REVIEWS

Anticholinergics for Treatment of Asthma

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■ **Abstract**

Asthma management guidelines emphasize the importance of effective treatment to achieve and maintain control of asthma. However, despite widely available and effective treatments, achieving control of asthma is still an unmet need for many patients. Adding a second bronchodilator with a different mechanism of action for the treatment of uncontrolled asthma can be a suitable therapeutic approach. This review focuses on the role of long-acting muscarinic antagonists, particularly tiotropium, in the treatment of asthma.

A number of studies have evaluated the efficacy and safety of tiotropium in asthma patients whose disease is poorly controlled with inhaled corticosteroids (ICSs) with or without long-acting β_2-agonists (LABAs). The effect on several clinical and lung function variables of adding tiotropium to an ICS is greater than doubling the dose of the latter and is not inferior to the addition of a LABA (salmeterol). Studies assessing the role of tiotropium as add-on therapy to ICS combined with a LABA have shown modest but clinically significant and dose-dependent improvements in forced expiratory volume in 1 second, as well as a decrease in the risk of exacerbations. In addition, time to the next episode is longer, particularly in patients who experience severe exacerbations.

In conclusion, tiotropium proved noninferior to salmeterol and superior to placebo in patients with moderate-severe asthma who were not adequately controlled using ICSs or ICSs combined with a LABA. The major benefits are the increase in lung function and, in the case of severe asthma, the reduction in the frequency of exacerbations. In patients with asthma, tiotropium is usually well tolerated, and no potential safety signals have been observed.

Key words: Asthma treatment. Anticholinergics. Bronchodilators. Tiotropium.

■ **Resumen**

Las guías de manejo del asma destacan la importancia de un tratamiento efectivo del asma para lograr y mantener el control. Sin embargo, a pesar de disponer de tratamientos eficaces, alcanzar el control del asma sigue siendo un reto en muchos pacientes. La adición de un segundo broncodilatador con un mecanismo de acción diferente en el tratamiento de asma no controlada puede representar una aproximación terapéutica apropiada. Esta revisión va enfocada al papel de los antagonistas muscarínicos de acción prolongada (LAMA), especialmente el tiotropio, en el tratamiento del asma.

Diversos estudios han evaluado la eficacia y al seguridad del tiotropio en pacientes con asma no controlada en tratamiento con corticosteroides inhalados (CSI) con o sin agonistas β_2 de acción prolongada (LABA). El efecto de añadir tiotropio a CSI es superior a doblar la dosis de estos, y no es inferior a la adición de un LABA (salmeterol) en diversas variables clínicas y de función pulmonar. Los estudios que analizan el efecto de tiotropio como terapia adicional a la combinación de CSI y LABA han mostrado mejorías modestas pero clínicamente significativas y dependientes de la dosis en el FEV_1, así como una disminución del riesgo de exacerbaciones, con una prolongación del tiempo hasta el siguiente episodio, especialmente en pacientes con exacerbaciones graves.

En conclusión, tiotropio ha resultado no ser inferior a salmeterol y es superior al placebo en pacientes con asma moderada a grave no controlada a pesar del tratamiento con CSI o CSI/LABA. Los principales beneficios se observan sobre la función pulmonar, y en el caso de pacientes con asma grave, en la reducción de las exacerbaciones. En los pacientes con asma el tiotropio es por lo general bien tolerado y no se han observado potenciales problemas de seguridad.

Palabras clave: Tratamiento del asma. Anticolinérgicos. Broncodilatadores. Tiotropio.

Background

Asthma is a chronic inflammatory disorder of the airways involving many different cell types and cellular elements. Chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, shortness of breath, chest tightness, and coughing. These episodes are associated with widespread and variable airflow obstruction in the lung, which often resolves spontaneously or is reversed with treatment [1]. There is increasing evidence that asthma is a complex syndrome made up of a number of disease variants known as asthma phenotypes [2].

Current drug treatments for asthma relieve bronchospasm and airway inflammation but do not offer a cure, and symptoms return when treatment is stopped. International asthma management guidelines [1] and Spanish asthma management guidelines [3] emphasize the importance of effective treatment for achieving and maintaining control. Asthma control consists of 2 domains: current impairment or day-to-day asthma control (absence of symptoms, minimal reliever use, and normal activity levels and lung function) and control of future risk (absence of exacerbations, prevention of decline in lung function, and absence of side effects from drugs) [4,5]. Despite widely available and effective treatments and uniform management guidelines [1,2], over half of patients with asthma cannot control their disease effectively and remain at risk of exacerbations [6].

Inhaled corticosteroids (ICSs), whether administered alone or in combination with a long-acting β_2-agonist (LABA), are the mainstay of asthma therapy. Therapy with LABAs improves symptoms in patients whose asthma is poorly controlled using an ICS alone. Despite being prescribed regular maintenance therapy with an ICS or an ICS combined with a LABA, 74% of patients in the INSPIRE study used short-acting β_2-agonists daily, and 51% were classified as having uncontrolled asthma according to the Asthma Control Questionnaire [7]. These data strongly indicate that alternative treatments are needed for patients with uncontrolled asthma.

Current Asthma Therapies and Their Limitations

Bronchodilators target variable airflow obstruction, while corticosteroids target eosinophilic airway inflammation. If eosinophilic airway inflammation is not present, as often occurs in severe asthma, it is unlikely that corticosteroids will be effective [8]. On the other hand, LABAs do not benefit patients with eosinophilic bronchitis who do not show bronchial hyperresponsiveness [9]. In randomized controlled trials, leukotriene-receptor antagonists have been shown to be significantly better than placebo but usually less effective than ICSs, whether alone or in combination with a LABA, for relieving asthma symptoms and improving lung function [10]. Several randomized clinical trials and observational real-world studies have confirmed the long-term efficacy of omalizumab, a monoclonal antibody that binds to IgE, in improving clinical outcomes when added to guideline-recommended maintenance treatment (ICS and LABA) in patients with moderate-to-severe allergic asthma [11]. Its main restrictions are its high cost and the fact that it is limited to a specific subset of patients affected by allergic asthma.

The effectiveness of combining anticholinergics and β_2-agonists has been compared with β_2-agonists alone for the treatment of acute asthma in a systematic review [12]. The results strongly suggest that the addition of multiple doses of inhaled ipratropium bromide to β_2-agonists is indicated as the standard treatment in children, adolescents, and adults with moderate to severe exacerbations of asthma in the emergency setting. In children hospitalized for acute asthma, however, no evidence of benefit in terms of length of hospital stay and other markers of response to therapy was noted when nebulized anticholinergics (ipratropium bromide) were added to short-acting β_2-agonists. These findings support current national and international recommendations indicating that healthcare practitioners should refrain from using anticholinergics in children hospitalized for acute asthma [13].

