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CME Review

Understanding the role of long-acting muscarinic antagonists in asthma treatment

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Key Messages

- Long-acting muscarinic antagonists (LAMAs) improve lung function, reduce exacerbations, and modestly improve asthma control when added to inhaled corticosteroid plus long-acting β-agonist in patients with moderate to severe asthma who are uncontrolled.
- LAMAs are effective in all asthma phenotypes and endotypes.
- LAMAs are equally effective as long-acting β-agonists with potentially even a higher efficacy in improving lung function.
- LAMAs have additional anti-inflammatory effects in animals and in vitro, but human studies in asthma have not yet been concluded.

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ABSTRACT

Objective: Long-acting muscarinic antagonists (LAMAs) have been used in the treatment of obstructive pulmonary diseases for years. Long-acting muscarinic antagonists were previously mainly used as bronchodilators in chronic obstructive pulmonary disease, but the use of LAMAs in the treatment of asthma has gained great interest. There is now ample evidence of the efficacy and safety of LAMAs as add-on therapy to inhaled corticosteroid (ICS) plus long-acting β_2-agonist (LABA) combinations in patients with moderate to severe uncontrolled asthma. Long-acting muscarinic antagonists have subsequently been included in asthma guidelines. This review summarizes the scientific evidence on the use of LAMAs in asthma and aims to provide a better understanding of the role of LAMAs in the asthma treatment care algorithm and the current gaps in our knowledge.
Data sources: PubMed review using the following words: long-acting muscarinic antagonists, asthma, muscarinic receptors, tiotropium, glycopyrronium, umeclidinium.
Study selections: This review focused on the key trials that led to the inclusion of LAMAs in asthma guidelines. In addition, we highlighted a number of studies with other study designs and populations.
Results: We identified 6 major studies that led to inclusion in asthma guidelines and 3 studies with other study designs and populations.
Conclusion: Long-acting muscarinic antagonists add-on therapy to ICS-LABA improves lung function, reduces exacerbations, and modestly improves asthma control in patients with moderate to severe asthma who are uncontrolled despite the use of ICS-LABA. Long-acting muscarinic antagonists are effective in all asthma phenotypes and endotypes.

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- Describe the mechanisms of action of long-acting muscarinic antagonists (LAMA).
- Discuss where LAMAs fit in the clinical treatment of asthma.

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Introduction

Muscarinic antagonists have been used for the treatment of obstructive pulmonary diseases for several centuries.[1] In 1859, the anticholinergic agent atropine was found to successfully treat an asthma attack,[2] and, *Datura stramonium*, which contains atropine, has even been added to cigarettes.[3,4] After this, muscarinic antagonists were predominantly used in chronic obstructive pulmonary disease.[1] First, this was by the short-acting muscarinic antagonist, mainly ipratropium bromide, a synthetic quaternary ammonium derivative of atropine.[5] This quaternary derivative is unable to cross the blood-brain barrier and, therefore, prevents severe adverse effects that were seen with traditional anticholinergics, such as atropine.[6] In asthma, short-acting muscarinic antagonists were also used especially during attacks; but mostly, β_2-agonists were regarded as more effective bronchodilators than anticholinergic agents.[7] But in recent years, the use of muscarinic antagonists in asthma has regained interest. The effects of LAMAs specifically as an add-on therapy have now been widely studied among patients with asthma having persistent symptoms despite the use of inhaled corticosteroids (ICS) and long-acting β_2-agonists (LABAs).[8–10] These studies have led to the inclusion of LAMAs in the asthma treatment guidelines.[11,12] This review is not intended as a systematic analysis, of which other useful articles exist,[8–10] but aims to discuss scientific evidence on the use of LAMAs in asthma to provide a better understanding of the role of LAMAs in the asthma treatment care algorithm and the possible gaps in our knowledge.

Muscarinic Receptors

In asthma, parasympathetic neuronal activity, mediated by the vagal nerve, is increased, which is partially explained by the increased release of the neurotransmitter acetylcholine (Fig 1).[13,14] Furthermore, it was recently documented that airway cholinergic neuronal density is increased in asthma, potentially enhancing this effect.[15] Acetylcholine is released from airway neurons and also from nonneuronal cells, such as many inflammatory cells and airway epithelial cells, and subsequently binds to muscarinic receptors causing, among others, airway smooth muscle contraction and mucus production.[16] Specifically, the muscarinic receptors M_1, M_2, and M_3 have been found to play important roles in airway physiology.[17,18] M_3 receptors are predominantly found on airway smooth muscle cells and submucosal glands and cause airway smooth muscle contraction and mucus secretion, respectively.[17,18] M_2 receptors are expressed on both airway smooth muscle cells and airway neurons. Their role in airway smooth muscle contraction is less substantial, but M_2 receptors on airway neurons play a role as autoreceptors limiting the release of acetylcholine and thereby inhibiting bronchoconstriction and mucus secretion.[17,18] Finally, M_1 receptors are found in parasympathetic ganglia in which they regulate neurotransmission by depolarizing the resting membrane potential, which facilitates nicotinic receptor–mediated neurotransmission and increases bronchoconstriction.[17,18] In asthma, both M_2 autoreceptor dysfunction and increased cholinergic activation of M_1 and M_3 receptors increase bronchoconstriction, mucus secretion, inflammation, and airway remodeling.[17] It is important to note that all current LAMAs dissociate faster from M_2 receptors than from M_1 and M_3 receptors[19,20] increasing their combined effectiveness in obstructive airway diseases. Finally, the combined use of LAMAs with ICS or ICS-LABA has been suggested to have synergistic interactions, primarily on the basis of animal and in vitro work.[21]

Main Clinical Effects

Major Studies for Inclusion in Asthma Guidelines

In this section, we will discuss the large trials that led to the inclusion of LAMAs in the asthma guidelines. All tested the addition of a LAMA to patients uncontrolled on medium or high-dose ICS plus LABA, Global Initiative for Asthma (GINA) step 4 to 5 (Table 1 and eTable 1).

