

EXPERT OPINION

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Tiotropium bromide as add-on therapy to inhaled corticosteroids for treating asthma

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Introduction: Bronchial asthma is becoming increasingly prevalent worldwide. Although first-line therapy with inhaled corticosteroids (ICS) with or without long-acting β_2 agonists (LABA) has significantly improved the clinical outcomes of asthma, they cannot provide all asthmatics with good control and thus alternatives or add-on drugs are required. Tiotropium is a long-acting muscarinic antagonist that has been used to treat chronic obstructive pulmonary disease and it has been approved for treating asthma in some countries. This agent has similar bronchodilatory effects to those of LABA and might also have anti-inflammatory and anti-remodeling effects.

Areas covered: Some pivotal clinical trials have found tiotropium effective as an add-on medication for low-to-medium doses of ICS for treating symptomatic asthma and asthma that remains uncontrolled despite ICS plus LABA therapy.

Expert opinion: Whether or not tiotropium has anti-inflammatory and anti-remodeling effects in humans with asthma is an important issue. Predictors that would identify patients who would derive the maximal potential benefit from treatment with tiotropium in addition to their current therapy are also needed. Although the cardiovascular toxicity of tiotropium is less remarkable in asthma than in chronic obstructive pulmonary disease, longer and larger studies are still needed to confirm the safety of tiotropium for treating asthma.

Keywords: airway hyperresponsiveness, airway remodeling, long-acting muscarinic antagonist, long-acting β_2 agonist

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1. Pathophysiology and epidemiology of asthma

1.1 Introduction

Bronchial asthma is a common airway disease and one survey has found that asthma affects 5 – 16% of people worldwide, although the prevalence significantly varies among countries [1]. The annual direct medical expenditure for asthma treatment in the USA in 2007 was \$37.2 billion [2], and the estimated annual direct cost of asthma in Europe was €7.9 billion [3]. Furthermore, the total incremental cost (including indirect costs) of asthma to society in the USA was \$56 billion during 2007 [4]. Asthma is clinically characterized by the acute onset of dyspnea with expiratory wheezing and physiologically characterized by reversible airway obstruction and airway hyperresponsiveness (AHR) to various stimuli. AHR is associated with allergic airway inflammation, wherein various types of cells and mediators are involved [5]. Based on these facts, anti-inflammatory inhaled corticosteroids (ICS) with or without inhaled long-acting β_2 agonists (LABA) continue to be the mainstay of pharmacological treatment for asthma [6]. Clinical trials have shown that patients

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Box 1. Drug summary.

Drug name	Tiotropium bromide
Phase	Approved for asthma in EU, Japan, Korea and some South American countries
Indication	Bronchial asthma in patients who remain symptomatic on ICS or ICS plus LABA
Pharmacology description/mechanism of action	Muscarinic M ₃ -receptor antagonist
Route of administration	Inhalation via Respimat®
Chemical structure	(1 α , 2 β , 4 β , 5 α , 7 β)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo [3.3.1.0 ^{2,4}]nonane bromide monohydrate
Pivotal trials	[18–22]

who continue to have symptomatic asthma despite treatment with ICS benefit from added LABA [7]. Nonetheless, one study showed that a combination of ICS and LABA could control asthma of various degrees of severity in only 71% of patients [8]. Another concern about LABA is increased risk of severe asthma exacerbation and death among patients treated with LABA alone, and whether ICS completely prevents such side effects remains to be determined [9]. These concerns have prompted a search for alternative add-on therapies for patients with asthma that is not controlled well with ICS alone or with ICS plus LABA. Anticholinergic agents show promise as add-ons to current drugs used to manage asthma.

Short-acting anticholinergic agents can relieve acute exacerbation of asthma. A combination of short-acting β_2 agonists (SABA) and short-acting muscarinic antagonists (SAMA) has significantly reduced the number of hospital admissions and increased pulmonary function in adults with moderate-to-severe asthma exacerbation in the emergency setting [10]. In contrast, a meta-analysis has not provided any justification for regularly adding SAMA to treat asthma that is not controlled well by standard therapies [11]. On the other hand, long-acting muscarinic antagonists (LAMA), including tiotropium, aclidinium and glycopyrronium, have become established in international guidelines as first-line medications for treating chronic obstructive pulmonary disease (COPD) [12], although they were not historically licensed for asthma. Tiotropium became licensed for treating uncontrolled asthma in 2014, even in patients using ICS in the European Union, Japan, Korea and some South American countries.

