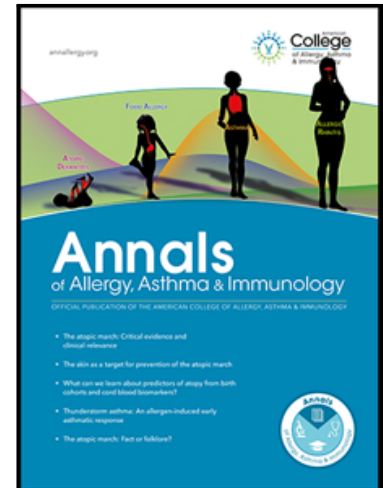


Understanding the role of long-acting muscarinic antagonists in asthma treatment

S. Muiser MD , R. Gosens PhD , M. van den Berge MD,PhD ,
H.A.M. Kerstjens MD,PhD

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Title

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

Authors

S. Muiser, MD,^{1,2}, R. Gosens, PhD,^{2,3}, M. van den Berge, MD,PhD,^{1,2}, H.A.M. Kerstjens, MD,PhD,^{1,2}

1. University of Groningen, University Medical Center Groningen, Department of Pulmonology and Tuberculosis, Groningen, The Netherlands.
2. University of Groningen, University Medical Center Groningen, Groningen Research Institute for Asthma and COPD (GRIAC), Groningen, The Netherlands.
3. University of Groningen, University Medical Center Groningen, Department of Molecular Pharmacology, Groningen, The Netherlands.

Corresponding author information

Prof. H.A.M. Kerstjens, MD, PhD

Department of Pulmonology and Tuberculosis

University Medical Center Groningen

Hanzeplein 1

9713 GZ Groningen

The Netherlands

E-mail address: h.a.m.kerstjens@umcg.nl

Telephone number: +31(0)50 361 02 80

Fax number: +31(0)50 361 93 20

E-mail address of corresponding author: h.a.m.kerstjens@umcg.nl

Conflict of interest

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Keywords

Asthma, Muscarinic antagonists, Bronchodilators, Muscarinic receptors, Exacerbations

Abbreviations/Acronyms

ACQ	Asthma Control Questionnaire
AQLQ	Asthma Quality of Life Questionnaire
BDP	Beclomethasone dipropionate
COPD	Chronic Obstructive Pulmonary Disease
FEV₁	Forced Expiratory Volume in 1 second
FLUf	Fluticasone furoate
FLUp	Fluticasone propionate
FOR	Formoterol fumarate
FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
GLY	Glycopyrronium
ICS	Inhaled Corticosteroids
IND	Indacaterol
LABA	Long-Acting Beta(2)-Agonist
LAMA	Long-Acting Muscarinic Antagonist
MCID	Minimal clinically important difference
MOM	Mometasone furoate
NAEPP	National Asthma Education and Prevention Program
PEF	Peak Expiratory Flow
SAL	Salmeterol
SAMA	Short-Acting Muscarinic Antagonist
T2	Type 2
TIO	Tiotropium
UME	Umeclidinium
VIL	Vilanterol

Key Messages

- Long-acting muscarinic antagonists (LAMAs) improve lung function, reduce exacerbations and modestly improve asthma control, when added to inhaled corticosteroid (ICS) plus long-acting beta-agonist (LABA) in patients with moderate to severe asthma who are uncontrolled.
- LAMAs are effective in all asthma phenotypes and endotypes
- LAMAs are equally effective as LABAs 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.

Abstract

Objective: Long-acting muscarinic antagonists (LAMAs) have been used in the treatment of obstructive pulmonary diseases for years. LAMAs were previously mainly used as bronchodilators in chronic obstructive pulmonary disease (COPD), but interest in 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 moderate to severe uncontrolled asthma patients. LAMAs have subsequently been included in asthma guidelines. This review summarizes the scientific evidence about the use of LAMAs in asthma and aims to provide better understanding of the role of LAMAs in the asthma treatment care algorithm as well as 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 which led to the inclusion of LAMAs in asthma guidelines. Additionally, we highlighted a number of studies with other study designs and populations.

Results: We identified 6 major studies which led to inclusion in asthma guidelines and 3 studies with other study designs and populations.

Conclusion: LAMA 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 use of ICS/LABA. LAMAs are effective in all asthma phenotypes and endotypes.