It is widely accepted that anticholinergics are less effective than β_2-agonists in the symptomatic treatment of chronic asthma [14], although there is considerable variation in treatment effect between patients. A Cochrane systematic review published in 2004 analyzed the effectiveness of short-acting anticholinergic agents (ipratropium bromide) compared with placebo and β_2-agonists or as adjunctive therapy with β_2-agonists for chronic asthma in adults [15]. It found no justification for routinely introducing anticholinergics as part of add-on treatment for patients whose asthma is not well controlled using standard therapies. Nevertheless, at that time, the role of long-acting anticholinergics such as tiotropium bromide had yet to be established in patients with asthma [15].

Improving the clinical course of asthma patients whose condition remains uncontrolled with currently available treatments is a key issue. Bronchial smooth muscle contraction is the primary cause of reversible airway narrowing in asthma, and the baseline level of contraction is predominantly set by the level of cholinergic tone [16]. Thus, adding a second bronchodilator with a different mechanism of action to the treatment of uncontrolled asthma might be a suitable approach.

Adherence is also an important issue in asthma treatment, with rates that are often below 50% and associated with a higher risk of severe exacerbations [17]. The recent incorporation of novel long-acting bronchodilators that require only 1 daily dose has helped to improve adherence considerably and is the regimen preferred by most patients. A variety of β_2-agonists and antimuscarinic agents with longer half-lives and inhalers containing a combination of several classes of long-acting bronchodilators are currently available or under development [18]. Once-daily dosing with a bronchodilator would be very convenient and probably enhance adherence, thus leading to improved clinical outcomes.

Several long-acting muscarinic antagonists (LAMAs) are under investigation or are available for the treatment of obstructive airway diseases. Three LAMAs have been approved for the treatment of chronic obstructive pulmonary disease (COPD) in several European countries, including Spain. The drugs are once-daily tiotropium bromide (Spiriva, Boehringer Ingelheim), once-daily glycopyrronium bromide

(Seebri Breezhaler, Novartis Farmacéutica), and twice-daily aclidinium bromide (Eklira Genuair, Almirall). Several studies recently described the potential use of these treatments in the management of mainly severe forms of asthma. Tiotropium (Spiriva Respimat, Boehringer Ingelheim) was recently approved by the European Medicines Agency as add-on bronchodilator maintenance treatment in adults with asthma who are treated with a combination of an ICS (budesonide ≥800 µg daily or equivalent) and a LABA and who have experienced ≥1 severe asthma exacerbation in the previous year.

This review focuses on the profile of LAMAs, particularly tiotropium, in the treatment of asthma.

The Airway Cholinergic System

Patients with asthma have increased bronchial smooth muscle tone and mucus hypersecretion, possibly as a result of elevated cholinergic activity. Acetylcholine is synthesized from choline and acetyl-CoA mainly by the enzyme choline acetyltransferase expressed in airway epithelial cells, which release acetylcholine [19]. It is the primary parasympathetic neurotransmitter in the airways and a paracrine/autocrine hormone released from nonneuronal origins [20]. The parasympathetic network in the airway wall regulates bronchoconstriction and mucus secretion. Acetylcholine exerts an inflammatory effect by inducing attraction and survival of inflammatory cells, with subsequent cytokine release [21].

The distribution of muscarinic receptors throughout the bronchial tree includes muscarinic M_1, M_2, and M_3 receptors [22,23]. Muscarinic M_1 receptors are expressed by epithelial cells, where they play a modulatory role in electrolyte and water secretion, and in the ganglia, where they facilitate parasympathetic neurotransmission. Muscarinic M_2 receptors are expressed by neurons, where they function as autoreceptors, inhibiting the release of acetylcholine from both preganglionic nerves and from parasympathetic nerve terminals. Muscarinic M_2 autoreceptors are dysfunctional in allergic asthma owing to eosinophil-derived release of major basic protein, which acts as an allosteric antagonist of the M_2 receptor, thus augmenting acetylcholine release. Furthermore, M_2 receptors are widely expressed by airway mesenchymal cells such as fibroblasts and smooth muscle cells [24]. Muscarinic M_3 receptors are probably the best-characterized subtype and the dominant receptor subtype in the regulation of mucus secretion from submucosal glands and airway smooth muscle contraction [24] (Figure 1). As a result, muscarinic M_3 receptors are the primary target for LAMAs. Aclidinium, glycopyrronium, and tiotropium bind to human receptors M_1 to M_5 in a concentration-dependent manner. They all have higher selectivity for M_3 receptors than for M_2 receptors, and dissociate more slowly from M_3 receptors than from M_2 receptors [22,23].

The 3 LAMAs used for the treatment of COPD, as well as tiotropium for asthma, have higher selectivity for M_3 receptors than for M_2 receptors and dissociate more slowly from the M_3 receptors than from the M_2 receptors. Furthermore, anticholinergic compounds may also have anti-inflammatory properties. Some LAMAs show anti-inflammatory effects,
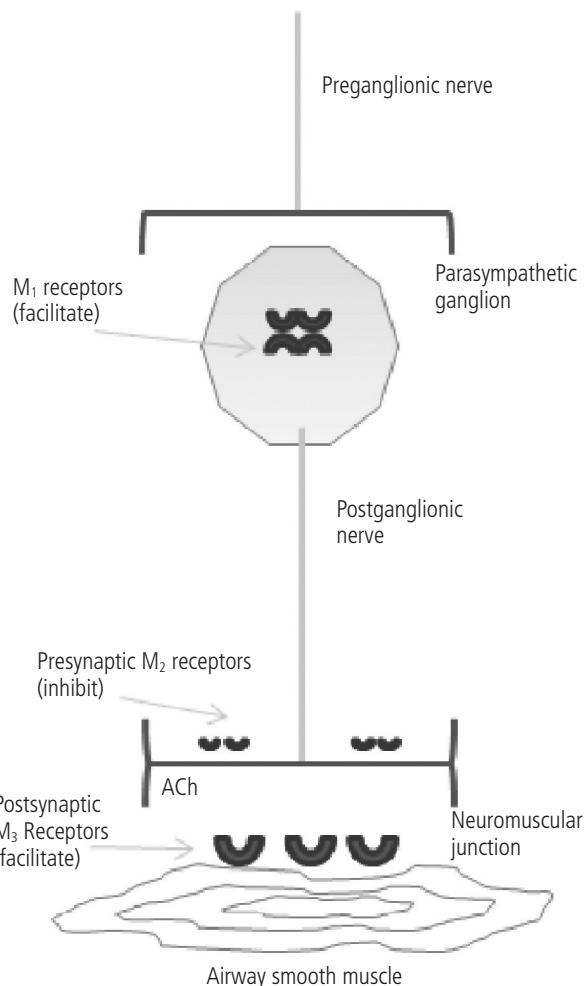
M_1 and M_3 tend to facilitate acetylcholine release. M_2 tends to be inhibitory. Ach indicates acetylcholine; M, muscarinic receptor.