The first 2 studies, tiotropium in asthma (PrimoTinA-asthma) 1 and 2, were replicate double-blind, randomized, placebo-controlled trials comprising 912 patients with severe uncontrolled asthma. Patients were randomized to either 5 μg of tiotropium (TIO) or placebo once daily as add-on therapy to high-dose ICS plus LABA for 48 weeks.[22] After 24 weeks, the mean change in peak forced expiratory volume in 1 second (FEV_1) was greater with TIO compared with placebo in both trials (86 mL in trial 1 $P = .01$; 154 mL in trial 2 $P < .001$). Trough FEV_1 improved with TIO compared with placebo (88 mL in trial 1 $P < .01$; 111 mL in trial 2 $P < .001$) (Fig 2A). Moreover, the time to first severe exacerbation increased with the use of TIO, and a 21% reduction in risk of developing an exacerbation was observed (hazard

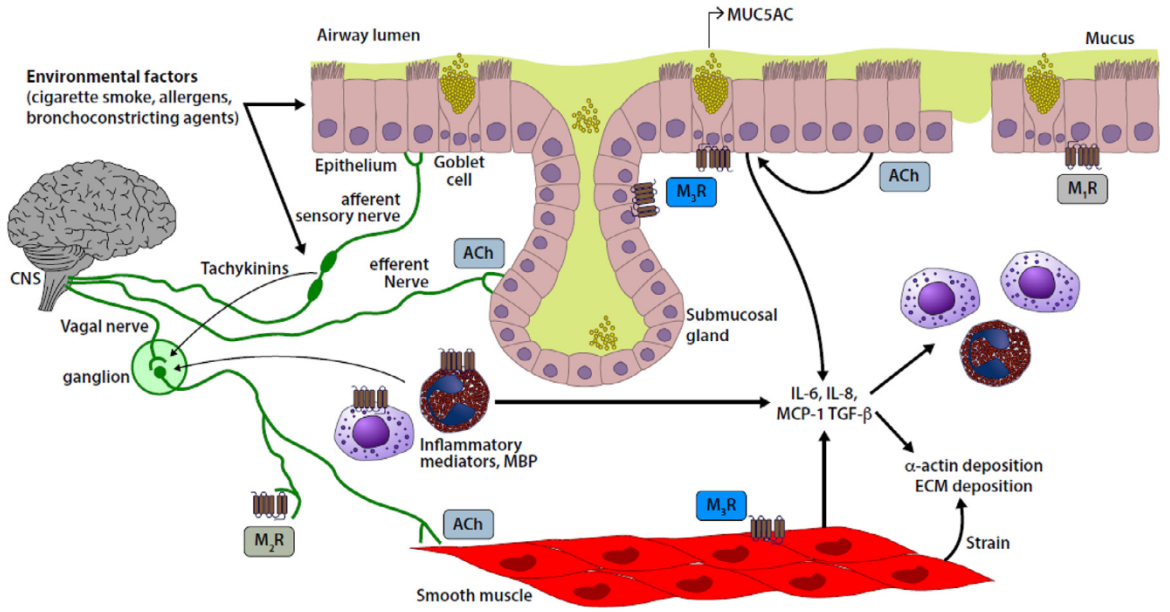

Figure 1. Muscarinic receptors and mechanisms of action of long-acting muscarinic antagonists. ACh, acetylcholine; CNS, central nervous system; ECM, extracellular matrix; IL-6, interleukin 6; IL-8, interleukin 8; MCP-1, monocyte chemoattractant protein-1; M_xR, muscarinic receptor; MUC5AC, mucin 5AC; TGF-β, transforming growth factor–beta.

Table 1
Summary of Study Designs of the Key Long-Acting Muscarinic Antagonist Trials in Asthma Patients