Introduction

Muscarinic antagonists have been used for the treatment of obstructive pulmonary diseases for several centuries¹. Already in 1859, the anticholinergic agent atropine was found to successfully treat an asthma attack², 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 (COPD)¹. This was first by short-acting muscarinic antagonist (SAMA), mainly ipratropium bromide, a synthetic quaternary ammonium derivative of atropine⁵. 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 atropine⁶. There was use of SAMAs in asthma, especially during attacks, but mostly β 2-agonists were regarded as more effective bronchodilators in asthma than anticholinergic agents⁷. In recent years, the use of muscarinic antagonists in asthma has regained interest. Specifically, the effects of LAMAs as add-on therapy have now been widely studied among asthma patients with 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 asthma treatment guidelines^{11,12}. This review is not intended as a systematic analysis, of which other useful articles exist⁸⁻¹⁰, but aims to discuss scientific evidence about 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 increased release of the neurotransmitter acetylcholine (Figure 1)^{13,14}. Furthermore, it was recently documented that airway cholinergic neuronal density is increased in asthma, potentially enhancing this effect¹⁵. Acetylcholine is released from airway

neurons and also from non-neuronal cells, such as many inflammatory cells and airway epithelial cells, and subsequently binds to muscarinic receptors causing, amongst others, airway smooth muscle contraction and mucus production¹⁶. Specifically, the muscarinic receptors M₁, M₂ and M₃ have been shown to play important roles in airway physiology^{17,18}. M₃ receptors are predominantly found on airway smooth muscle cells and submucosal glands and cause airway smooth muscle contraction and mucus secretion, respectively^{17,18}. M₂ receptors are expressed on both airway smooth muscle cells and airway neurons. Their role in airway smooth muscle contraction is less significant, but M₂ receptors on airway neurons play a role as autoreceptors limiting the release of acetylcholine and thereby inhibiting bronchoconstriction and mucus secretion^{17,18}. Finally, M₁ receptors are found in parasympathetic ganglia where they regulate neurotransmission by depolarizing the resting membrane potential which facilitates nicotinic receptor mediated neurotransmission and increases bronchoconstriction^{17,18}. In asthma, both M₂ autoreceptor dysfunction and increased cholinergic activation of M₁ and M₃ receptors increase bronchoconstriction, mucus secretion, inflammation, and airway remodeling¹⁷. It is important to note that all current LAMAs dissociate faster from M₂ receptors than from M₁ and M₃ receptors^{19,20} increasing their combined effectiveness in obstructive airway diseases. Finally, the combined use of LAMAs with ICS and/or LABAs has been suggested to have synergistic interactions, primarily based on animal and *in vitro* work²¹.

Main clinical effects

Major studies for inclusion in asthma guidelines

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

The first two studies, 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 or placebo once daily as add-on therapy to high dose ICS plus LABA for 48 weeks²². After 24 weeks, mean change in peak Forced Expiratory Volume in 1 second (FEV₁) was greater with tiotropium compared to placebo in both trials (86 ml in trial 1 P=0.01; 154 ml in trial 2 P<0.001). Trough FEV₁ improved with tiotropium compared to placebo (88 ml in trial 1 P<0.01; 111 ml in trial 2 P<0.001, Figure 2A).

Moreover, time to first severe exacerbation increased with the use of tiotropium and a 21% reduction in risk of developing an exacerbation was observed (hazard ratio, 0.79; P = 0.03, Figure 2B). Large improvements in Asthma Control Questionnaire 7 (ACQ-7) and Asthma Quality of Life Questionnaire (AQLQ) scores were observed versus baseline in both studies, but these improvements were only significantly greater with tiotropium compared to placebo in PrimoTina-asthma-2.

The first studies investigating the efficacy of single-inhaler triple therapy with ICS/LABA/LAMA versus ICS/LABA were the TRIMARAN and TRIGGER²³. These two 52-week, randomized studies investigated the use of single inhaler beclomethasone dipropionate (BDP), formoterol fumarate (FOR), and glycopyrronium (GLY) versus the same medium-dose BDP/FOR (TRIMARAN), the same high-dose BDP/FOR (TRIGGER), or open-label BDP/FOR plus tiotropium (TRIGGER) in 1155 uncontrolled asthma patients in TRIMARAN and 1437 in TRIGGER. Trough FEV₁ improved with BDP/FOR/GLY compared to BDP/FOR in both TRIMARAN (57 ml [95% CI 15-99], p=0.0080) and TRIGGER (73 ml [26-120], p=0.0025, Figure 2A). In TRIMARAN, a 15% reduction in moderate or severe exacerbation rates was observed with BDP/FOR/GLY compared to BDP/FOR (RR 0.85 [95% CI 0.73–0.99], p=0.033, Figure 2B). The reduction in moderate or severe exacerbations was 12% in TRIGGER, which was not statistically significant (0.88

[0.75–1.03], $p=0.11$). Peak FEV₁ and morning peak expiratory flow (PEF) improved significantly with BDP/FOR/GLY compared to 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 as well as asthma control (ACQ-7) improved in all study groups compared to baseline, with no statistically significant differences between the groups.

