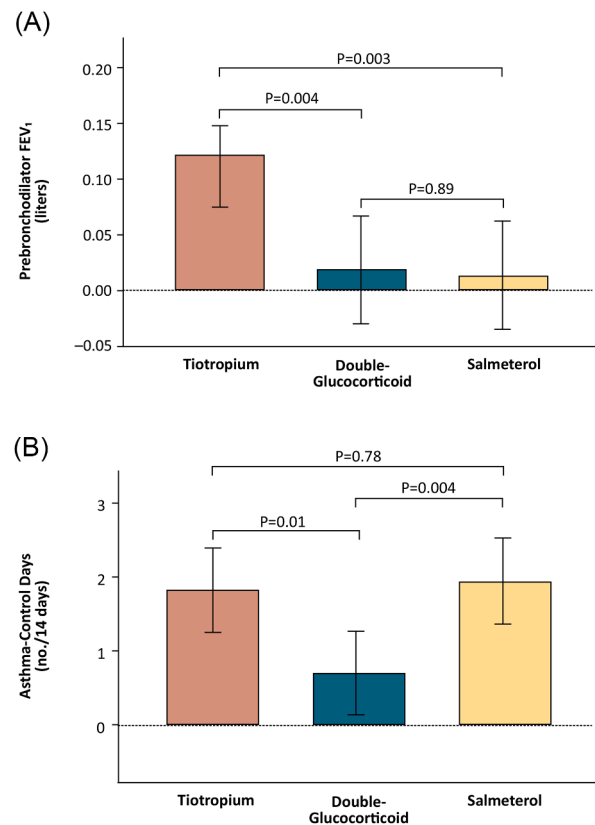

Figure 2. Shown are the mean differences among patients receiving tiotropium, those receiving double-glucocorticoid, and those receiving salmeterol with respect to the prebronchodilator forced expiratory volume in 1 second (FEV_1) (Panel A), and the proportion of asthma-control days per 14-day period (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.

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

(A)

(B)
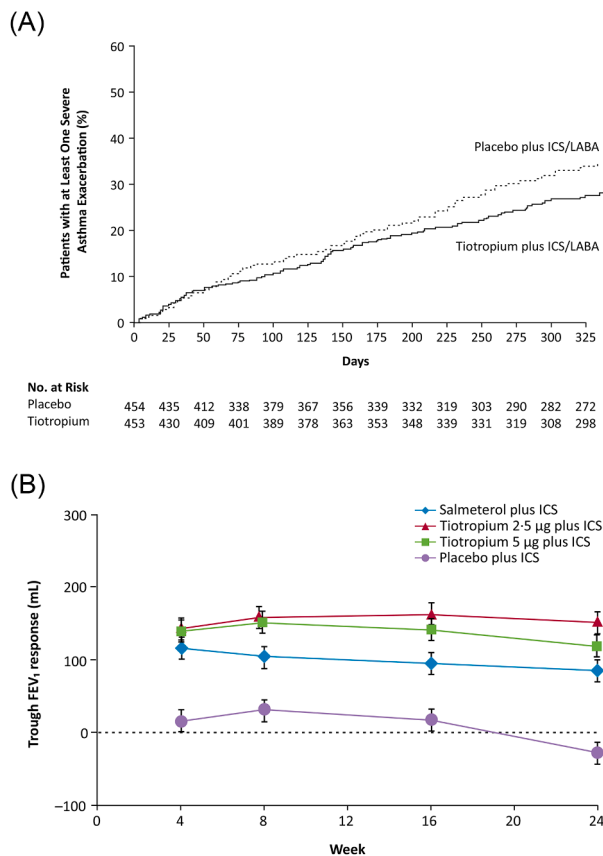
Figure 3. A. Cumulative number of severe exacerbations, with a risk reduction of 21% (hazard ratio, 0.79; p=0.03 in pooled analysis) in PrimoTinA study. From Kerstjens et al. N Engl J Med 2012;367:1198–207 [40]. Copyright © 2010 Massachusetts Medical Society. Reprinted with permission from Massachusetts 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.