Major studies for inclusion in guidelines	Intervention	Comparator(s)	Treatment duration	Number of patients	Lung function	Exacerbations	Asthma control	Quality of life
Kerstjens et al,[22] 2012 (PrimoTinA)	TIO 5 μg OD	Placebo	48 wk	912	Peak FEV_1 Trough FEV_1	Time to first severe exacerbation	ACQ-7 score	AQLQ-score
Virchow et al,[23] 2019 (TRIMARAN/TRIGGER)	BDP-FOR-GLY 2 inhalations BID (TRIMARAN: 100/6/10 μg; TRIGGER: 200/6/10 μg)	BDP-FOR 2 inhalations BID (TRIMARAN: 100/6 μg; TRIGGER: 200/6 μg)	52 wk	2592	Predose FEV_1 Peak FEV_1 Morning PEF	Rate of moderate and severe exacerbations	ACQ-7 score	—
Kerstjens et al,[24] 2020 (IRIDIUM)	MOM-IND-GLY 80/150/50 μg OD; MOM-IND-GLY 160/150/50 μg OD	MOM-IND 160/150 μg OD; MOM-IND 320/150 μg OD; FLU-SAL 500/50 μg BID	52 wk	3092	Trough FEV_1 Postdose FEV_1	Rate of exacerbations Time to first exacerbation	ACQ-7 score	AQLQ-score
Lee et al,[25] 2021 (CAPTAIN)	FLUf-VIL-UME 100/25/31.25; 100/25/62.5; 200/25/31.25; 200/25/62.5 μg, OD	FLUf-VIL 100/25 μg OD; FLUf-VIL 200/25 μg OD	24 wk 36 wk 52 wk	2436	Trough FEV_1	Annualized rate of moderate and severe exacerbations	ACQ-7 score	—
Other studies								
Peters et al,[26] 2010 (TALC)	TIO 18 μg OD	BDP 160 μg BID; SAL 50 μg BID	14 wk	210	Morning PEF Trough FEV_1	Number of exacerbations	Asthma control days ACQ-7 score	AQLQ-score
Kerstjens et al,[27] 2015 (MezzoTinA)	TIO 5 μg OD; TIO 2.5 μg OD	SAL 50 μg BID; Placebo	24 wk	2103	Peak FEV_1 Trough FEV_1	Time to first severe exacerbation	ACQ-7 score	AQLQ-score
Gessner et al,[28] 2020 (ARGON)	MOM-IND-GLY 80/150/50 μg OD; MOM-IND-GLY 160/150/50 μg OD	FLUp-SAL 500/50 μg BID + TIO 5 μg OD	24 wk	1426	Trough FEV_1 Morning PEF	Rate of exacerbations	ACQ-7 score	AQLQ-score

Abbreviations: ACQ, asthma control questionnaire; AQLQ, asthma quality of life questionnaire; BDP, beclometasone dipropionate; BID, twice daily; FEV_1, forced expiratory volume in 1 second; FLUf, fluticasone furoate; FLUp, fluticasone propionate; FOR, formoterol fumarate; GLY, glycopyrronium; MOM, mometasone furoate; OD, once daily; PEF, peak expiratory flow; SAL, salmeterol; TIO, tiotropium; UMEC, umeclidinium; VIL, vilanterol.

ratio, 0.79; $P = .03$) (Fig 2B). Large improvements in asthma control questionnaire 7 (ACQ-7) and asthma quality of life questionnaire scores were observed vs baseline in both studies, but these improvements were only significantly greater with TIO compared with placebo in PrimoTinA-asthma 2.

The first set of studies investigating the efficacy of single-inhaler triple therapy with ICS-LABA-LAMA vs ICS-LABA was the TRIMARAN and TRIGGER.[23] These two 52-week, randomized studies investigated the use of single-inhaler beclomethasone dipropionate (BDP), formoterol fumarate (FOR), and glycopyrronium (GLY) vs the same medium-dose BDP-FOR (TRIMARAN), the same high-dose BDP-FOR (TRIGGER), or open-label BDP-FOR plus TIO (TRIGGER) in 1155 patients with uncontrolled asthma in TRIMARAN and 1437 patients in TRIGGER. The trough FEV_1 improved with BDP-FOR-GLY compared with BDP/FOR in both TRIMARAN (57 mL [95% confidence interval (CI), 15-99]; $P = .008$) and TRIGGER (73 mL [95% CI, 26-120]; $P = .002$) (Fig 2A). In TRIMARAN, a 15% reduction in moderate or severe exacerbation rates was observed with BDP-FOR-GLY compared with BDP-FOR (relative risk [RR], 0.85 [95% CI, 0.73-0.99]; $P = .03$) (Fig 2B). The reduction in moderate or severe exacerbations was 12% in TRIGGER, which was not statistically significant (0.88 [0.75-1.03]; $P = .11$). Peak FEV_1 and morning peak expiratory flow (PEF) improved significantly with BDP-FOR-GLY compared with BDP-FOR in both studies (84 mL and 8.5 L/min, respectively, in TRIMARAN, and 105 ml and 7.8 L/min in TRIGGER). Asthma symptoms and asthma control (ACQ-7) improved in all study groups compared with baseline, with no statistically significant differences between the groups.

The use of the LAMA GLY was further investigated in the IRIDIUM trial in which the efficacy of once-daily, single-inhaler therapy with mometasone furoate (MOM), indacaterol acetate (IND), and glycopyrronium bromide (GLY) was compared with ICS-LABA.[24] In this 52-week, double-blind, double-dummy study, 3092 patients were randomly assigned to either medium or high-dose MOM-IND-GLY or MOM-IND once-daily, or high-dose fluticasone propionate/salmeterol (FLUp-SAL) twice daily. At 26 weeks, both medium- and high-dose MOM-IND-GLY exhibited greater improvement in trough FEV_1 vs corresponding doses of MOM-IND (medium-dosage 76 mL [95% CI, 41-111]; $P < .001$, and high-dosage 65 mL [31-99]; $P < .001$) (Fig 2A). Both medium and high-dose MOM-IND-GLY also exhibited greater improvement in trough FEV_1 compared with high-dose FLUp-SAL (change from baseline with medium-dosage MOM-IND-GLY 99 mL [95% CI, 64-133]; $P < .001$; with high-dosage MOM-IND-GLY 119 mL [85-154], $P < .001$) (Fig 2A). The improvements with the addition of the LAMA were large but not significantly different for the comparison medium or high-dose MOM-IND-GLY vs the respective dose of MOM-IND. Significant improvements in ACQ-7 scores were observed with both medium and high-dose MOM-IND/GLY compared with high-dose FLUp-SAL at 26 weeks (medium-dose: −0.084 [$P = .03$], high-dose: −0.086 [$P = .03$]). The annualized rates of moderate or severe exacerbations decreased with MOM-IND-GLY compared with MOM-IND, although this improvement did not reach statistical significance (Fig 2B). Significant reductions in the annualized rate of moderate or severe exacerbations were indeed observed with both medium as well high-dose MOM-IND-GLY compared with high-dose FLUp-SAL (medium-dose: RR, 0.81 [95% CI, 0.66-0.99]; $P = .04$; high-dose: RR, 0.64 [0.52-0.78]; $P < .001$) (Fig 2B).