The use of the LAMA glycopyrronium 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/LABA²⁴. 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 showed greater improvement in trough FEV₁ versus corresponding doses of MOM/IND (medium dose 76 mL [95% CI 41–111]; $p<0.001$, and high-dose 65 mL [31–99]; $p<0.001$, Figure 2A). Both medium and high-dose MOM/IND/GLY also demonstrated greater improvement in trough FEV₁ compared to high-dose FLUp/SAL (change from baseline with medium-dose MOM/IND/GLY 99 ml [95% CI 64–133], $p<0.001$; with high-dose MOM/IND/GLY 119 ml [85–154], $p<0.001$, Figure 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 versus the respective dose of MOM/IND. Significant improvements in ACQ-7 scores were observed with both medium and high-dose MOM/IND/GLY compared to high-dose FLUp/SAL at 26 weeks (medium-dose: –0.084 [$p=0.038$], high-dose: –0.086 [$p=0.034$]). The annualized rates of moderate or severe exacerbations decreased with MOM/IND/GLY compared to MOM/IND, although this improvement did not reach statistical significance (Figure 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 to high-dose FLUp/SAL (medium-dose: RR 0.81 [95% CI 0.66-0.99], $p=0.041$; high-dose: RR 0.64 [0.52-0.78], $p<0.001$, Figure 2B).

In the CAPTAIN study the LAMA umeclidinium (UME) was studied, at two doses in single-inhaler triple therapy together with fluticasone furoate (FLUf) at two doses and vilanterol (VIL)²⁵. In this 24-52 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 FLUf/VIL 100/25 µg and 200/25 µg led to significant improvements in trough FEV₁ 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, Figure 2A). No statistically significant difference in reduction of annualized moderate or severe exacerbation rate was observed between the groups (Figure 2B). ACQ-7 scores improved in all treatment groups when compared to baseline, but responder rates were significantly higher only with FLUf/ VIL/UME 62.5 µg groups when compared to FLUf/VIL (OR 1.43 [95% CI 1.16–1.76], $p=0.0009$).

LAMAs in other study designs and populations

In patients with milder disease, symptomatic on low dose ICS and without LABA, the addition of tiotropium was compared to the addition of salmeterol and to doubling the ICS dose²⁶. Adding tiotropium was superior to doubling the ICS dose with respect to improvement in morning PEF, evening PEF, pre-bronchodilator FEV₁, and number of asthma control days. Next to that, the addition of tiotropium was noninferior to add-on salmeterol with regard to morning PEF, prebronchodilator FEV₁, and proportion of asthma control days. The increase in prebronchodilator FEV₁ was significantly greater with tiotropium add-on compared to salmeterol (0.11 liters improvement with tiotropium [95% CI 0.05-0.10], $p=0.003$).

The MezzoTinA-asthma-1 and 2 trials were replicate 24-week, randomized, double-blind, double-dummy studies involving 2103 asthma patients uncontrolled on medium dose ICS who were randomly assigned to addition of either tiotropium 5 µg or 2.5 µg once daily, salmeterol 50 µg twice daily, or placebo²⁷. At 24 weeks, improvements in peak FEV₁ were greater with both tiotropium doses and with salmeterol compared to placebo (tiotropium 5 µg: 185 mL [95% CI 146–223]; tiotropium 2.5 µg: 223 mL [185–262]; salmeterol: 196 mL [158–234]; $p < 0.0001$). Trough FEV₁ also improved; 146 mL (95% CI 105–188) with tiotropium 5 µg, 180 mL (138–221) with tiotropium 2.5 µg, and 114 mL (73–155) with salmeterol (Figure 3). A statistically significant improvement in the proportion of patients achieving the minimal clinical important difference (MCID) in ACQ-7 was also observed with both tiotropium arms and with salmeterol compared to placebo (tiotropium 5 µg: OR 1.32 [95% CI 1.02–1.71], $p = 0.035$; tiotropium 2.5 µg: 1.33 [1.03–1.72], $p = 0.031$; salmeterol: 1.46 [1.13–1.89], $p = 0.0039$). Exacerbation rates were low in this population: a significant reduction in the risk of first severe exacerbation was observed only with tiotropium 2.5 µg compared to placebo over 24 weeks.