Figure 1. Cholinergic tone results from acetylcholine binding to muscarinic receptors.

namely, inhibition of neutrophil chemotactic activity, migration of alveolar neutrophils, decreased levels of cytokines (IL-6, TNF-α) and leukotriene B_4 in bronchoalveolar lavage fluid, as well as antiremodeling effects, such as inhibition of mucus gland hypertrophy and decrease in MUC5AC-positive goblet cell number [22,23].

Long-Acting Muscarinic Antagonists in Asthma

Anticholinergic drugs are an emergent treatment option in asthma, particularly in cases of suboptimal disease control. Thanks to their bronchodilatory effects, these drugs lessen the risk of adverse effects following high-dose β-agonist treatment [25]. Anticholinergic drugs act as reversible competitive inhibitors of the muscarinic (cholinergic) receptors of acetylcholine, thus reducing secretions and intervening
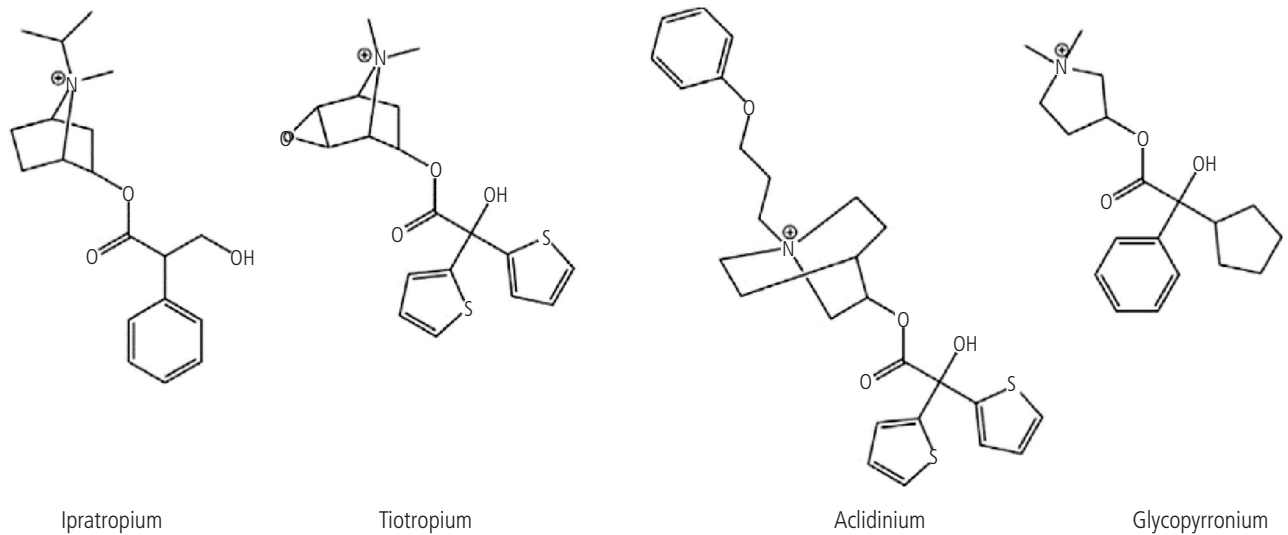
Figure 2. Anticholinergic drugs used for the treatment of COPD and asthma.

in airway remodeling and inflammation [25]. A number of anticholinergic drugs provide therapeutic action over 24 hours. These include tiotropium, aclidinium, and glycopyrronium (Figure 2), although only tiotropium and aclidinium have been studied in relation to asthma therapy [26,27]. Tiotropium acts within 35 minutes [28]. It can be delivered using a Respimat soft mist inhaler (5 μg, 2 puffs of 2.5 μg), an aqueous aerosol formulation, or with a single-dose dry powder inhaler (18 μg) (HandiHaler, Boehringer Ingelheim). Both doses are equivalent. However, the Respimat inhaler releases fine particles, resulting in improved delivery in the lung and possibly higher plasma concentrations [29].

There are some concerns about the safety of regular use of LABAs in patients with asthma [30], particularly among those with a single-nucleotide polymorphism at amino acid 16 (16-Arg/Arg) in the coding region of the *ADRB2* [31]. Since the efficacy and safety of LABAs in asthmatic patients with the 16-Arg/Arg genotype in *ADRB2* has been questioned, antimuscarinics have been proposed as an alternative in patients whose symptoms are not controlled by ICSs.

Tiotropium bromide is a long-acting anticholinergic agent for the treatment of COPD that was recently approved for asthma. Recent findings have increased interest in the use of anticholinergics, especially tiotropium, for the treatment of asthma.

Tiotropium in Moderate Persistent Asthma

Peters et al [32] carried out a 3-way, double-blind, triple-dummy crossover trial involving 210 patients with moderate persistent asthma to compare the addition of tiotropium bromide (HandiHaler 18 μg) to an ICS with doubling the dose of the ICS (primary superiority comparison) or adding salmeterol (secondary noninferiority comparison). The primary outcome of tiotropium was superior to doubling the dose of the ICS (assessed based on morning peak expiratory flow [PEF]), with a mean difference of 25.8 L/min and superiority in most secondary outcomes, including evening PEF, number of asthma

control days, prebronchodilator forced expiratory volume in 1 second (FEV_1), and daily symptom scores. The addition of tiotropium was also noninferior to the addition of salmeterol for all assessed outcomes and increased prebronchodilator FEV_1 more than salmeterol. Thus, when added to an ICS, tiotropium improved symptoms and lung function in patients with uncontrolled asthma, and its effects appeared to be equivalent to those observed with the addition of salmeterol.