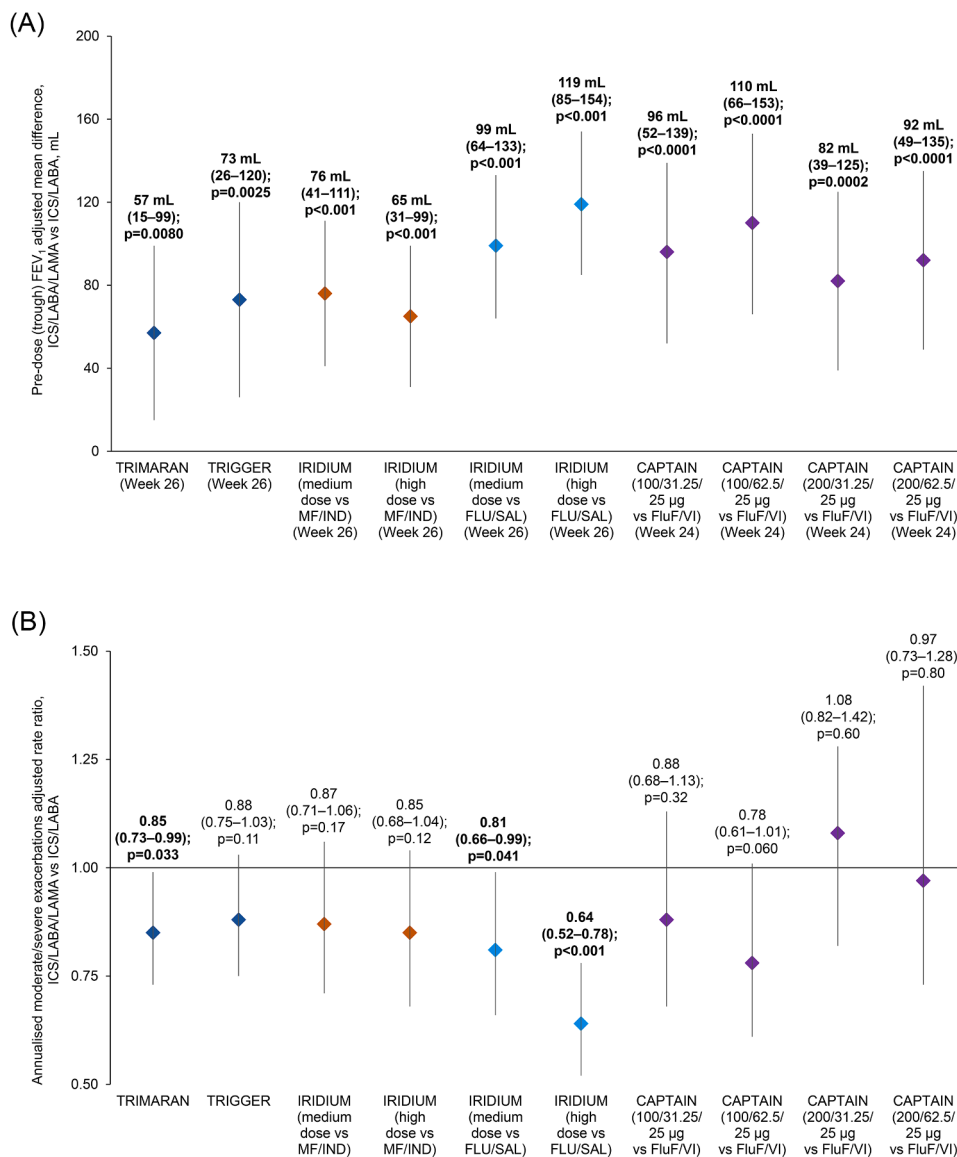| Study	Single-inhaler triple therapy	Comparator(s)	Population	Primary endpoint(s)	Key secondary endpoint(s)
TRIMARAN and TRIGGER (Virchow et al) [47]	BDP/FF/G (TRIMARAN 100/6/10 μg; TRIGGER 200/6/10 μg, both 2 inhalations BID)	TRIMARAN: BDP/FF 100/6 μg, 2 inhalations BID TRIGGER: BDP/FF 200/6 μg, 2 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 β2-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

(A)

(B)

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

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References

[1] Mansfield L, Bernstein JA. Tiotropium in asthma: From bench to bedside. Respir Med 2019;154:47–55. https://doi.org/10.1016/j.rmed.2019.06.008.