In the ARGON study, two triple schemes were compared: once daily single-inhaler triple therapy with mometasone furoate (MOM), indacaterol (IND), and glycopyrronium (GLY) versus high-dose of fluticasone/salmeterol twice daily plus tiotropium once daily (FLUp/SAL + TIO) in patients with uncontrolled asthma on medium or high-dose ICS/LABA²⁸. 1426 patients were entered in this 24-week, partially blinded, randomized, non-inferiority study. The primary endpoint, the number of AQLQ responders was non-inferior with medium-dose MOM/IND/GLY versus FLUp/SAL + TIO, and higher with high-dose MOM/IND/GLY compared to FLUp/SAL + TIO (73.3 versus 67.8%, $p = 0.013$). Similarly, the improvements in ACQ-7 scores were non-inferior for medium-dose (difference of -0.032, $p = 0.245$) MOM/IND/GLY compared to FLUp/SAL + TIO and superior for high-dose (difference of -

0.124, $p=0.004$). Trough FEV_1 was significantly higher with high-dose MOM/IND/GLY compared to FLUp/SAL + TIO at 24 weeks (difference of 96 ml, $p<0.001$), and comparable between medium-dose MOM/IND/GLY and FLUp/SAL + TIO (difference of 9 ml, $p=0.713$) (Figure 3). Rates of both moderate and/or 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 shown a differential effect of baseline FEV_1 , reversibility or age on the subsequent response of the LAMA when added to ICS/LABA^{24,25,29}, with the exception of the pooled TRIMARAN and TRIGGER studies²³.

It is interesting to look specifically at the relation of response to baseline eosinophil number or type 2 (T2) inflammatory status. Post-hoc analyses of the PrimoTinA, TRIMARAN/TRIGGER and CAPTAIN trials found that both improvement in trough FEV_1 and reduction in moderate and/or severe exacerbations were independent of baseline blood eosinophil levels^{25,30,31}. Of interest, two 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 showed 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 study²⁵. This indicates that T2-high asthma patients 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.* (2021) presented a systematic review and meta-analysis on the use of ICS/LABA/LAMA versus ICS/LABA in asthma patients¹⁰. Overall, this review included 18 articles describing 20 randomized controlled trials, including all mentioned above. Three studies were performed in children. *Kim et al.* also shortly discuss 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 (non-smoker, ex-smoker, current smoker), exacerbation frequency (<1 previous exacerbation, ≥1 previous exacerbations), inflammatory phenotype (T2-high, T2-low, defined by peripheral blood eosinophil count), type and dose of LAMA, type and dose of ICS (intervention or comparator). In summary, so far no clear characteristics of responders to LAMA therapy have been identified; they exert their effects across all subgroups studied.

Anti-inflammatory effects

Overall, the addition of LAMAs in asthma reduces exacerbation rates and/or increases time to first exacerbation¹⁰. These results could indicate that LAMAs have anti-inflammatory properties. Anti-inflammatory effects of anticholinergics alone have indeed been demonstrated 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 on airway smooth muscle cells^{32,33}. Next to that, *in vivo* animal models have demonstrated inhibitory effects of tiotropium or muscarinic M₃ receptor knockout on ovalbumin-induced inflammation, the anti-inflammatory effects of tiotropium being comparable to those of the corticosteroid budesonide³⁴. *In vitro*, it has been shown that glycopyrronium 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. Additionally, the combination of tiotropium with corticosteroid ciclesonide was more effective than either

compound alone in inhibiting allergen-induced airway inflammation in a guinea pig model³⁶. 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 mometasone/indacaterol/glycopyrronium versus mometasone/indacaterol on the allergen-induced late asthmatic response in humans with asthma is currently being performed (NCT04259164)³⁷.

Limitations of current studies / gaps in our knowledge

There are still several gaps in our knowledge about the use of anticholinergics in asthma patients. First of all, 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}. Secondly, anticholinergics have so far mainly been tested on top of ICS +/- LABA, though recently a study comparing mometasone or tiotropium to placebo in mild asthma patients was performed which indicated no significant differences in treatment response in that population³⁹. Next to that, little is still known about the use of LAMAs in asthma patients who are current smokers (only 2 studies included active smokers) or who have cardiac comorbidities, and in patients who are older than 75 years¹⁰. Additionally, it would be useful to perform a study in a large population of asthma-COPD overlap patients, in which we would expect good effectiveness. Results of the study by *Park et al.* (2021) in this population are promising⁴⁰. Lastly, all studies that have been published about the use of LAMAs in asthma patients demonstrate the effects in a closely monitored experimental setting. It would be very relevant to have data about the use of LAMAs in a real-life setting.

Different formulations of LAMAs

Currently, there are three different LAMA molecules that have been investigated as add-on therapy to ICS/LABA in asthma: tiotropium, glycopyrronium and umeclidinium, which differ

somewhat in onset of action and half-life, although complete comparisons are lacking. Glycopyrronium has a slightly faster onset of action than tiotropium (Figure 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 to open label triple combinations in more inhalers and with variable drugs, showing 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+TIO (ARGON)²⁸. The recent meta-analysis by *Kim et al.* included a subgroup analysis by LAMA type and dose and did not find major differences in outcomes¹⁰. 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 to ICS/LABA + LAMA, but from the same meta-analysis, there was no discernible difference between use of a single inhaler or separate inhalers¹⁰. Similarly, one could argue that once daily therapy could improve treatment compliance and adherence versus twice daily therapy, but no studies have investigated these differences in posology yet while employing the same molecules and device.