2. Tiotropium bromide (Box 1)

2.1 Parasympathetic nervous system in the human airway

The parasympathetic nervous system is a major bronchoconstrictor pathway in the human airway. Cholinergic fibers

run through the vagus nerves into the parasympathetic ganglia within the airway wall. From the parasympathetic ganglia, postsynaptic fibers reach the smooth muscle and mucous glands in the airway, where the primary neurotransmitter acetylcholine (ACh) is released and acts via the activation of muscarinic cholinergic receptors (Figure 1 [13]). The binding of ACh to these receptors on target cells results in airway smooth muscle constriction and mucous secretion, both of which are representative of the pathophysiology of asthma. The effects of ACh are mediated by a family of five G-protein-coupled receptors (M₁–M₅) with distinct anatomical distribution and functions. Only the M₁–M₃ subtypes are present in the airways [14]. M₁ receptors are located in parasympathetic ganglia where they facilitate neurotransmission. Presynaptic M₂ receptors act as autoreceptors that modulate ACh release and M₃ receptors are expressed on airway smooth muscle, submucosal glands, and vascular endothelium in the lung. M₃ receptors primarily mediate the constriction of airway smooth muscle cells in response to ACh [15].

2.2 Introduction to the compound

The LAMA tiotropium bromide administered using the single-dose dry-powder inhaler (DPI) HandiHaler® (RPC Group, Mellrichstadt, Germany) was marketed in 2004 and initially licensed only for treating COPD. Another propellant-free inhaler system, Respimat®, that delivers a slow-moving mist of aerosolized solution (Boehringer Ingelheim microParts GmbH, Dortmund, Germany), was subsequently approved. Tiotropium bromide administered using the Respimat® was approved in 2014 for the long-term, daily add-on maintenance of patients with asthma who remain symptomatic while under ICS treatment in the European Union, Japan, Korea and some South American countries.

2.3 Chemistry and pharmacokinetics/pharmacodynamics of tiotropium

Tiotropium bromide is a synthetic, non-chiral quaternary ammonium compound that is structurally related to the SAMA ipratropium (Figure 2). The quaternary ammonium causes low penetration of the blood–brain barrier and low absorption after oral administration. Tiotropium is sparingly soluble in water and soluble in methanol. Tiotropium bromide is about 10-fold more potent than ipratropium in terms of binding to muscarinic receptors. The binding affinity of tiotropium and ipratropium for M₁, M₂, and M₃ receptors is similar, whereas kinetic studies have shown that although tiotropium dissociates from M₁ and M₃ > 100-fold more slowly than ipratropium, the two compounds similarly dissociate from M₂ [16]. This suggests that tiotropium has high potency as a selective antagonist for the M₃ muscarinic receptor. Consequently, it provides 24-h bronchodilation as maintenance therapy for patients with COPD and asthma. Tiotropium starts to act within 30 min of administration,

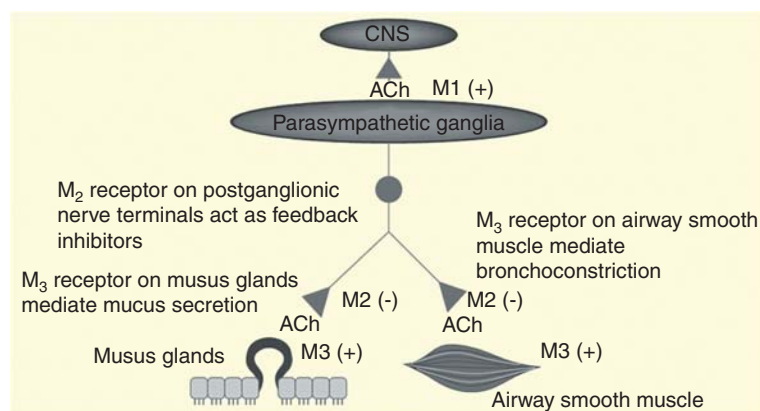


Figure 1. Muscarinic receptors in human airways. ACh released at neuromuscular junction binds to muscarinic M2 and M3 receptors located at smooth muscle cell. ACh is autoinhibitory on presynaptic M2 receptors.