In the Clinical Study in Asthma Patients Receiving Triple Therapy in a Single Inhaler (CAPTAIN study), the LAMA umeclidinium (UME) was studied, at 2 doses in single-inhaler triple therapy together with fluticasone furoate (FLUf) at 2 doses and vilanterol (VIL).[25] In this 24- to 52-week, double-blind, randomized study, 2439 patients with uncontrolled asthma were randomly assigned to once-daily FLUf-VIL (100/25 μg or 200/25 μg) or FLUf-VIL-UME (100/25/31.25 μg, 100/25/62.5 μg, 200/25/31.25 μg, 200/25/62.5 μg). Addition of both 62.5 μg and 31.25 μg UME to

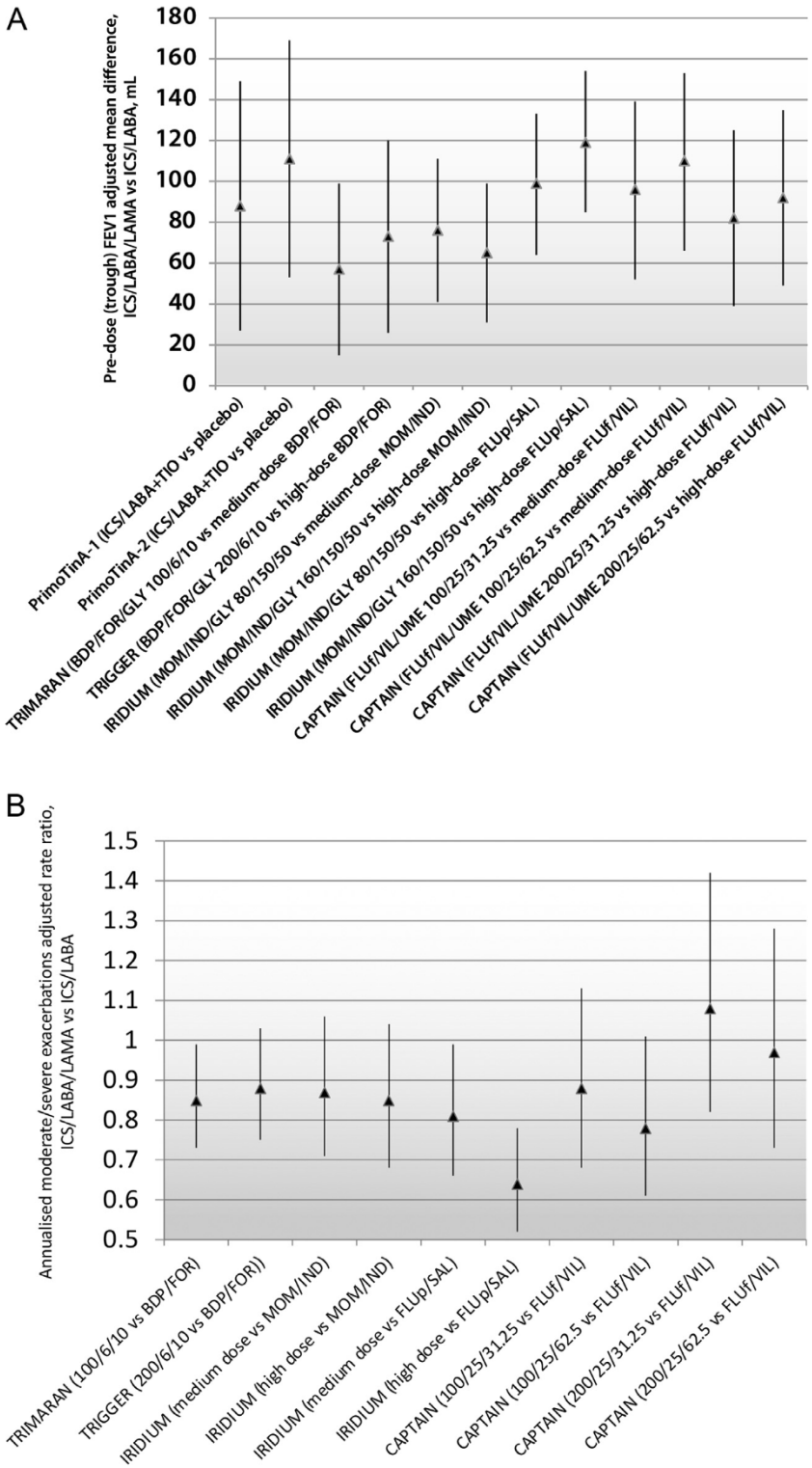

Figure 2. ICS-LABA-LAMA vs ICS-LABA. (A) Trough (predose) FEV_1 at 24-26 weeks: adjusted mean differences and 95% CI. (B) Annualized moderate/severe exacerbations: adjusted rate ratios and 95% CI. BDP, beclomethasone dipropionate; CI, confidence intervals; FEV_1, forced expiratory volume in 1 sec; FLUf, fluticasone furoate; FLUp, fluticasone propionate; FOR, formoterol; GLY, glycopyrronium; ICS, inhaled corticosteroid; IND, indacaterol; LABA, long-acting beta (2)-agonist; MOM, mometasone; SAL, salmeterol; TIO, tiotropium; VIL, vilanterol.