Adverse events of LAMAs in asthma

The daily use of LAMAs in asthma patients is safe and well tolerated. Clinical trials consistently show a similar safety profile of the different types of LAMAs^{10,22-25}. Side effects that are reported more frequently are dry mouth and dysphonia (RR 1.65, 1.14-2.38) with no other significant differences, including cardiac effects and mortality¹⁰.

Positioning

All the larger clinical studies consistently show greater improvement of lung function with add-on LAMA to ICS/LABA (either as single-inhaler or with separate inhalers) compared to

ICS/LABA alone (Figure 2A). The efficacy of triple therapy in reducing the exacerbation rates compared to the same ICS/LABA was less consistent per trial, but was 17% overall, as shown in the meta-analysis of *Kim et al.* (Figure 2B)¹⁰. 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 MCID of 0.5. The addition of a LAMA was not associated with an improvement in asthma-related quality of life compared to ICS/LABA.

LAMAs are included in both the Global Initiative for Asthma (GINA) and the National Asthma Education and Prevention Program (NAEPP) guidelines^{11,12}. The NAEPP guidelines were updated in 2020 when only tiotropium was approved by the U.S. Food and Drug Administration.

The most recent GINA report of 2021 includes more recent literature¹¹. LAMAs are recommended in GINA step 5 (i.e. 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 versus LABA as 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 about the use of LAMAs in moderate or mild asthma patients, 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 three studies of a direct comparison of LAMA to LABA, all tiotropium versus salmeterol, when added to ICS in severe²², moderate²⁷, and mild-moderate²⁶ asthma, all showing a similar or greater FEV₁ response with the LAMA. A recent review by *Kaplan et al.* (2020) 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 exacerbations⁴². Some patients have side effects on LABAs, and some patients respond better to either one of both drugs, making the use of LAMAs a viable alternative to LABA⁴³.

It is important to carefully consider when to add LAMA to ICS/LABA, and when to increase ICS dose. As shown 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 importantly eosinophilia or T2 inflammatory phenotype¹⁰. 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 T2-low patients^{25,30} thereby preventing the systemic burden of increased ICS, overall and especially in T2-high patients LAMAs are less effective than doubling ICS^{24,25}.

Both the GINA as well as the NAEPP guidelines recommend the use of a LAMA in uncontrolled asthma patients before starting with oral corticosteroids or biologic drugs, such as anti-IgE and anti-IL-5 antibodies^{11,12}. As opposed to LAMAs, the use of the biological therapies is limited to a minority of patients with asthma, mainly T2-high. When these characteristics are present however, reductions in asthma exacerbations with the use of

biological agents in patients with T2-high phenotype are much higher than the use of LAMAs in these patients⁴⁴. On the other hand, costs for biological therapies are much higher than for the use of LAMAs and the necessary injections may be cumbersome⁴⁵.

A separate, difficult topic is the use of as needed medication on top of triple maintenance. GINA has suggested using ICS/LABA virtually for all reliever medication. Whether 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, could also be contemplated. Important in the choice of preferred reliever therapy is efficacy, onset of action (Figure 4), duration of action, and risk of side 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 moderate to severe asthma patients who are uncontrolled despite use of ICS/LABA.

LAMAs work independently of all patient characteristics tested so far, including age, baseline FEV₁, reversibility, asthma duration, and importantly also T2 status. In studies comparing the addition of LAMA versus doubling of ICS, the latter clearly gives a greater reduction in exacerbation frequency in T2-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 add-on to ICS in moderate disease but data are limited to tiotropium, and that LAMAs are also viable bronchodilators in mild disease. Since 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.

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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 (PrimoTina), 2012	TIO 5 µg OD	Placebo	48 weeks	912	Peak FEV ₁ Trough FEV ₁	Time to first severe exacerbation	ACQ-7 score	AQL Q-score
Virchow et al (TRIMARAN/ TRIGGER), 2019	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 weeks	2592	Predose FEV ₁ Peak FEV ₁ Morning PEF	Rate of moderate and severe exacerbations	ACQ-7 score	-
Kerstjens et al (IRIDIUM), 2020	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 weeks	3092	Trough FEV ₁ Postdose FEV ₁	Rate of exacerbations Time to first exacerbation	ACQ-7 score	AQL Q-score
Lee et al (CAPTAIN), 2021	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 weeks 36 weeks 52 weeks	2436	Trough FEV ₁	Annualised rate of moderate and/or severe exacerbations	ACQ-7 score	-
Other studies								
Peters et al (TALC), 2010	TIO 18 µg OD	BDP 160 µg BID; SAL 50 µg BID	14 weeks	210	Morning PEF Trough FEV ₁	Number of exacerbations	Asthma-control days ACQ-7 score	AQL Q-score
Kerstjens et al (MezzoTina), 2015	TIO 5 µg OD; TIO 2.5 µg OD	SAL 50 µg BID; Placebo	24 weeks	2103	Peak FEV ₁ Trough FEV ₁	Time to first severe exacerbation	ACQ-7 score	AQL Q-score
Gessner et al (ARGON), 2020	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 weeks	1426	Trough FEV ₁ Morning PEF	Rate of exacerbations	ACQ-7 score	AQL Q-score