[2] Moulton BC, Fryer AD. Muscarinic receptor antagonists, from folklore to pharmacology; Finding drugs that actually work in asthma and COPD. Br J Pharmacol 2011;163:44–52. https://doi.org/10.1111/j.1476-5381.2010.01190.x.

[3] Gross NJ. Ipratropium bromide. N Engl J Med 1988;319:486–94. https://doi.org/10.1056/NEJM198808253190806.

[4] Barnes PJ. Distribution of receptor targets in the lung. Proc Am Thorac Soc 2004;1:345–51. https://doi.org/10.1513/pats.200409-045MS.

[5] Buhl R, FitzGerald JM, Busse WW. Tiotropium add-on to inhaled corticosteroids versus addition of long-acting β2-agonists for adults with asthma. Respir Med 2018;143:82–90. https://doi.org/10.1016/j.rmed.2018.08.014.

[6] Bateman ED, Kornmann O, Schmidt P, Pivovarova A, Engel M, Fabbri LM. Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma. J Allergy Clin Immunol 2011;128:315–22. https://doi.org/10.1016/j.jaci.2011.06.004.

[7] Matera MG, Rinaldi B, Berardo C, Rinaldi M, Cazzola M. A review of the pharmacokinetics of M3 muscarinic receptor antagonists used for the treatment of

asthma. Expert Opin Drug Metab Toxicol 2020;16:143–8. https://doi.org/10.1080/17425255.2020.1716730.

[8] US Food and Drug Administration. Application number 21-395 Approval letter(s) 2004. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-395.pdf_Spiriva_Approv.pdf (accessed August 31, 2020).

[9] O'Connor BJ, Towse LJ, Barnes PJ. Prolonged effect of tiotropium bromide on methacholine-induced bronchoconstriction in asthma. Am J Respir Crit Care Med 1996;154:876–80. https://doi.org/10.1164/ajrccm.154.4.8887578.

[10] Global Initiative For Asthma. Global strategy for asthma management and prevention 2020. https://ginasthma.org/gina-reports/ (accessed September 8, 2020).

[11] Cloutier MM, Dixon AE, Krishnan JA, Lemanske Jr RF, Pace W, Schatz M. Managing asthma in adolescents and adults: 2020 asthma guideline update from the National Asthma Education and Prevention Program. JAMA 2020;324:2301–17. https://doi.org/10.1001/jama.2020.21974.

[12] Holguin F, Cardet JC, Chung KF, Diver S, Ferreira DS, Fitzpatrick A, et al. Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. Eur Respir J 2020;55:1900588. https://doi.org/10.1183/13993003.00588-2019.

[13] Magnussen H, Bugnas B, van Noord J, Schmidt P, Gerken F, Kesten S. Improvements with tiotropium in COPD patients with concomitant asthma. Respir Med 2008;102:50–6. https://doi.org/10.1016/j.rmed.2007.08.003.

[14] Albertson TE, Chenoweth JA, Pearson SJ, Murin S. The pharmacological management of asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS). Expert Opin Pharmacother 2020;21:213–31. https://doi.org/10.1080/14656566.2019.1701656.

[15] Matera MG, Page CP, Calzetta L, Rogliani P, Cazzola M. Pharmacology and therapeutics of bronchodilators revisited. Pharmacol Rev 2020;72:218–52. https://doi.org/10.1124/pr.119.018150.