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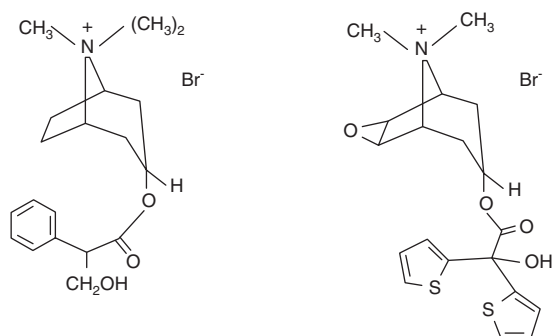


Figure 2. Molecular structures of ipratropium bromide (left) and tiotropium bromide (right).

and peaks within 3 – 4 h in patients with COPD. The reported duration of action of tiotropium can persist for up to 32 h after a single inhalation. Forced expiratory volume in one second (FEV_{1.0}) reaches a steady state within 48 h, whereas forced vital capacity might continue to improve for over 1 week after tiotropium administration [17].

3. Clinical use of LAMA for asthma

3.1 Asthma treatment guidelines

The ultimate goal of treatment for asthma includes minimizing symptoms, preventing acute exacerbation and avoiding adverse effects. The International Asthma Treatment Guidelines recommend an ICS to treat persistent asthma [6]. For patients who do not respond well to ICS alone, the guidelines recommend adding a LABA, leukotriene receptor antagonist or theophylline. The guidelines also recommend systemic corticosteroids and anti-immunoglobulin E antibody to treat particularly severe and persistent asthma. The guidelines presently do not recommend the use of LAMA.

3.2 LAMA or LABA as add-ons to ICS

A three-way crossover study by Peters *et al.* [18] compared the effects of adding salmeterol (100 µg/day) or tiotropium (18 µg/day) delivered using a HandiHaler[®] with a double dose of extra-fine hydrofluoroalkane (HFA)-beclomethasone for over 14 weeks after an initial run-in period on 160 µg daily, among 210 patients with moderate asthma. The primary outcome of morning peak expiratory flow (PEF) was significantly better with added tiotropium than with a double dose of HFA-beclomethasone, and not inferior to that of salmeterol. Mean differences in the secondary end point, FEV₁, were significantly improved by adding tiotropium compared with a double dose of HFA-beclomethasone and with add-on salmeterol. The results of secondary outcomes including asthma control determined from a questionnaire and asthma quality-of-life scores were similar between salmeterol and tiotropium.

In a larger, longer-term study in 1972, Kerstjens *et al.* [19] compared the effects of adding tiotropium (5 µg/day, or 2.5 µg/day via Respimat[®]), salmeterol (2 × 50 µg/day), or a placebo to a stable medium dose of ICS (equivalent to 400 – 800 µg of budesonide) upon moderate symptomatic asthma for 24 weeks. Peak and trough FEV₁ responses were significantly greater with tiotropium and salmeterol than with the placebo and were statistically comparable. More responders had asthma-related symptoms in the tiotropium and salmeterol groups than in the placebo group. The safety and tolerability of all active compounds were acceptable. These results collectively indicated that tiotropium is safe and effective as an add-on medication to low-to-medium doses of ICS and can be an alternative to LABA in patients with symptomatic asthma.

3.3 LAMA as add-on to ICS/LABA

Fardon *et al.* [20] implemented the first proof-of-concept study in 18 nonsmokers aged 54 years with severe, persistent

asthma. After an initial run-in period on fluticasone propionate (1000 µg/day), the patients were treated in randomized crossover fashion for 4 weeks under half the dose of fluticasone propionate (500 µg/day) and with either the addition of both salmeterol and tiotropium (triple therapy with a fluticasone propionate/salmeterol combination of 500 or 100 µg/day + tiotropium 18 µg/day) salmeterol (double therapy with fluticasone propionate/salmeterol 500 or 100 µg/day + placebo). There was a small but significant improvement in FEV1 and a significant reduction in the amount of exhaled nitric oxide in response to triple, but not double therapy, compared with baseline therapy with twice the dose of fluticasone propionate alone. Morning PEF significantly increased in both randomized treatments compared with baseline, but the improvements generated with double and triple therapy on asthma quality-of-life scores did not significantly differ among treatments.