Abbreviations: ACQ, asthma control questionnaire; AQLQ, asthma quality of life questionnaire; BDP, beclometasone dipropionate; BID, twice daily; FEV₁, 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

Figure legend

Figure 1. Muscarinic receptors and mechanisms of action of long-acting muscarinic antagonists. *Abbreviations:* 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.

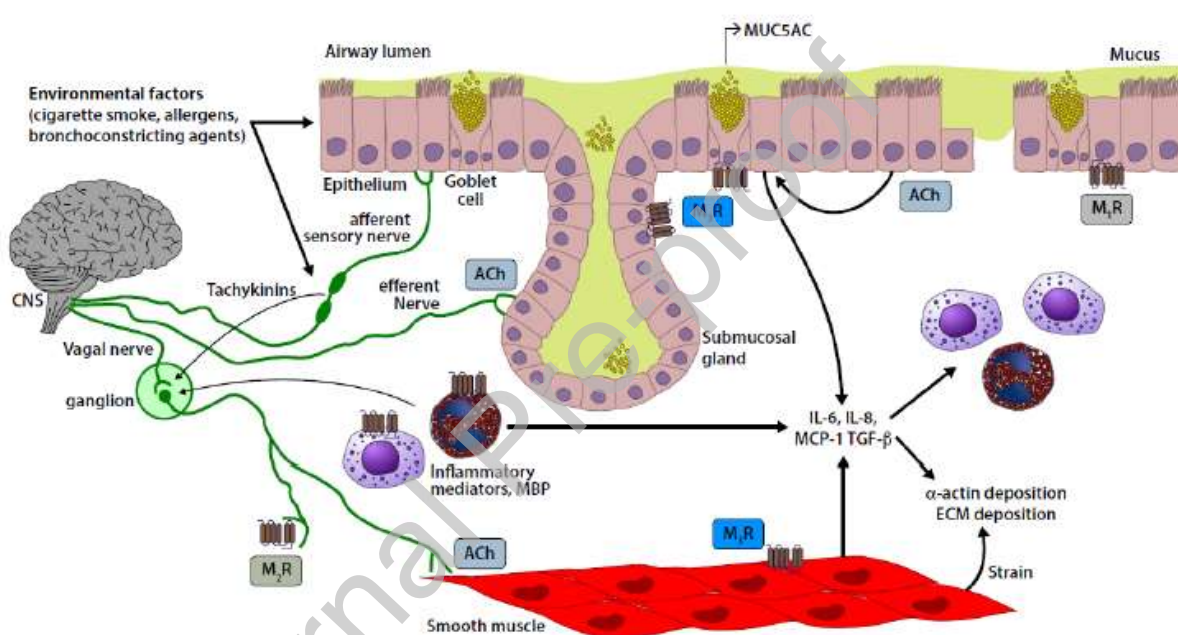
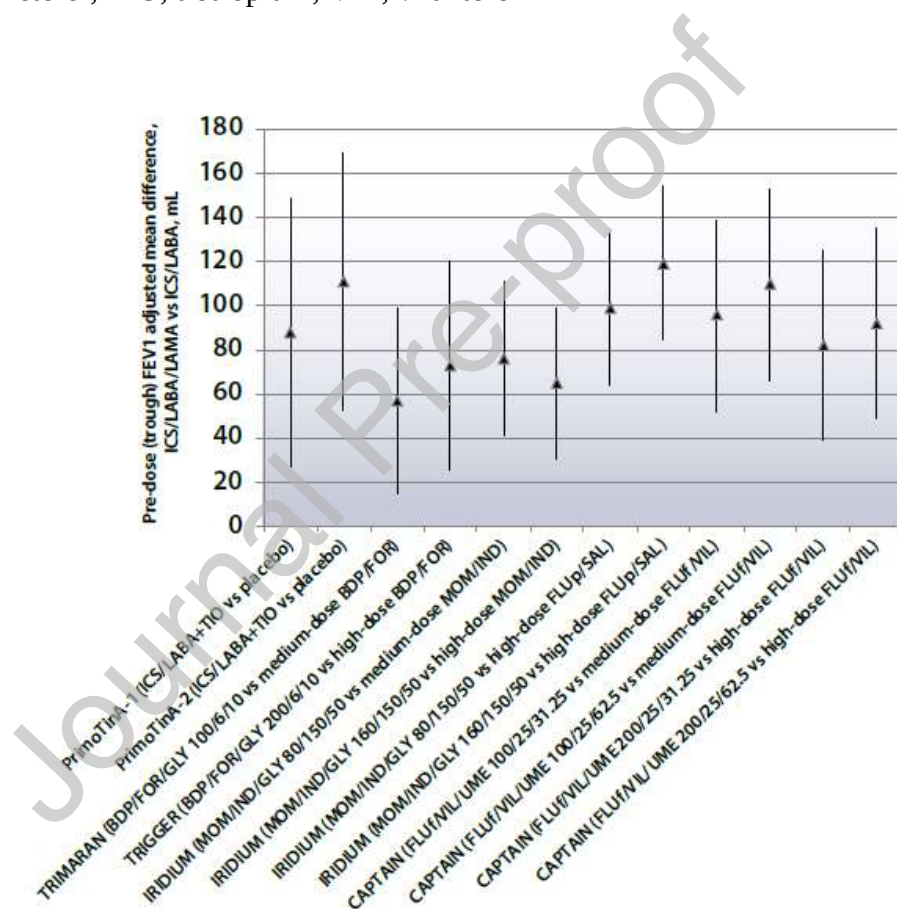