In order to further explore the dose-response curve in asthma, Beeh et al [33] investigated the efficacy and safety of 3 different doses of tiotropium (Respimat) as an add-on to an ICS in 149 symptomatic patients with moderate persistent asthma. In this randomized, double-blind, placebo-controlled, 4-way crossover study, patients were randomized to 5 μg, 2.5 μg, or 1.25 μg or placebo once daily in the evening. Each treatment was administered for 4 weeks without a washout between treatment periods. The eligibility criteria included ≥60% and ≤90% of predicted normal FEV_1 and a 7-question mean Asthma Control Questionnaire score of ≥1.5. Patients were required to continue maintenance treatment with stable medium-dose ICS for at least 4 weeks prior to and during the treatment period. LABAs were not permitted during the treatment phase. The primary efficacy endpoint was peak FEV_1 measured within 3 hours after dosing (peak FEV_1, 0-3 hours) at the end of each 4-week period and analyzed as a response (change from study baseline). Statistically significant improvements in peak FEV_1 (0-3 hours) were observed with each dose compared with placebo. The largest difference was with 5 μg (188 mL). Trough FEV_1 and FEV_1 area under the curve (AUC) (0-3 hours) were greater with all 3 doses of tiotropium than with placebo, and both were greatest with 5 μg. Peak forced vital capacity (FVC) (0-3 hours), trough FVC, and FVC AUC (0-3 hours) were significantly greater with 5 μg than with placebo. The incidence of adverse events was comparable between the placebo and the Respimat groups. It was concluded that combining once-daily Respimat with a medium-dose ICS improves lung function

in symptomatic patients with moderate asthma. Overall, the largest improvements were seen with 5 µg.

In their randomized, double-blind, placebo-controlled, incomplete crossover study, Vogelberg et al [34] compared the efficacy and safety profile of 3 once-daily doses of tiotropium (Respimat, 5 µg, 2.5 µg, and 1.25 µg) over 4 weeks with that of placebo in symptomatic asthmatic adolescents who were taking an ICS. The primary efficacy endpoint was change in peak FEV_1 3 hours after taking the drug. Of the 139 patients enrolled, 105 were randomized to receive 1 of 4 treatment sequences. The peak FEV_1 response for tiotropium 5 µg was significantly greater than for placebo. Trough FEV_1 responses were significantly greater for 5 µg and 1.25 µg than for placebo, but not for 2.5 µg, whereas the FEV_1 AUC response was significant for all doses. This first study of tiotropium in adolescents with symptomatic asthma demonstrated that the drug is well tolerated and efficacious as an add-on to maintenance treatment with an ICS.

Tiotropium in Severe Persistent Asthma

A study published in 2009 [35] showed an additional improvement in lung function when tiotropium was added to regular therapy in patients with severe asthma. A total of 138 severe asthmatics on conventional medications and with decreased lung function were recruited. Tiotropium 18 µg (via HandiHaler) was added once a day, and lung function was assessed every 4 weeks. Responders were defined as those with an improvement of ≥15% (or 200 mL) in FEV_1 that was maintained for at least 8 successive weeks. Forty-six of the 138 asthmatics (33.3%) responded to tiotropium. Logistic regression analyses (controlled for age, gender, and smoking status) showed that Arg/Gly in codon 16 of *ADRB2* (gene coding β_2 adrenoreceptor) was significantly associated with response to tiotropium. As many as 30% of patients with severe asthma and reduced lung function receiving conventional medications were found to respond to adjuvant tiotropium. The presence of 16-Arg/Gly in *ADRB2* may predict response to tiotropium.

Bateman et al [36] carried out a double-blind, double-dummy, placebo-controlled trial to compare the efficacy and safety profile of tiotropium (Respimat 5 µg, administered daily in the evening) with that of salmeterol and placebo added to an ICS in 16-Arg/Arg patients with asthma that was not controlled by ICSs alone. The study population comprised patients aged 18 to 67 years with reversibility to bronchodilators and symptoms that were not controlled by regular therapy with an ICS (400-1000 µg of budesonide equivalent maintained throughout the trial). Changes in weekly PEF (primary endpoint) from the last week of the run-in period to the last week of treatment showed that tiotropium was noninferior to salmeterol. The authors found that tiotropium combined with an ICS improved symptoms and lung function in patients with uncontrolled asthma, and its effects appeared to be equivalent to those observed after addition of salmeterol.

It has also been evaluated whether tiotropium might be an effective bronchodilator in patients with severe asthma who remain symptomatic and obstructed despite receiving the maximum recommended doses of the combination of an ICS and a LABA. In a randomized, double-blind, crossover study with three 8-week treatment periods, Kerstjens et al [37] compared the efficacy and safety profile of 2 doses of tiotropium (Respimat, 5 and 10 µg daily) with placebo as add-on therapy in 100 patients with uncontrolled severe asthma despite maintenance treatment with at least a high-dose ICS combined with a LABA. The primary endpoint was peak FEV_1 at the end of each treatment period. Peak FEV_1 was significantly higher with 5 µg and 10 µg of tiotropium than with placebo, whereas there was no significant difference between the active doses. Daily home PEF measurements were higher with both tiotropium doses. Adverse events were balanced across groups except for dry mouth, which was more common in patients taking tiotropium 10 µg. This study shows that the addition of once-daily tiotropium to asthma treatment, including a high-dose ICS combined with a LABA, significantly improves lung function over 24 hours in patients with uncontrolled, severe persistent asthma.

The results of the largest study of tiotropium to date in patients whose asthma was poorly controlled with standard combination therapy were published in 2012 by Kerstjens et al [38]. In 2 replicate, randomized controlled trials involving 912 patients (mean age, 53 years) with asthma who were receiving an ICS and a LABA, the authors compared the effect on lung function and exacerbations of adding tiotropium (Respimat, 5 µg) or placebo once daily for 48 weeks. All the patients were symptomatic, had a postbronchodilator FEV_1 of 80% or less of the predicted value, and had had at least 1 severe exacerbation in the previous year. These patients had a mean baseline FEV_1 of 62% of the predicted value. At 24 weeks, the mean (±SE) change in the peak FEV_1 from baseline was greater with tiotropium than with placebo in the 2 trials: a difference of 86 (34) mL in trial 1 (*P*=.01) and 154 (32) mL in trial 2 (*P*<.001). The predose trough FEV_1 also improved in trials 1 and 2 with tiotropium compared with placebo (a difference of 88 [31] mL [*P*=.01] and 111 [30] mL [*P*<.001], respectively). The addition of tiotropium increased the time to the first severe exacerbation (282 days vs. 226 days), with an overall reduction of 21% in the risk of severe exacerbation (hazard ratio, 0.79; *P*=.03). It was concluded that in patients with poorly controlled asthma despite the use of ICSs and LABAs, the addition of tiotropium significantly increased the time to the first severe exacerbation and provided modest sustained bronchodilation.