FLUf-VIL 100/25 μg and 200/25 μg led to significant improvements in trough FEV_1 at 24 weeks (110 mL [95% CI, 66-153] for UME 62.5 μg added to FLUf-VIL 100/25 μg and 92 mL [49-135] when added to FLUf-VIL 200/25 μg; and similarly 96 mL [52-139] and 82 mL [39-125], respectively, when adding UME 31.25 μg) (Fig 2A). No statistically significant difference in reduction of annualized moderate or severe exacerbation rate was observed between the groups (Fig 2B). The ACQ-7 scores improved in all treatment groups when compared with baseline, but responder rates were significantly higher only with FLUf-VIL-UME 62.5 μg groups when compared with FLUf-VIL (OR, 1.43 [95% CI, 1.16-1.76]; $P < .001$).

Long-Acting Muscarinic Antagonists in Other Study Designs and Populations

In patients with milder disease, symptomatic on low-dose ICS and without LABA, the addition of TIO was compared with the addition of SAL and doubling the ICS dose.[26] Adding TIO was superior to doubling the ICS dose with respect to improvement in morning PEF, evening PEF, prebronchodilator FEV_1, and the number of asthma control days. Next to that, the addition of TIO was noninferior to add-on SAL with regard to morning PEF, prebronchodilator FEV_1, and the proportion of asthma control days. The increase in prebronchodilator FEV_1 was significantly greater with TIO add-on compared with SAL (0.11 L improvement with TIO [95% CI, 0.05-0.10]; $P = .003$).

The MezzoTinA-asthma 1 and 2 trials were replicated 24-week, randomized, double-blind, double-dummy studies involving 2103 patients with uncontrolled asthma on medium-dose ICS who were randomly assigned to the addition of either TIO 5 μg or 2.5 μg once daily, SAL 50 μg twice daily, or placebo.[27] At 24 weeks, improvements in peak FEV_1 were greater with both TIO doses and with SAL compared with placebo (TIO 5 μg: 185 mL [95% CI, 146-223]; TIO 2.5 μg: 223 mL [185-262]; SAL: 196 mL [158-234]; $P < .001$). Trough FEV_1 also improved; 146 mL (95% CI, 105-188) with TIO 5 μg, 180 mL (138-221) with TIO 2.5 μg, and 114 mL (73-155) with SAL (Fig 3). A statistically significant improvement in the proportion of patients achieving the minimal clinical important difference in ACQ-7 was also observed with both TIO arms and with SAL compared with placebo (TIO 5 μg: OR, 1.32 [95% CI, 1.02-1.71]; $P = .03$; TIO 2.5 μg: 1.33 [1.03-1.72], $P = .03$; SAL: 1.46 [1.13-1.89]; $P = .003$). Exacerbation rates were low in this population: a significant reduction in the risk of first severe exacerbation was observed only with TIO 2.5 μg compared with placebo over 24 weeks.

In the ARGON study, 2 triple schemes were compared: once-daily single-inhaler triple therapy with MOM, IND, and GLY vs high-dose of FLUp-SAL twice daily plus TIO once daily (FLUp-SAL + TIO) in patients with uncontrolled asthma on medium or high-dose ICS-LABA.[28] 1426 patients were entered in this 24-week, partially blinded, randomized, noninferiority study. The primary end point, the number of asthma quality of life questionnaire responders was noninferior with medium-dose MOM-IND-GLY vs FLUp-SAL plus TIO, and higher with high-dose MOM-IND-GLY compared with FLUp-SAL plus TIO (73.3 vs 67.8%; $P = .01$). Similarly, the improvements in ACQ-7 scores were noninferior for medium-dose (difference of −0.032; $P = .24$) MOM-IND-GLY compared with FLUp-SAL plus TIO and superior for high-dose (difference of −0.124; $P = .004$). Trough FEV_1 was significantly higher with high-dose MOM-IND-GLY compared with FLUp-SAL plus TIO at 24 weeks (difference of 96 mL; $P < .001$), and comparable between medium-dose MOM-IND-GLY and FLUp-SAL plus TIO (difference of 9 mL; $P = .71$) (Fig 3). The rates of both moderate and severe exacerbations were similar among all treatment groups.