Figure 2. ICS/LABA/LAMA vs. ICS/LABA

A. Trough (pre-dose) FEV₁ at 24-26 weeks: adjusted mean differences and 95% CI

B. Annualized moderate/severe exacerbations: adjusted rate ratios and 95% CI

Abbreviations: BDP, beclomethasone dipropionate; CI, confidence intervals; FEV₁, 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



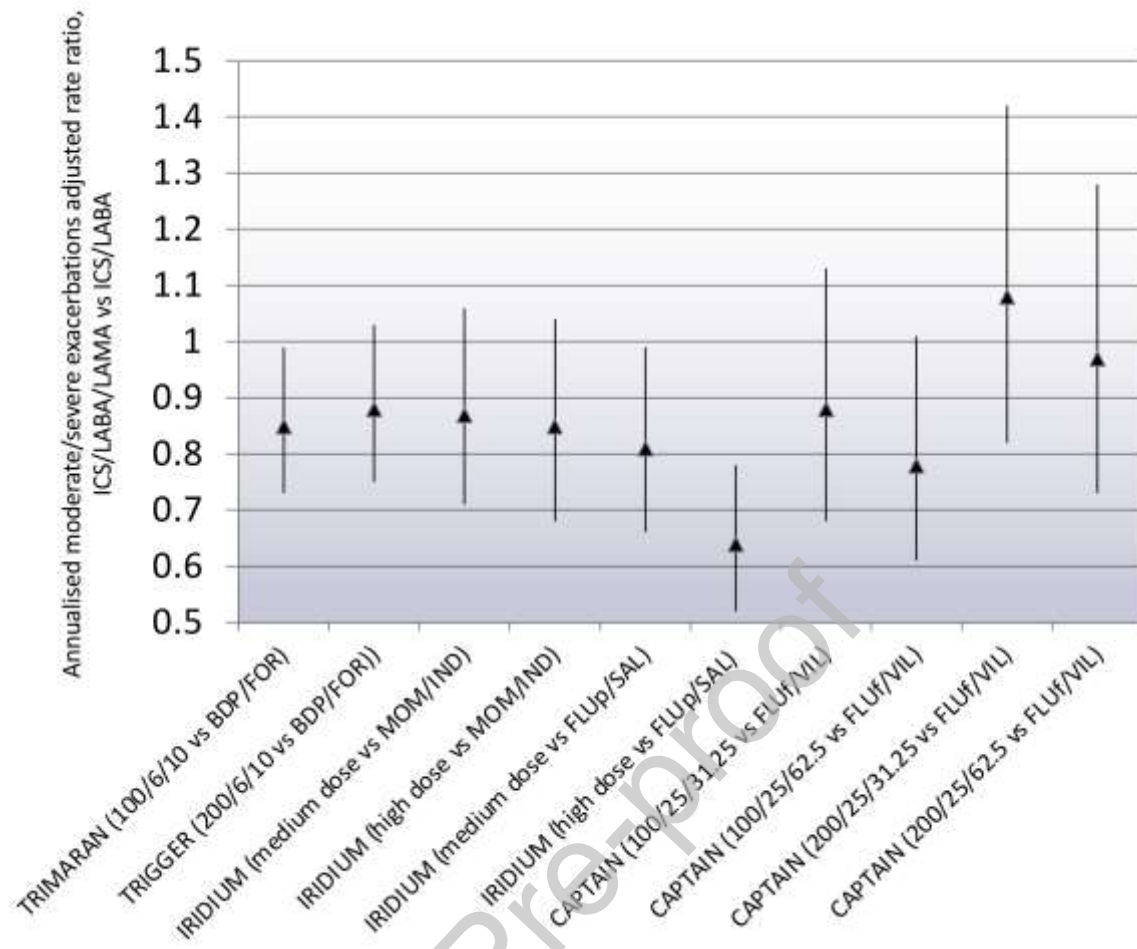


Figure 3. Trough (pre-dose) FEV₁ at 24 weeks in MezzoTinA and ARGON: adjusted mean differences and 95% CI. *Abbreviations:* CI, confidence intervals; FEV₁, forced