In a real-life study, Abodoglu and Berk [39] assessed the effectiveness of tiotropium as an add-on to standard treatment with high-dose ICS/LABA in asthma control and lung function in patients with severe asthma. Of the 633 asthmatic patients recruited, 64 (10.1%) patients with severe asthma who had received add-on treatment for at least 3 months were evaluated. The authors compared the number of exacerbations, emergency department visits, and hospitalizations and the lung function of patients during the 12 months before starting add-on treatment with the 12 months after starting add-on treatment. The mean duration of add-on tiotropium treatment was 8.3 (0.5) months. For patients with severe asthma that was poorly controlled with standard combination therapy, tiotropium improved asthma control in 42.2%, decreased the number of emergency department visits in 46.9%, and decreased the number of hospitalizations in 50.0%. The mean baseline FEV_1 before add-

on tiotropium was 57.5% (1.9%), and FVC was 74.3% (15.6%). However, after 12 months of add-on tiotropium these rates rose to 65.5% (1.9%) and 82.5% (15.1%), respectively. The addition of tiotropium significantly improved the number of emergency department visits and the number of hospitalizations (*P*<.05). These results suggested that in patients with poorly controlled asthma despite ICS/LABA, the addition of tiotropium to standard care may be beneficial.

Systematic Reviews and Meta-analyses

Three studies of the role of tiotropium in patients with asthma were published in 2014 [40-42].

Tian et al [40] performed a meta-analysis to evaluate the efficacy and safety of adding tiotropium to standard treatment regimens for inadequately controlled asthma. The authors reviewed 6 randomized, double-blind clinical trials on the treatment of inadequately controlled asthma for ≥4 weeks with tiotropium compared with placebo. Addition of tiotropium was significantly better than placebo for all spirometric indices, including morning and evening peak expiratory flow (weighted mean difference [WMD], 20.59 L/min [95%CI, 15.36-25.81 L/min], *P*<.001; and WMD 24.95 L/min [95%CI, 19.22-30.69 L/min], respectively *P*<.001), trough and peak FEV_1 (WMD 0.13 L [95%CI 0.09-0.18 L], *P*<.001; and WMD 0.10 L [95%CI, 0.06-0.14 L], respectively *P*<.001), the area under the curve of the first 3 hours of FEV_1 (WMD 0.13 L [95%CI, 0.08-0.18 L], *P*<.001), trough and peak FVC (WMD 0.1 L [95%CI 0.05-0.15 L], *P*<0.001; and WMD 0.08 L [95%CI, 0.04-0.13 L], respectively *P*<.001), and the area under the curve of the first 3 hours of FVC (WMD 0.11 L [95%CI, 0.06-0.15 L], *P*<.001). The mean change in the 7-point Asthma Control Questionnaire score (WMD –0.12 [95%CI, –0.21 to –0.03], *P*=.01) was markedly lower in the tiotropium group, but not clinically relevant. There were no significant differences in the Asthma Quality of Life Questionnaire score, night awakenings, or need for rescue medication. No significant increase was recorded in adverse events in the tiotropium group (OR, 0.80; 95%CI, 0.62-1.03; *P*=.08). It was concluded that the addition of tiotropium to standard treatment regimens significantly improved lung function without increasing the frequency of adverse events in patients with inadequately controlled asthma. Long-term trials are required to assess the effects of adding tiotropium on asthma exacerbations and mortality.

Befekadu et al [41] conducted a systematic review on the effectiveness and safety profile of LAMAs as add-on therapy in patients with uncontrolled asthma despite treatment with ICSs; however, the marked heterogeneity of the study designs precluded statistical pooling of results for a meta-analysis. The 5 clinical studies included in this systematic review focused on evaluating the efficacy of tiotropium as add-on therapy with an ICS or an ICS in combination with a LABA in patients with uncontrolled moderate to severe persistent asthma. Tiotropium maintained lung function when ICSs were tapered and when a LABA was discontinued. Tiotropium improved lung function when added to an ICS alone or in combination with a LABA. In the only trial to have compared the addition of tiotropium with doubling the dose of the ICS, tiotropium provided significantly superior results. In trials in which the addition of tiotropium was compared with salmeterol, the beneficial effects of both

bronchodilators were similar. The authors concluded that tiotropium could have a beneficial role in moderate to severe persistent asthma despite use of an ICS or an ICS combined with a LABA. Tiotropium as add-on therapy poses no safety concerns.

The efficacy and safety of tiotropium in asthma patients was evaluated in the recent systematic review and meta-analysis by Rodrigo and Castro-Rodríguez [42]. Primary outcomes were peak and trough FEV_1 and morning and evening PEF. Thirteen studies (4966 patients) were included, and 3 different therapeutic protocols were identified. Tiotropium used as an add-on to an ICS showed statistically and clinically significant increases in PEF (22-24 L/min) and FEV_1 (140-150 mL). Furthermore, tiotropium decreased the rate of exacerbations (number needed to treat for benefit, 36) and improved asthma control. Tiotropium administered to patients whose disease was poorly controlled despite the use of medium to high doses of ICSs was not inferior to salmeterol. Finally, tiotropium as an add-on in the combination ICS/salmeterol produced a clinically significant improvement in pulmonary function, reduced asthma exacerbations (relative risk, 0.70; 95%CI, 0.53-0.94 [*P*<.02]; number needed to treat for benefit, 17), and improved asthma control compared with ICS/salmeterol. Therefore, tiotropium was noninferior to salmeterol and superior to placebo in patients with moderate to severe asthma whose disease was not adequately controlled with an ICS or ICS/salmeterol. The major benefits were improved lung function and, in the case of severe asthmatics, reduced frequency of exacerbations.

Predictors of Response to Anticholinergics

Attempts to identify subgroups that respond better to anticholinergics have not been very successful. Notwithstanding, several years ago it was reported that anticholinergics may be better in the following groups: older patients [14], patients intolerant to ß2-agonists, patients with nocturnal asthma, patients with chronic asthma and concurrent fixed airway obstruction, patients with intrinsic asthma, and patients with a longer duration of asthma [14,43].

More recently, Peters et al [44] examined the individual and differential responses of asthmatic patients to salmeterol and tiotropium when added to an ICS, as well as predictors of a positive clinical response. Data from the double-blind, 3-way, crossover trial were analyzed for individual and differential treatment responses to salmeterol and tiotropium and predictors of a positive response to the endpoints FEV_1, morning PEF, and asthma control days. Although approximately equal numbers of patients showed a differential response to salmeterol and tiotropium in terms of morning PEF (n=90 and 78, respectively) and asthma control days (n=49 and 53, respectively), more showed a differential response to tiotropium for FEV_1 (n=104) than to salmeterol (n=62). An acute response to a short-acting bronchodilator, especially salbutamol, predicted a positive clinical response to tiotropium for FEV_1 (OR, 4.08; 95%CI, 2.00-8.31; *P*<.001) and morning PEF (OR, 2.12; 95%CI, 1.12-4.01; *P*=.021), as did a decreased FEV_1/FVC ratio (FEV_1 response increased 0.39% of baseline for every 1% decrease in FEV_1/FVC ratio). Higher cholinergic tone was also a predictor, whereas ethnicity, sex, atopy, IgE level, sputum eosinophil count, fraction of exhaled nitric oxide, asthma duration,

and body mass index were not. The authors concluded that, although these results require confirmation, predictors of a positive clinical response to tiotropium include a positive response to salbutamol and airway obstruction, factors that could help identify appropriate patients for this therapy.