[16] Molfino NA, Slutsky AS, Julia-Serda G, Hoffstein V, Szalai JP, Chapman KR, et al. Assessment of airway tone in asthma: Comparison between double lung transplant patients and healthy subjects. Am Rev Respir Dis 1993;148:1238–43. https://doi.org/10.1164/ajrccm.148.5.1238.

[17] Cazzola M, Puxeddu E, Matera MG, Rogliani P. A potential role of triple therapy for asthma patients. Expert Rev Respir Med 2019;13:1079–85. https://doi.org/10.1080/17476348.2019.1657408.

[18] Meurs H, Oenema TA, Kistemaker LEM, Gosens R. A new perspective on muscarinic receptor antagonism in obstructive airways diseases. Curr Opin Pharmacol 2013;13:316–23. https://doi.org/10.1016/j.coph.2013.04.004.

[19] Bossé Y, Chin LYM, Paré PD, Seow CY. Adaptation of airway smooth muscle to basal tone relevance to airway hyperresponsiveness. Am J Respir Cell Mol Biol 2009;40:13–8. https://doi.org/10.1165/rcmb.2008-0150OC.

[20] Verbout NG, Lorton JK, Jacoby DB, Fryer AD. Atropine pretreatment enhances airway hyperreactivity in antigen-challenged guinea pigs through an eosinophil-dependent mechanism. Am J Physiol Lung Cell Mol Physiol 2007;292:L1126–35. https://doi.org/10.1152/ajplung.00455.2006.

[21] Ichinose M, Miura M, Tomaki M, Oyake T, Kageyama N, Ikarashi Y, et al. Incubation with IgE increases cholinergic neurotransmission in human airways in vitro. Am J Respir Crit Care Med 1996;154:1272–6. https://doi.org/10.1164/ajrccm.154.5.8912735.

[22] Gosens R, Gross N. The mode of action of anticholinergics in asthma. Eur Respir J 2018;52:1701247. https://doi.org/10.1183/13993003.01247-2017.

[23] Lee-Gosselin A, Gendron D, Blanchet MR, Marsolais D, Bossé Y. The gain of smooth muscle's contractile capacity induced by tone on in vivo airway responsiveness in mice. J Appl Physiol 2015;118:692–8. https://doi.org/10.1152/japplphysiol.00645.2014.

[24] Gazzola M, Lortie K, Henry C, Mailhot-Larouche S, Chapman DG, Couture C, et al. Airway smooth muscle tone increases airway responsiveness in healthy young adults. Am J Physiol Lung Cell Mol Physiol 2017;312:L348–57. https://doi.org/10.1152/ajplung.00400.2016.

[25] Calzetta L, Matera MG, Cazzola M. Pharmacological interaction between LABAs and LAMAs in the airways: Optimizing synergy. Eur J Pharmacol 2015;761:168–73. https://doi.org/10.1016/j.ejphar.2015.05.020.

[26] Cazzola M, Calzetta L, Puxeddu E, Ora J, Facciolo F, Rogliani P, et al. Pharmacological characterisation of the interaction between glycopyrronium bromide and indacaterol fumarate in human isolated bronchi, small airways and bronchial epithelial cells. Respir Res 2016;17:70. https://doi.org/10.1186/s12931-016-0386-8.

[27] Nabishah BM, Morat PB, Khalid BAK, Kadir BA. Effect of acetylcholine and morphine on bronchial smooth muscle contraction and its modulation by steroid hormones. Clin Exp Pharmacol Physiol 1990;17:841–7. https://doi.org/10.1111/j.1440-1681.1990.tb01287.x.

[28] Jacoby DB, Yost BL, Kumaravel B, Chan-Li Y, Xiao HQ, Kawashima K, et al. Glucocorticoid treatment increases inhibitory M2 muscarinic receptor expression and function in the airways. Am J Respir Cell Mol Biol 2001;24:485–91. https://doi.org/10.1165/ajrcmb.24.4.4379.

[29] Emala CW, Clancy J, Hirshman CA. Glucocorticoid treatment decreases muscarinic receptor expression in canine airway smooth muscle. Am J Physiol Lung Cell Mol Physiol 1997;272:L745–51. https://doi.org/10.1152/ajplung.1997.272.4.l745.