Characteristics of Responders

It would be useful to determine specific phenotypes or endotypes of asthma that are associated with a greater or smaller response to LAMAs. However, most studies have not found a differential effect of baseline FEV_1, reversibility, or age on the subsequent response of LAMA when added to ICS-LABA,[24,25,29] with the exception of the pooled TRIMARAN and TRIGGER studies.[23]

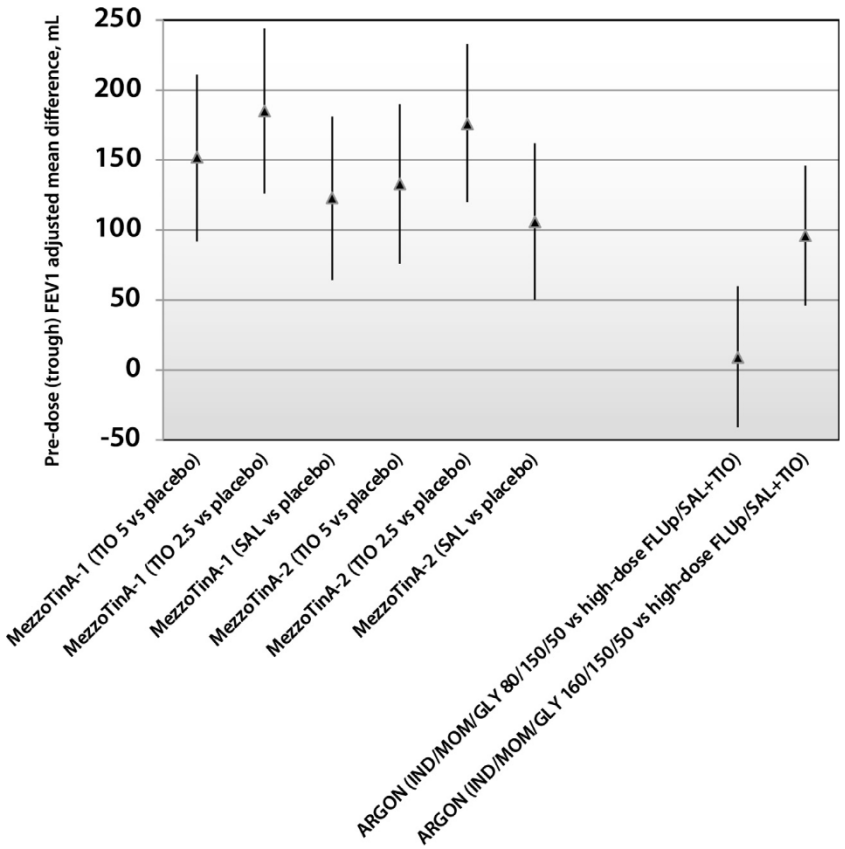

Figure 3. Trough (predose) FEV_1 at 24 weeks in MezzoTinA and ARGON: adjusted mean differences and 95% CI. CI, confidence intervals; FEV_1, forced expiratory volume in 1 sec; FLUp, fluticasone propionate; GLY, glycopyrronium; IND, indacaterol; MOM, mometasone; SAL, salmeterol; TIO, tiotropium.

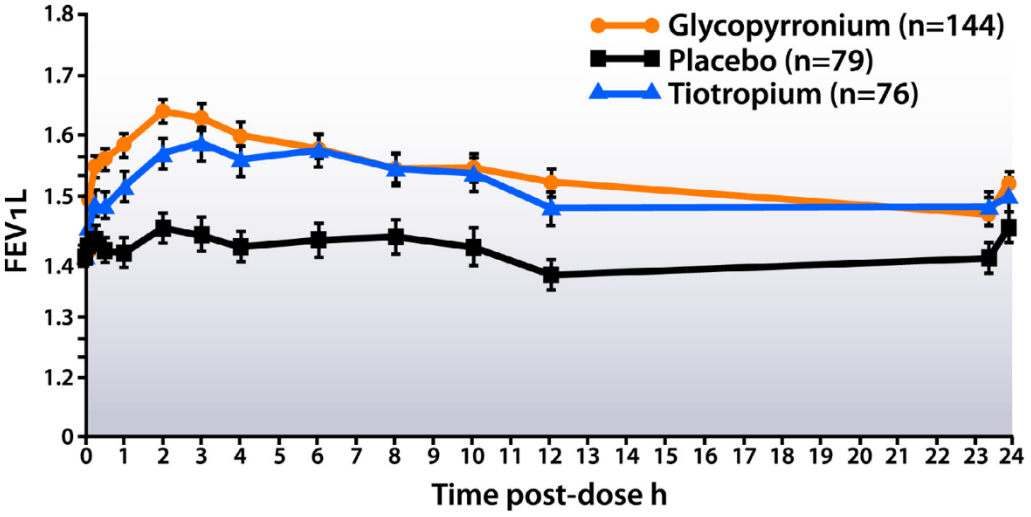

Figure 4. The onset of action glycopyrronium vs tiotropium. Serial spirometry: glycopyrronium superior to placebo at all time points ($P < .01$), and to tiotropium at 5, 15 and 30 minutes, 1 and 2 hours ($P < .05$). FEV_1, forced expiratory volume in 1 sec. Reproduced with permission from Kerwin et al.[41] *Eur Respir J*. 2012;40:1106-1114.

It is interesting to look specifically at the relation of response to baseline eosinophil number or type 2 (T_2) inflammatory status. Post hoc analyses of the PrimoTinA, TRIMARAN and TRIGGER, and CAPTAIN trials found that both improvements in trough FEV_1 and reduction in moderate and severe exacerbations were independent of baseline blood eosinophil levels.[25,30,31] Of interest, 2 studies had a multiple arm design also testing the effect of doubling the ICS dose instead of adding a LAMA, or even doing both.[24,25] These illustrate that doubling the ICS had a larger effect on moderate and severe exacerbation rates, which was found to be driven by patients with higher blood eosinophil counts in the CAPTAIN study.[25] This indicates that patients with T_2-high asthma benefit more from increasing ICS dose than from adding a LAMA, although the effect of both doubling the ICS and adding a LAMA was numerically the largest.[24,25] In summary, the results of these trials indicate that a targeted, biomarker-directed approach might result in the most effective choices for therapy.