The possible differences in responsiveness to anticholinergics between different patient groups illustrate the heterogeneous nature of asthma, which is further compounded by the overlap between asthma and COPD. At one end of the spectrum are patients whose airflow limitation shows marked spontaneous fluctuations and improves considerably with treatment (asthma). At the other end are patients whose disease fluctuates to a very limited extent and is irreversible. Whilst an improvement of greater than 12% after inhaling a short-acting ß2-agonist indicates some degree of reversibility, any such figure is inevitably arbitrary in a spectrum of airway disease ranging from reversible to irreversible. Clinical features (eg, age, nature of symptoms, atopic status, and smoking history) play a key role in diagnosis. The overlap between asthma and COPD is important in the case of anticholinergics, which could have a small but proportionately greater effect than ß2-agonists in patients with COPD.

Safety

The relative safety of ß2-agonists and anticholinergics is an important area, since the former can increase heart rate and have been associated with increased bronchial activity and increased mortality [45]. In comparison, anticholinergics have relatively few side effects.

Dry mouth was the most commonly reported adverse event in a meta-analysis [46] performed in patients aged ≥40 years with stable COPD (16 trials and 16 301 patients). The cumulative incidence was 7.4% with tiotropium and 2.0% with placebo. When tiotropium was compared with placebo, the summary odds estimate for the number of patients who experienced a serious adverse event was not statistically significant [46]. A meta-analysis performed in 2011 [47] in patients with COPD investigated the safety profile of 5 randomized controlled trials (n=6522) comparing tiotropium with placebo. The tiotropium inhaler was associated with a significantly increased risk of mortality. Another meta-analysis examined 42 randomized controlled trials (n=52 516) of tiotropium (2 formulations), LABAs, ICSs, and combined LABA and ICS after a period of at least 6 months [48]. One formulation of tiotropium was associated with a universally increased risk of overall death compared with placebo (OR, 1.51; 95%CI, 1.06-2.19), the other tiotropium formulation (OR, 1.65; 95%CI, 1.13-2.43), LABAs (OR, 1.63; 95%CI, 1.10–2.44), and LABAs with ICSs (OR, 1.90; 95%CI, 1.28-2.86). The risk was clear for cardiovascular death in patients with severe COPD who were taking a higher daily dose.

In a more recent randomized, double-blind, parallel-group trial, TIOSPIR [49], involving 17 135 patients with COPD, 10% had stable and non–life-threatening arrhythmia and 15% had ischemic heart disease, which was treated with tiotropium (inhaler) 18 µg once daily, tiotropium 5 µg once daily, or tiotropium 2.5 µg once daily. The authors evaluated the risk of death (noninferiority study, tiotropium at 5 or 2.5 µg vs

tiotropium 18 µg) and found that tiotropium 5 or 2.5 µg was noninferior to tiotropium 18 µg with respect to the risk of death (5 µg vs 18 µg: HR, 0.96 [95%CI, 0.84-1.09]; 2.5 µg vs 18 µg: HR, 1.00 [95%CI, 0.87-1.14]) and that tiotropium 2.5 µg or 5 µg was not associated with higher mortality than tiotropium 19 µg in patients with previous heart disease, including stable arrhythmias at baseline, and that it was not associated with a higher incidence of arrhythmias. There were no significant differences between the 3 study groups in terms of SAEs and nonfatal and fatal major cardiovascular adverse events. The limitations of this study were the absence of a placebo group and the exclusion of patients with unstable cardiovascular conditions (myocardial infarction within the previous 6 months, hospitalization for class III or IV heart failure, and unstable or life-threatening arrhythmia) or moderate or severe renal impairment. Therefore, the study findings cannot be extended to these populations.

The findings presented above indicate that tiotropium (Respimat) may be prescribed to patients with COPD and good tolerance, even in the case of stable ischemic heart disease or stable non–life-threatening arrhythmias. However, tiotropium (Respimat) should not be prescribed in cases of unstable ischemic heart disease and unstable or life-threatening cardiac arrhythmia.

A meta-analysis of 6 studies revealed no statistically significant increase in the total number of adverse events with tiotropium as compared with placebo in patients with asthma [40]. Exacerbations and PEF decreased markedly in the tiotropium group. There was no statistically significant difference in SAEs between the 2 groups [40]. No deaths were recorded in the large studies of Kerstjens et al [38] in patients with uncontrolled severe asthma, and adverse events were similar in the placebo and tiotropium groups. In their systematic review, Befekadu et al [41] found no safety concerns with tiotropium as add-on therapy, and in the meta-analysis by Rodrigo and Castro-Rodríguez [42], tiotropium was well tolerated, and no potential safety signals were observed.

Costs

Asthma is associated with enormous healthcare expenditure. This includes both direct costs, in the form of hospitalizations and medications, and indirect costs, in the form of loss of work, which is a combination of directly missed days of work/school during the exacerbation and the loss of future potential earnings associated with morbidity and mortality. Despite the availability of effective preventive therapy, costs associated with asthma are increasing [50]. The comparison of studies assessing direct and indirect costs of asthma yields important observations. Hospitalization and medications are the most important drivers of direct costs, while work/school absenteeism accounts for the greatest percentage of indirect costs [50,51]. The costs of asthma depend on disease severity and the extent to which exacerbations are avoided or controlled [52,53]. Patients with difficult-to-treat or suboptimally controlled asthma consume a large part of asthma health care resources [52,53].

A study published by Willson et al [54] based on a Markov model from the perspective of the British national health

system, showed that the addition of tiotropium to the regular treatment of patients with uncontrolled asthma with high-dose ICS/LABA to result in 0.24 quality-adjusted life-years gained, which, assuming a cost of £5238, implied an incremental cost-effectiveness ratio of £21 906 per quality-adjusted life-year gained. The results were found to be highly dependent upon the management of uncontrolled asthma and the direct cost of tiotropium. In any case, additional studies are needed to further clarify the cost-effectiveness of tiotropium in asthmatic patients.