[30] Cazzola M, Calzetta L, Rogliani P, Puxeddu E, Facciolo F, Matera MG. Interaction between corticosteroids and muscarinic antagonists in human airways. Pulm Pharmacol Ther 2016;36:1–9. https://doi.org/10.1016/j.pupt.2015.11.004.

[31] Rogliani P, Matera MG, Facciolo F, Page C, Cazzola M, Calzetta L. Beclomethasone dipropionate, formoterol fumarate and glycopyrronium bromide: synergy of triple combination therapy on human airway smooth muscle ex vivo. Br J Pharmacol 2020;177:1150–63. https://doi.org/10.1111/bph.14909.

[32] Sobieraj DM, Baker WL, Nguyen E, Weeda ER, Coleman CI, White CM, et al. Association of inhaled corticosteroids and long-acting muscarinic antagonists with asthma control in patients with uncontrolled, persistent asthma. JAMA 2018;319:1473–84. https://doi.org/10.1001/jama.2018.2757.

[33] Petrie GR, Palmer KNV. Comparison of aerosol ipratropium bromide and salbutamol in chronic bronchitis and asthma. Br Med J 1975;1:430–2. https://doi.org/10.1136/bmj.1.5955.430.

[34] Hansel TT, Neighbour H, Erin EM, Tan AJ, Tennant RC, Maus JG, et al. Glycopyrrolate causes prolonged bronchoprotection and bronchodilatation in patients with asthma. Chest 2005;128:1974–9. https://doi.org/10.1378/chest.128.4.1974.

[35] Joos GF. Potential for long-acting muscarinic antagonists in chronic obstructive pulmonary disease. Expert Opin Investig Drugs 2010;19:257–64. https://doi.org/10.1517/13543780903505084.

[36] Iwamoto H, Yokoyama A, Shiota N, Shoda H, Haruta Y, Hattori N, et al. Tiotropium bromide is effective for severe asthma with noneosinophilic phenotype. Eur Respir J 2008;31:1379–80. https://doi.org/10.1183/09031936.00014108.

[37] Kapoor AS, Olsen SR, O'Hara C, Puttagunta L, Vethanayagam D. The efficacy of tiotropium as a steroid-sparing agent in severe asthma. Can Respir J 2009;16:99–101. https://doi.org/10.1155/2009/206506.

[38] Peters SP, Kunselman SJ, Icitovic N, Moore WC, Pascual R, Ameredes BT, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. N Engl J Med 2010;363:1715–26. https://doi.org/10.1056/NEJMoa1008770.

[39] Halpin DM, Kaplan AG, Russell RK. Why choose tiotropium for my patient? A comprehensive review of actions and outcomes versus other bronchodilators. Respir Med 2017;128:28–41. https://doi.org/10.1016/j.rmed.2017.04.008.

[40] Kerstjens HAM, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, et al. Tiotropium in asthma poorly controlled with standard combination therapy. N Engl J Med 2012;367:1198–207. https://doi.org/10.1056/NEJMoa1208606.

[41] Kerstjens HAM, Casale TB, Bleecker ER, Meltzer EO, Pizzichini E, Schmidt O, et al. Tiotropium or salmeterol as add-on therapy to inhaled corticosteroids for patients with moderate symptomatic asthma: two replicate, double-blind, placebo-controlled, parallel-group, active-comparator, randomised trials. Lancet Respir Med 2015;3:367–76. https://doi.org/10.1016/S2213-2600(15)00031-4.

[42] Kerstjens HAM, Moroni-Zentgraf P, Tashkin DP, Dahl R, Paggiaro P, Vandewalker M, et al. Tiotropium improves lung function, exacerbation rate, and asthma control, independent of baseline characteristics including age, degree of airway obstruction, and allergic status. Respir Med 2016;117:198–206. https://doi.org/10.1016/j.rmed.2016.06.013.