Recently, Kim et al[10] presented a systematic review and meta-analysis on the use of ICS-LABA-LAMA vs ICS-LABA in patients with asthma. Overall, this review included 18 articles describing 20 randomized controlled trials, including all mentioned above. There were 3 studies performed on children. Kim et al[10] also shortly discussed several subgroup analyses. The addition of a LAMA to ICS-LABA did not yield any differences in subgroups defined by the following characteristics: age (<18 years, ≥18 years), smoking history (nonsmoker, ex-smoker, current smoker), exacerbation frequency (<1 previous exacerbation, ≥1 previous exacerbation), inflammatory phenotype (T_2-high, T_2-low, defined by peripheral blood eosinophil count), type and dose of LAMA, type, and dose of ICS (intervention or comparator). In summary, no clear characteristics of responders to LAMA therapy have been identified so far; they exert their effects across all subgroups studied.

Anti-inflammatory Effects

Overall, the addition of LAMAs in asthma reduces exacerbation rates and increases time to first exacerbation.[10] These results could indicate that LAMAs have anti-inflammatory properties. Anti-inflammatory effects of anticholinergics alone have indeed been exhibited in in vitro and in vivo studies using various experimental models. In vitro, anticholinergics exert direct anti-inflammatory effects on T cells, macrophages, epithelial cells, and airway smooth muscle cells.[32,33] Next to that, in vivo animal models have exhibited inhibitory effects of TIO or muscarinic M_3 receptor knockout on ovalbumin-induced inflammation, the anti-inflammatory effects of TIO being comparable to those of the corticosteroid budesonide.[34] In vitro, it has been found that GLY acts synergistically with budesonide in inhibiting tumor necrosis factor α release from isolated monocytes, suggesting that combining anticholinergics and corticosteroids might be more effective than the monotherapies in vivo.[35] In addition, the combination of TIO with corticosteroid ciclesonide was more effective than either compound alone in inhibiting allergen-induced airway inflammation in a guinea pig model.[36] The effects of add-on LAMA to ICS-LABA on airway inflammation in humans with asthma are currently largely unknown. A clinical study specifically investigating the anti-inflammatory effects of MOM-IND-GLY vs MOM-IND on the allergen-induced late asthmatic response in people with asthma is currently being performed (ClinicalTrials.gov Identifier NCT04259164).[37]

Limitations of Current Studies/Gaps in Our Knowledge

There are still several gaps in our knowledge regarding the use of anticholinergics in asthma patients. First, there is considerably more information on LAMA therapy in moderate-severe asthma than in milder disease, although there are some smaller studies in mild asthma.[26,38] Second, anticholinergics have, so far, only mainly been tested on top of ICS with or without LABA, though recently a study comparing MOM or TIO to placebo in patients with mild asthma was performed, which indicated no significant differences in treatment response in that population.[39] Next to that, little is still known regarding the use of LAMAs in patients with asthma who are current smokers (only 2 studies included active smokers) or who have cardiac comorbidities, and in patients who are older than 75 years.[10] In addition, it would be useful to perform a study in a large population of patients with asthma–chronic obstructive pulmonary disease overlap, in which we would expect good effectiveness. Results of the study by Park et al,[40] in this population are promising. Finally, all studies that have been published on the use of LAMAs in patients with asthma exhibit the effects in a closely monitored experimental setting. It would be very relevant to have data on the use of LAMAs in a real-life setting.

Different Formulations of Long-Acting Muscarinic Antagonists

Currently, 3 different LAMA molecules have been investigated as add-on therapy to ICS-LABA in asthma: TIO, GLY, and umeclidinium,

which differ somewhat in the onset of action and half-life, although complete comparisons are lacking. Glycopyrronium has a slightly faster onset of action than TIO (Fig 4), as might umeclidinium.[19,20,41] The LAMA molecules are also delivered in different devices and combinations. There have been no head-to-head comparisons of the fixed triple therapies. Fixed triple combinations have been compared with open-label triple combinations in more inhalers and with variable drugs, illustrating no clear evidence of any major difference (TRIGGER; BDP-FOR-GLY vs BDP-FOR+TIO)[23] or additional benefit of the MOM-IND-GLY vs FLUp-SAL plus TIO (ARGON).[28] The recent meta-analysis by Kim et al[10] included a subgroup analysis by LAMA type and dose and did not find major differences in outcomes. It is intuitive to expect that the use of single-inhaler triple therapy is more convenient for the patient and might, therefore, increase treatment compliance and adherence when compared with ICS-LABA plus LAMA, but from the same meta-analysis, there was no discernible difference between the use of a single inhaler or separate inhalers.[10] Similarly, one could argue that once-daily therapy could improve treatment compliance and adherence vs twice-daily therapy, but no studies have investigated these differences in posology yet while using the same molecules and device.