Concluding Remarks

Available evidence indicates that tiotropium can be considered a maintenance medication for patients with asthma that is not well controlled with ICSs with or without LABAs. The most plausible indication for tiotropium in asthma therapy is moderate-severe asthma not adequately controlled by ICS/LABA, particularly if the patient has fixed airflow obstruction and/or frequent severe exacerbations. However, ascertaining the precise role of tiotropium (and other LAMAs) in standard asthma therapy warrants additional efficacy and safety trials. Moreover, further studies evaluating the efficacy of tiotropium in children with asthma, particularly in those younger than 12 years, are expected. It would be very interesting to identify which subgroups of asthma patients or clinical phenotypes could benefit from anticholinergics, including more pharmacogenomic studies to clarify whether asthma patients with single-nucleotide polymorphisms could benefit more from adding a LABA or a LAMA to therapy with an ICS.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. GINA$_{2014}$. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention 2014. Available from www.ginasthma.org
2. Wenzel SE. Complex phenotypes in asthma: current definitions. Pulm Pharmacol Ther. 2013;26:710-5.
3. Executive Committee GEMA 2009. GEMA 2009 (Spanish guideline on the management of asthma). J Investig Allergol Clin Immunol. 2010;20 Suppl 1:1-59.
4. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, Casale TB, Chanez P, Enright PL, Gibson PG, de Jongste JC, Kerstjens HA, Lazarus SC, Levy ML, O'Byrne PM, Partridge MR, Pavord ID, Sears MR, Sterk PJ, Stoloff SW, Sullivan SD, Szefler SJ, Thomas MD, Wenzel SE. An official American Thoracic Society/European Respiratory Society statement: Asthma control and exacerbations. Standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med. 2009;180:59-99.
5. Bateman ED, Reddel HK, Eriksson G, Peterson S, Ostlund O, Sears MR, Jenkins C, Humbert M, Buhl R, Harrison TW, Quirce S, O'Byrne PM. Overall asthma control: the relationship between current control and future risk. J Allergy Clin Immunol. 2010;125:600-8.
6. Olaguibel JM, Quirce S, Juliá B, Fernández C, Fortuna AM, Molina J, Plaza V; MAGIC Study Group. Measurement of asthma control according to Global Initiative for Asthma guidelines: a comparison with the Asthma Control Questionnaire. Respir Res. 2012;13:50.
7. Partridge MR, van der Molen T, Myrseth SE, Busse WW. Attitudes and actions of asthma patients on regular maintenance therapy: the INSPIRE study. BMC Pulm Med. 2006;6:13.
8. Berry M, Morgan A, Shaw DE, Parker D, Green R, Brightling C, Bradding P, Wardlaw AJ, Pavord ID. Pathological features and inhaled corticosteroid response of eosinophilic and non-eosinophilic asthma. Thorax. 2007;62:1043-9.
9. Sastre B, Fernández-Nieto M, Mollá R, López E, Lahoz C, Sastre J, del Pozo V, Quirce S. Increased prostaglandin E2 levels in the airway of patients with eosinophilic bronchitis. Allergy. 2008;63:58-66.
10. Dahlén SE. Treatment of asthma with antileukotrienes: first line or last resort therapy? Eur J Pharmacol. 2006;533:40-56.
11. Kuhl K, Hanania NA. Targeting IgE in asthma. Curr Opin Pulm Med. 2012;18:1-5.
12. Rodrigo GJ, Castro-Rodriguez JA. Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis. Thorax. 2005;60:740-6.
13. Vézina K, Chauhan BF, Ducharme FM. Inhaled anticholinergics and short-acting beta2-agonists versus short-acting beta2-agonists alone for children with acute asthma in hospital. Cochrane Database Syst Rev. 2014 Jul 31;7:CD010283.
14. Cazzola M, Centanni S, Donner CF. Anticholinergic agents. Pul Pharmacol Ther. 1998;11:381-92.
15. Westby M, Benson M, Gibson P. Anticholinergic agents for chronic asthma in adults. Cochrane Database Syst Rev. 2004;(3):CD003269.
16. Price D, Fromer L, Kaplan A, van der Molen T, Román-Rodríguez M. Is there a rationale and role for long-acting anticholinergic bronchodilators in asthma? NPJ Prim Care Respir Med. 2014;24:14023.
17. Engelkes M, Janssens HM, de Jongste JC, Sturkenboom MC, Verhamme KM. Medication adherence and the risk of severe asthma exacerbations: a systematic review. Eur Respir J. 2014 Oct 16. pii: erj00756-2014.
18. Quirce S, Bobolea I, Barranco P. Emerging drugs for asthma. Expert Opin Emerg Drugs. 2012;17:219-37.
19. Proskocil BJ, Sekhon HS, Jia Y, Savchenko V, Blakely RD, Lindstrom J, Spindel ER. Acetylcholine is an autocrine or paracrine hormone synthesized and secreted by airway bronchial epithelial cells. Endocrinology. 2004;145:2498-506.
20. Grando SA, Kawashima K, Kirkpatrick CJ, Meurs H, Wessler I. The non-neuronal cholinergic system: basic science, therapeutic implications and new perspectives. Life Sci. 2012;91(21-22):969-72.
21. Racké K, Matthiesen S. The airway cholinergic system: physiology and pharmacology. Pulm Pharmacol Ther. 2004;17:181-98.

22. Alagha K, Palot A, Sofalvi T, Pahus L, Gouitaa M, Tummino C, Martinez S, Charpin D, Bourdin A, Chanez P. Long-acting muscarinic receptor antagonists for the treatment of chronic airway diseases. Ther Adv Chronic Dis. 2014;5:85-98.

23. Perpiñá Tordera M. Anticolinérgicos en el asma. Espacio Asma. 2011;4:70-5.

24. Gosens R, Zaagsma J, Meurs H, Halayko AJ. Muscarinic receptor signaling in the pathophysiology of asthma and COPD. Respir Res. 2006;7:73.

25. Antoniu SA, Antohe I. Evaluation of inhaled tiotropium in asthma uncontrolled with standard combination therapy. Expert Opin Pharmacother. 2013;14:967-9.

26. Albertson TE, Schivo M, Gidwani N, Kenyon NJ. Pharmacotherapy of critical asthma syndrome: current and emerging therapies. Clin Rev Allergy Immunol. 2013; Nov 2. [Epub ahead of print]

27. Antoniu SA. Aclidinium bromide in experimental asthma. Expert Opin Investig Drugs. 2011;20:871-3.

28. Guyer AC, Long AA. Long-acting anticholinergics in the treatment of asthma. Curr Opin Allergy Clin Immunol. 2013;13:392-8.

29. Adams KS, Lowe DK. Tiotropium for adults with inadequately controlled persistent asthma. Ann Pharmacother. 2013;47:117-23.

30. Chowdhury BA, Dal Pan G. The FDA and safe use of long-acting beta-agonists in the treatment of asthma. N Engl J Med. 2010;362:1169-71.