expiratory volume in 1 sec; FLUp, fluticasone propionate; GLY, glycopyrronium; IND, indacaterol; MOM, mometasone; SAL, salmeterol; TIO, tiotropium.

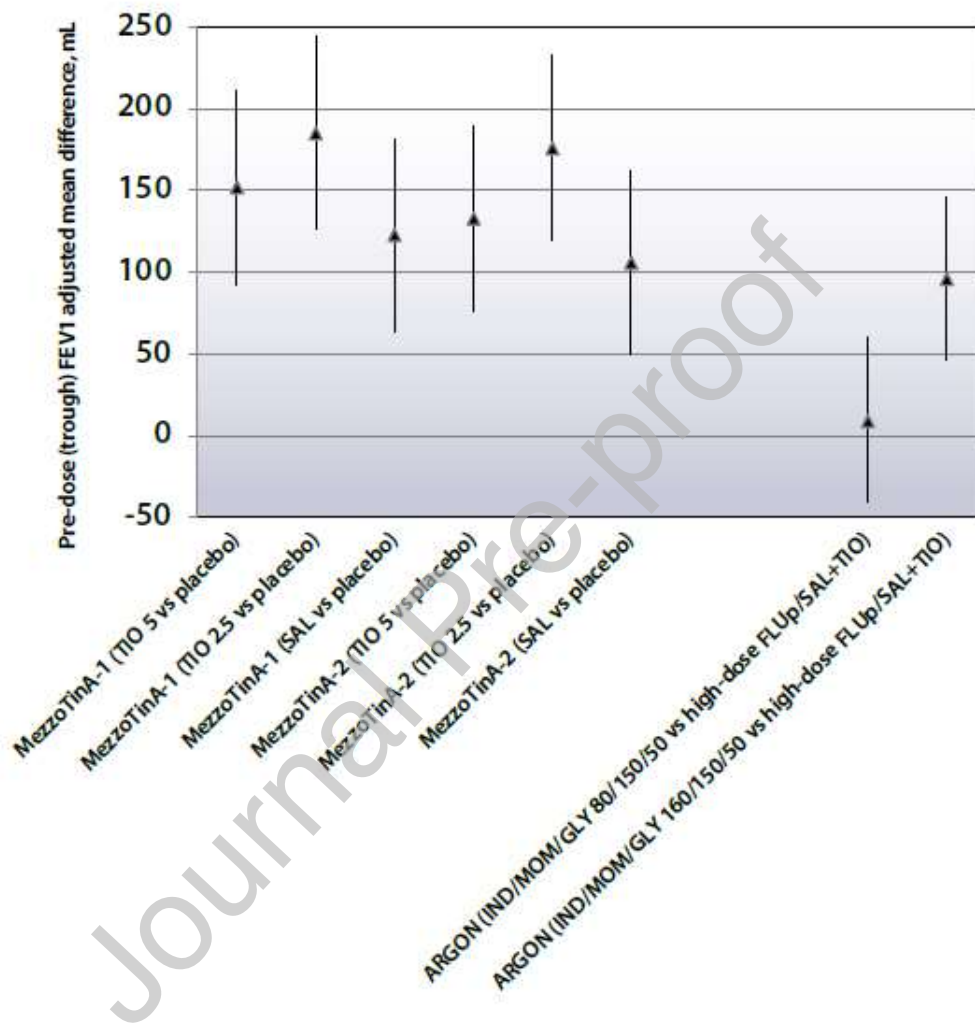


Figure 4. Onset of action glycopyrronium versus tiotropium. Serial spirometry:

glycopyrronium superior to placebo at all time points ($p < 0.01$), and to tiotropium at 5, 15 and 30 min, 1 and 2 h ($p < 0.05$). *Abbreviations:* FEV₁, forced expiratory volume in 1 sec. Adapted from Kerwin *et al.*, Eur Respir J (2012) 40:1106-1114; permission requested.