[43] Casale TB, Aalbers R, Bleecker ER, Meltzer EO, Zaremba-Pechmann L, de la Hoz A, et al. Tiotropium Respimat® add-on therapy to inhaled corticosteroids in patients with symptomatic asthma improves clinical outcomes regardless of baseline characteristics. Respir Med 2019;158:97–109. https://doi.org/10.1016/j.rmed.2019.09.014.

[44] Casale TB, Bateman ED, Vandewalker M, Virchow JC, Schmidt H, Engel M, et al. Tiotropium Respimat add-on is efficacious in symptomatic asthma, independent of T2 phenotype. J Allergy Clin Immunol Pract 2018;6:923–35. https://doi.org/10.1016/j.jaip.2017.08.037.

[45] Buhl R, FitzGerald JM, Meltzer EO, de la Hoz A, Sigmund R, Kerstjens HAM, et al. Efficacy of once-daily tiotropium Respimat in adults with asthma at GINA Steps 2–5. Pulm Pharmacol Ther 2020;60:101881. https://doi.org/10.1016/j.pupt.2019.101881.

[46] Murphy KR, Chipps BE. Tiotropium in children and adolescents with asthma. Ann Allergy, Asthma Immunol 2020;124:267–76. https://doi.org/10.1016/j.anai.2019.11.030.

[47] Virchow JC, Kuna P, Paggiaro P, Papi A, Singh D, Corre S, et al. Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind, parallel-group, randomised, controlled phase 3 trials. Lancet 2019;394:1737–49. https://doi.org/10.1016/S0140-6736(19)32215-9.

[48] Kerstjens HAM, Maspero J, Chapman KR, van Zyl-Smit RN, Hosoe M, Tanase A-M, et al. Once-daily, single-inhaler mometasone–indacaterol–glycopyrronium versus mometasone–indacaterol or twice-daily fluticasone–salmeterol in patients with inadequately controlled asthma (IRIDIUM): a randomised, double-blind, controlled phase 3 study. Lancet Respir Med 2020;8:1000–12. https://doi.org/10.1016/S2213-2600(20)30190-9.

[49] Gessner C, Kornmann O, Maspero J, van Zyl-Smit R, Krüll M, Salina A, et al. Fixed-dose combination of indacaterol/glycopyrronium/mometasone furoate once-daily versus salmeterol/fluticasone twice-daily plus tiotropium once-daily in patients with uncontrolled asthma: A randomised, Phase IIIb, non-inferiority study (ARGON). Respir Med 2020;170:106021. https://doi.org/10.1016/j.rmed.2020.106021.

[50] Lee LA, Bailes Z, Barnes N, Boulet L-P, Edwards D, Fowler A, et al. Efficacy and safety of once-daily single-inhaler triple therapy (FF/UMEC/VI) versus FF/VI in patients with inadequately controlled asthma (CAPTAIN): a double-blind, randomised, phase 3A trial. Lancet Respir Med 2021;9:69–84. https://doi.org/10.1016/S2213-2600(20)30389-1.

[51] Singh D, Virchow JC, Canonica GW, Vele A, Kots M, Georges G, et al. Extrafine triple therapy in patients with asthma and persistent airflow limitation. Eur Respir J 2020;56:2000476. https://doi.org/10.1183/13993003.00476-2020.

[52] Singh D, Virchow JC, Canonica GW, Vele A, Kots M, Georges G, et al. Determinants of response to inhaled extrafine triple therapy in asthma: analyses of TRIMARAN and TRIGGER. Respir Res 2020;21:285. https://doi.org/10.1186/s12931-020-01558-y.

[53] Vestbo J, Papi A, Corradi M, Blazhko V, Montagna I, Francisco C, et al. Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel

group, randomised controlled trial. Lancet 2017;389:1919–29. https://doi.org/10.1016/S0140-6736(17)30188-5.

[54] Ferguson GT, Brown N, Compton C, Corbridge TC, Dorais K, Fogarty C, et al. Once-daily single-inhaler versus twice-daily multiple-inhaler triple therapy in patients with COPD: lung function and health status results from two replicate randomized controlled trials. Respir Res 2020;21:131. https://doi.org/10.1186/s12931-020-01360-w.