31. Kazani S, Israel E. Long-acting beta-agonists and inhaled corticosteroids: is the whole greater than the sum of its parts? J Allergy Clin Immunol. 2010;125:357-8.

32. Peters SP, Kunselman SJ, Icitovic N, Moore WC, Pascual R, Ameredes BT, Boushey HA, Calhoun WJ, Castro M, Cherniack RM, Craig T, Denlinger L, Engle LL, DiMango EA, Fahy JV, Israel E, Jarjour N, Kazani SD, Kraft M, Lazarus SC, Lemanske RF Jr, Lugogo N, Martin RJ, Meyers DA, Ramsdell J, Sorkness CA, Sutherland ER, Szefler SJ, Wasserman SI, Walter MJ, Wechsler ME, Chinchilli VM, Bleecker ER. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. N Engl J Med. 2010;363:1715-26.

33. Beeh KM, Moroni-Zentgraf P, Ablinger O, Hollaenderova Z, Unseld A, Engel M, Korn S. Tiotropium Respimat® in asthma: a double-blind, randomised, dose-ranging study in adult patients with moderate asthma. Respir Res. 2014;15:61.

34. Vogelberg C, Engel M, Moroni-Zentgraf P, Leonaviciute-Klimantaviciene M, Sigmund R, Downie J, Nething K, Vevere V, Vandewalker M. Tiotropium in asthmatic adolescents symptomatic despite inhaled corticosteroids: a randomised dose-ranging study. Respir Med. 2014;108:1268-76.

35. Park HW, Yang MS, Park CS, Kim TB, Moon HB, MinKU, KimYY, Cho SH. Additive role of tiotropium in severe asthmatics and Arg16Gly in ADRB2 as a potential marker to predict response. Allergy. 2009;64:778-83

36. Bateman ED, Kornmann O, Schmidt P, Pivovarova A, Engel M, Fabbri LM. Tiotropium is noninferior to salmeterol in maintaining improved lung function in 16-Arg/Arg patients with asthma. J Allergy Clin Immunol. 2011;128:315-22.

37. Kerstjens HA, Disse B, Schröder-Babo W, Bantje TA, Gahlemann M, Sigmund R, Engel M, van Noord JA. Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial. J Allergy Clin Immunol. 2011;128:308-14.

38. Kerstjens HA, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, Sigmund R, Seibold W, Moroni-Zentgraf P, Bateman ED. Tiotropium in asthma poorly controlled with standard combination therapy. N Engl J Med. 2012;367:1198-207.

39. Abadoglu O, Berk S. Tiotropium may improve asthma symptoms and lung function in asthmatic patients with irreversible airway obstruction: The real life data. Clin Respir J. 2014 Oct 22. doi: 10.1111/crj.12230. [Epub ahead of print]

40. Tian JW, Chen JW, Chen R, Chen X. Tiotropium versus placebo for inadequately controlled asthma: a meta-analysis. Respir Care. 2014;59:654-66.

41. Befekadu E, Onofrei C, Colice GL. Tiotropium in asthma: a systematic review. J Asthma Allergy. 2014;7:11-21.

42. Rodrigo GJ, Castro-Rodríguez JA. What is the role of tiotropium in asthma? A systematic review with meta-analysis. Chest. 2015;147:388-96.

43. Boulet L-P, Becker A, Berube D, Beveridge R, Ernst P. Summary of recommendations from the Canadian Asthma Consensus Report 1999. Canadian Medical Association Journal. 1999;161(11 Suppl):S1-S12.

44. Peters SP, Bleecker ER, Kunselman SJ, Icitovic N, Moore WC, Pascual R, Ameredes BT, Boushey HA, Calhoun WJ, Castro M, Cherniack RM, Craig T, Denlinger LC, Engle LL, Dimango EA, Israel E, Kraft M, Lazarus SC, Lemanske RF Jr, Lugogo N, Martin RJ, Meyers DA, Ramsdell J, Sorkness CA, Sutherland ER, Wasserman SI, Walter MJ, Wechsler ME, Chinchilli VM, Szefler SJ. Predictors of response to tiotropium versus salmeterol in asthmatic adults. J Allergy Clin Immunol. 2013;132:1068-74. e1.

45. Beasley R, Martinez FD, Hackshaw A, Rabe KF, Sterk PJ, Djukanovic R. Safety of long-acting beta-agonists: urgent need to clear the air remains. Eur Respir J. 2009;33:3-5.

46. Yohannes AM, Willgoss TG, Vestbo J. Tiotropium for treatment of stable COPD: a meta-analysis of clinically relevant outcomes. Respir Care. 2011;56:477-87.

47. Singh S, Loke YK, Enright PL, Furberg CD. Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials. BMJ. 2011;342:d3215.

48. Dong YH, Lin HH, Shau WY, Wu YC, Chang CH, Lai MS. Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: systematic review and mixed treatment comparison meta-analysis of randomised controlled trials. Thorax. 2013;68:48-56.

49. Wise RA, Anzueto A, Cotton D, Dahl R, Devins T, Disse B, Dusser D, Joseph E, Kattenbeck S, Koenen-Bergmann M, Pledger G, Calverley P; TIOSPIR Investigators. Tiotropium Respimat inhaler and the risk of death in COPD. N Engl J Med. 2013;369:1491-501.

50. Bahadori K, Doyle-Waters MM, Marra C, Lynd L, Alasaly K, Swiston J, FitzGerald JM. Economic burden of asthma: a systematic review. BMC Pulm Med. 2009;9:24.

51. Ojeda P, Sanz de Burgoa V; Coste Asma Study. Costs associated with workdays lost and utilization of health care resources

because of asthma in daily clinical practice in Spain. J Investig Allergol Clin Immunol. 2013;23:234-41.

52. Martínez-Moragón E, Serra-Batlles J, De Diego A, Palop M, Casan P, Rubio-Terrés C, Pellicer C. Economic cost of treating the patient with asthma in Spain: the AsmaCost Study. Arch Bronconeumol. 2009;45:481-6.

53. Accordini S, Corsico AG, Braggion M, Gerbase MW, Gislason D, Gulsvik A, Heinrich J, Janson C, Jarvis D, Jõgi R, Pin I, Schoefer Y, Bugiani M, Cazzoletti L, Cerveri I, Marcon A, de Marco R. The cost of persistent asthma in Europe: an international population-based study in adults. Int Arch Allergy Immunol. 2013;160:93-101.

54. Willson J, Bateman ED, Pavord I, Lloyd A, Krivasi T, Esser D. Cost effectiveness of tiotropium in patients with asthma poorly controlled on inhaled glucocorticosteroids and long-acting B-agonists. Appl Health Econ Health Policy. 2014;12:447-59.

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