Adverse Events of Long-Acting Muscarinic Antagonists in Asthma

The daily use of LAMAs in patients with asthma is safe and well-tolerated. Clinical trials consistently report a similar safety profile of the different types of LAMAs.[10,22-25] Adverse effects that are reported more frequently are dry mouth and dysphonia (RR, 1.65; 95% CI, 1.14-2.38) with no other significant differences, including cardiac effects and mortality.[10]

Positioning

All the larger clinical studies consistently report greater improvement of lung function with add-on LAMA to ICS-LABA (either as single-inhaler or with separate inhalers) compared with ICS-LABA alone (Fig 2A). The efficacy of triple therapy in reducing the exacerbation rates compared with the same ICS-LABA was less consistent per trial, but was 17% overall, as reported in the meta-analysis of Kim et al[10] (Fig 2B). Asthma control improved markedly with all active therapies, but in many studies, the difference between the active arms was not significant. In the meta-analysis, there was a significant improvement in ACQ (−0.04 units; 95% CI, −0.07 to −0.01), which, however, was small given the minimal clinically important difference of 0.5. The addition of a LAMA was not associated with an improvement in asthma-related quality of life compared with ICS-LABA.

The LAMAs are included in both the GINA and the National Asthma Education and Prevention Program (NAEPP) guidelines.[11,12] The NAEPP guidelines were updated in 2020 when only TIO was approved by the US Food and Drug Administration.

The most recent GINA report of 2021 includes more recent literature.[11] Long-Acting Muscarinic Antagonists are recommended in GINA step 5 (ie, uncontrolled severe asthma despite correct ICS-LABA use) as add-on therapy to high-dose ICS-LABA as either a separate inhaler or a combination (triple) inhaler. In GINA step 4, the addition of a LAMA is provided as alternative controller therapy.

Questions not yet fully addressed in the guidelines include the role of LAMAs in milder disease, LAMA vs LABA as a first-choice bronchodilator, choice of adding LAMA or increasing the ICS dose, and finally, a comparison to other options such as biologic therapy.

Although the guidelines provide no clear recommendations on the use of LAMAs in patients with moderate or mild asthma, these patients have been studied in several trials of LAMAs, either added to ICS without LABA or as triple therapy.[26,27,38] From the literature, we believe the addition of LAMAs is a valid option in patients with uncontrolled asthma on medium-dose ICS,[25,27] and in milder asthma, at least improves lung function.[26,38]

There are now at least 3 studies of a direct comparison of LAMA to LABA, all TIO vs SAL, when added to ICS in severe,[22] moderate,[27] and mild-to-moderate[26] asthma, all exhibiting a similar or greater FEV_1 response with the LAMA. A recent review by Kaplan et al[42] concluded that LAMAs yield a greater improvement in lung function than LABAs and are as effective as LABAs with respect to achieving asthma control and preventing exacerbations. Some patients have adverse effects on LABAs, and some patients respond better to either one of both drugs, making the use of LAMAs a viable alternative to LABAs.[43]

It is important to carefully consider when to add LAMA to ICS-LABA and when to increase ICS dose. As detailed in the paragraph on predictors of response to LAMA, their effectiveness is independent of many baseline characteristics, including age, reversibility, level of obstruction, (past) smoking status, and more importantly, eosinophilia or T_2 inflammatory phenotype.[10] In GINA steps 4 and 5, adding a LAMA is more effective than increasing the ICS dose for improving lung function broadly independent of baseline characteristics including eosinophil status.[10,30] When aiming specifically at reduction of exacerbations, although LAMAs are equally effective as doubling steroids in T_2-low patients[25,30] thereby preventing the systemic burden of increased ICS overall and, especially in T_2-high patients, LAMAs are less effective than doubling ICS.[24,25]

Both the GINA and the NAEPP guidelines recommend the use of a LAMA in patients with uncontrolled asthma before starting with oral corticosteroids or biologic drugs, such as anti–immunoglobulin E and anti–interleukin-5 antibodies.[11,12] As opposed to LAMAs, the use of the biologic therapies is limited to a minority of patients with asthma, mainly T_2-high. When these characteristics are present, however, reductions in asthma exacerbations with the use of biologic agents in patients with T_2-high phenotype are much higher than the use of LAMAs in these patients.[44] On the other hand, costs for biologic therapies are much higher than for the use of LAMAs, and the necessary injections may be cumbersome.[45]

A separate, difficult topic is the use of as-needed medication on top of triple maintenance. It was suggested in GINA to use ICS-LABA virtually for all reliever medication. Whether or not that is a good choice on top of triple therapy has not been tested. The use of a LAMA combined with ICS or as triple therapy could also be contemplated. Important in the choice of preferred reliever therapy is efficacy, the onset of action (Fig 4), duration of action, and risk of adverse effects, specifically in relation to risk of accumulation because the drug might be used multiple times per day.[19,20,41]

Conclusion

In conclusion, LAMA add-on therapy to ICS-LABA improves lung function, modestly improves asthma control, and reduces exacerbations in patients with moderate to severe asthma who are uncontrolled despite the use of ICS-LABA.

Long-Acting Muscarinic Antagonists work independently of all patient characteristics tested so far, including age, baseline FEV_1, reversibility, asthma duration, and more importantly, T_2 status. In studies comparing the addition of LAMA vs doubling of ICS, the latter clearly gives a greater reduction in exacerbation frequency in T_2-high patients; but numerically, the effect of both doubling the ICS and adding the LAMA yields the largest effect.

Beyond the current guidelines, there is evidence that LAMAs may be a good alternative to LABAs as an add-on to ICS in moderate disease, but data are limited to TIO, and that LAMAs are also viable bronchodilators in mild disease. Because LAMAs have anti-inflammatory effects in animals and in vitro, the reduction in exacerbation rates

could signify anti-inflammatory effects in asthma, but this needs to be proven in humans with asthma.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.anai.2021.12.020.

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