Kerstjens *et al.* [21] evaluated 107 patients who had severe uncontrolled asthma that persisted despite ICS/LABA therapy and were randomized in crossover fashion to receive treatment with add-on placebo or tiotropium 5 or 10 µg/day delivered via a Respimat® for 8 weeks each. The primary end point, peak FEV1, did not significantly differ between tiotropium doses of 5 and 10 µg/day, which were both significantly more effective than the placebo. The mean values for trough morning PEF were significantly higher with tiotropium doses of 10, than 5 µg/day, but neither dose significantly improved asthma quality-of-life scores or asthma diary cards. The second study by Kerstjens *et al.* [22] involved a composite analysis of two parallel group trials that included 912 patients (mean age, 53 years) with severe uncontrolled asthma who were randomized to receive tiotropium 5 µg/day daily via Respimat® or a placebo for 48 weeks as an add-on to extant ICS/LABA. The two co-primary pulmonary function end points of peak and trough FEV1 after 24 weeks of therapy were significantly improved in terms of respective mean overall differences, and morning PEF also concurrently improved. The third co-primary end point of risk of a severe exacerbation over 48 weeks was also significantly reduced by 21% overall, and changes in asthma control, determined using a questionnaire and quality-of-life scores, were below the minimal important difference of 0.5 units. Taken together, these results indicated that tiotropium is an effective add-on therapy for treating severe asthma that remains uncontrolled despite ICS plus LABA therapy.

3.4 Asthma COPD overlap syndrome

Asthma is a representative respiratory disease among children and adults aged < 40 years, whereas COPD is more common among older adults aged > 40 years with a history of smoking. Since a significant proportion of asthmatics in developed countries probably have a history of smoking cigarettes [23], the numbers of those with both asthma and COPD (asthma-COPD overlap syndrome – ACOS) should become more prevalent. In fact, around 20% of patients have

concurrent doctor-diagnosed asthma and COPD [24]. Since tiotropium is clinically effective against COPD, it might also be effective for ACOS. Additionally, M₃ receptor expression is increased in the airways of aged asthmatic mice, suggesting that the M₃ antagonist, tiotropium, would be effective for older patients with asthma and COPD [25]. Magnussen *et al.* reported that patients with COPD and concomitant asthma treated with tiotropium experienced spirometric improvements along with the symptomatic benefit of a reduced need for rescue medication [26].

4. Areas of uncertainty regarding LAMA for asthma

4.1 Anti-inflammatory and anti-remodeling effects

The ACh is primarily a neurotransmitter that causes airway constriction and mucous hypersecretion through muscarinic M₃ receptors in the airway. Since M₃ receptors are expressed not only in structural, but also in inflammatory cells, including lymphocytes and macrophages [27], ACh might regulate airway inflammation and subsequent remodeling. ACh induces LTB₄, IL-6 and IL-8 from airway smooth muscle, as well as inflammatory and epithelial cells through M₃ receptors, which attract and activate inflammatory cells, including eosinophils and notably neutrophils [28]. The implication of these findings is that anti-muscarinic tiotropium might have additional anti-inflammatory effects beyond bronchodilation.

In addition to chronic airway inflammation, airway remodeling including goblet cell metaplasia, thickening of the reticular layer beneath the true basement membrane, smooth muscle, fibroblast and myofibroblast hyperplasia [29–31] are also closely associated with the pathophysiology of asthma, especially increased AHR and irreversible airway obstruction. The notion that airway constriction mediated by the cholinergic system plays a fundamental role in the development of airway remodeling in asthma has recently been reconsidered. Grainge *et al.* in a study of bronchial biopsy specimens found that methacholine-induced airway constriction without inflammation causes airway remodeling, including subepithelial collagen deposition and mucous gland hyperplasia in asthmatic airways [32]. They concluded that sustained and safe bronchodilation in addition to adequate control of inflammation should be the aim to avoid the long-term adverse consequences of airway remodeling in patients with asthma. The primary bronchodilatory and possibly anti-inflammatory properties of tiotropium have thus received focus as a means to prevent airway remodeling in patients with asthma. Although tiotropium does not have proven anti-remodeling effects in patients with asthma, it certainly attenuates airway inflammation and remodeling in a murine model of asthma [33].