[55] Worsley S, Snowise N, Halpin DMG, Midwinter D, Ismaila AS, Irving E, et al. Clinical effectiveness of once-daily fluticasone furoate/umeclidinium/vilanterol in usual practice: the COPD INTREPID study design. ERJ Open Research 2019;5: 00061–2019. https://doi.org/10.1183/23120541.00061-2019.

[56] Halpin DM, Worsley S, Ismaila AS, Astrom J, Beeh KM, Brintziki D, et al. INTREPID: Clinical effectiveness of once-daily single-inhaler fluticasone furoate/umeclidinium/vilanterol versus multiple-inhaler triple therapy in usual clinical practice. Am J Respir Crit Care Med 2020;201:A4313.

[57] Dusser D, Ducharme FM. Safety of tiotropium in patients with asthma. Ther Adv Respir Dis 2019;13. https://doi.org/10.1177/1753466618824010. 175346661882401.

[58] Kendzerska T, To TM, Aaron SD, Lougheed MD, Sadatsafavi M, FitzGerald JM, et al. The impact of a history of asthma on long-term outcomes of people with newly diagnosed chronic obstructive pulmonary disease: A population study. J Allergy Clin Immunol 2017;139:835–43. https://doi.org/10.1016/j.jaci.2016.06.026.

[59] Lipson DA, Crim C, Criner GJ, Day NC, Dransfield MT, Halpin DMG, et al. Reduction in all-cause mortality with fluticasone furoate/umeclidinium/vilanterol in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2020;201:1508–16. https://doi.org/10.1164/rccm.201911-2207oc.

[60] Rabe KF, Martinez FJ, Ferguson GT, Wang C, Singh D, Wedzicha JA, et al. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. N Engl J Med 2020;383:35–48. https://doi.org/10.1056/NEJMoa1916046.

[61] La Vecchia C, Fabbri LM. Prevention of death in COPD. N Engl J Med 2007;356: 2211–2. https://doi.org/10.1056/NEJMc070783.

[62] Celli B, Decramer M, Kesten S, Liu D, Mehra S, Tashkin DP, et al. Mortality in the 4-year trial of tiotropium (UPLIFT) in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2009;180:948–55. https://doi.org/10.1164/rccm.200906-0876OC.

[63] Vestbo J, Fabbri LM, Papi A, Petruzzelli S, Scuri M, Guasconi A, et al. Inhaled corticosteroid containing combinations and mortality in COPD. Eur Respir J 2018; 52:1801230. https://doi.org/10.1183/13993003.01230-2018.

[64] Lipson DA, Dransfield MT, Han MK. Reply to: Mortality in IMPACT: Confounded by asthma? Am J Respir Crit Care Med 2020;202:773–4. https://doi.org/10.1164/rccm.202004-1399le.

[65] Suissa S. Mortality in IMPACT: Confounded by asthma? Am J Respir Crit Care Med 2020;202:772–3. https://doi.org/10.1164/rccm.202004-1159LE.

[66] McDonald VM, Fingleton J, Agusti A, Hiles SA, Clark VL, Holland AE, et al. Treatable traits: A new paradigm for 21st century management of chronic airway diseases: Treatable Traits down under International Workshop report. Eur Respir J 2019;53:1802058. https://doi.org/10.1183/13993003.02058-2018.

[67] Pavord ID, Beasley R, Agusti A, Anderson GP, Bel E, Brusselle G, et al. After asthma: redefining airways diseases. Lancet 2018;391:350–400. https://doi.org/10.1016/S0140-6736(17)30879-6.

[68] Lazarus SC, Krishnan JA, King TS, Lang JE, Blake KV, Covar R, et al. Mometasone or tiotropium in mild asthma with a low sputum eosinophil level. N Engl J Med 2019;380:2009–19. https://doi.org/10.1056/NEJMoa1814917.