4.2 Predictors for effectiveness of LAMA

Whether or not LAMA will be effective against asthma cannot be predicted before its administration. A sub-analysis of the

clinical study described above [18] discovered that a positive response to SABA could predict a positive clinical response to tiotropium as well as salmeterol [34]. Whether or not genotyping the β_2 adrenergic receptor gene could predict the response to β_2 agonists [35,36] remains controversial. Bateman *et al.* [37] also found that tiotropium was not superior to salmeterol in genetically susceptible patients whose asthma was not controllable by ICS alone. An important issue will be to identify factors that could predict which patients would derive the most benefit from treatment with tiotropium in addition to current therapy.

5. Safety

A meta-analysis found that risk for mortality is increased when tiotropium is administered via a Respimat[®] to treat COPD compared with a placebo [38]. Since Respimat[®] improves lung deposition compared with standard DPI [39], the increased mortality might be a consequence of more effective drug delivery to the lungs that results in increased absorption and thus greater systemic exposure. A subsequent large-scale, long-term prospective trial compared the safety and efficacy of tiotropium delivered by Respimat[®] and Hand-iHaler[®] and found similar results for these two devices [40]. Furthermore, in the setting of asthma where patients tend to be younger nonsmokers without cardiovascular disease, concerns about potential tiotropium cardiotoxicity seem far less relevant.

From the viewpoint of safety, switching ICS/LABA combined in an inhaler to separate doses of ICS and tiotropium in separate inhalers could result in low patient compliance with the ICS. Since ICS are recognized as critical for treating persistent asthma at all levels of severity, stopping ICS could be very detrimental to patients. Therefore, if clinicians substitute tiotropium for LABA for patients using ICS, the patients should be monitored very closely to ensure compliance with ICS. Adding tiotropium to ICS/LABA would be less likely to lead to poor compliance with ICS.

6. Conclusion

ICS with or without LABA have significantly improved the clinical course of asthma. Nonetheless, some patients still develop asthma-related symptoms even with ICS and LABA, and require yet another add-on drug. In contrast to SAMA that cannot control asthma on a daily basis, several clinical trials have found that tiotropium, a LAMA, can be safely added to ICS with or without LABA to regularly treat uncontrolled asthma. Tiotropium is safe and as effective as LABA when added to low-to-medium doses of ICS to treat symptomatic asthma. Tiotropium is also an effective add-on drug to treat more severe uncontrolled asthma that persists despite therapy

with ICS together with LABA. Tiotropium should also be considered for treating ACOS. Safety should be less of a concern for patients with asthma taking tiotropium, since they are usually younger than patients with COPD, nonsmokers and do not have cardiovascular disease.

7. Expert opinion

Tiotropium causes bronchodilation through a different pathway from LABA and it might have anti-inflammatory and anti-remodeling effects. In addition, LAMA might synergistically work with LABA to improve asthma and COPD. Collective clinical findings have shown that tiotropium can improve unstable asthma via additional bronchodilation and possible anti-inflammatory pathways in patients under treatment with ICS regardless of added LABA.

Clinical studies have shown that LABA and LAMA are comparatively effective against asthma that remains uncontrolled under therapy with ICS alone. Tiotropium should be selected as a first-line add-on medication to ICS for patients with asthma who cannot tolerate the adverse effects of LABA [41]. Predictors of better responders to LAMA before initiation are presently unknown. Identifying genetic factors or surrogate markers that could predict responses to LAMA will be important.

While LAMA might have some anti-inflammatory and anti-remodeling activity in basic experiments, appropriately designed clinical trials are necessary to confirm whether this is true *in vivo*. Longer-term and larger-scale prospective studies will definitely be important to conclude whether or not LAMA are effective against airway inflammation and remodeling associated with asthma, especially for ICS-resistant, noneosinophilic asthma including that in the elderly [42], in smokers [43] and in patients with fungal sensitization [44]. Tiotropium cardiotoxicity should be less of a concern for patients with asthma compared with those who have COPD, but longer and larger studies are needed to confirm this.

Besides asthma and COPD, tiotropium could regulate the cough reflex in airway sensory nerves [45]. The clinical benefits of tiotropium for prolonged cough, which is a major concern in respiratory clinics, should also become a topic of future study.

Declaration of interest:

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