

Tiotropium in the add-on treatment of asthma in adults: clinical trial evidence and experience

Christian Vogelberg

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Abstract: Asthma is a chronic inflammatory airway disease, and its treatment is frequently challenging despite detailed national and international guidelines. While basic anti-inflammatory therapy usually consists of inhaled corticosteroids in doses adapted to the asthma severity, add-on treatment with bronchodilators is essential in more severe asthma. Only recently, the long-acting anticholinergic tiotropium was introduced into the GINA guidelines. This review reports on the studies that have been performed with tiotropium in adult asthmatic patients. Following early proof-of-concept studies, several studies with tiotropium as an add-on therapy to inhaled corticosteroids (ICS), with or without a long-acting beta agonist (LABA), demonstrated convincing clinical benefit for patients. Important lung function parameters and quality of life scores significantly improved shortly after onset of the add-on therapy with tiotropium, and some studies even demonstrated non-inferiority against salmeterol. All studies reported an excellent safety profile of tiotropium. The still growing body of tiotropium studies, both in adults and children, will help to identify the position of tiotropium in future asthma guidelines and might also indicate which patients benefit most from an add-on therapy with tiotropium.

Keywords: asthma, bronchodilator, inhaled anticholinergic agent, long-acting muscarinic receptor antagonist, tiotropium

Introduction

Asthma is one of the leading causes of morbidity worldwide, with up to 18% of the population affected [GINA, 2016]. The economic burden of asthma is tremendous, at €19 billion in Europe alone [Dominguez-Ortega *et al.* 2015]. According to common guidelines, the initial treatment of asthma consists of inhaled corticosteroids (ICS) with the option of increasing the dose or to add on a long-acting beta agonist (LABA) in case of a persistent lack of asthma control. However, up to 40% of asthma patients remain symptomatic despite undergoing treatment modification, which suggests a need for additional treatment alternatives beside leukotriene modifiers (LTRA), systemic corticosteroids, anti-immunoglobulin (Ig)E or methylxanthines [Rabe *et al.* 2004].

Short-acting anticholinergic substances such as ipratropium bromide in add-on therapy with

β_2 -agonists and ICSs have demonstrated a dose-dependent effect on hospital admission rates and pulmonary function parameters, both in children and adults [Rodrigo and Castro-Rodriguez, 2005]. Due to their lesser bronchodilatory potency and their short duration of action, their main therapeutic benefit may remain in managing an acute asthma exacerbation [Rodrigo and Rodrigo, 2002]. However, the release of acetylcholine has an influence on both bronchial tone and airway inflammation. Acetylcholine leads to contraction and proliferation of airway smooth muscles, mucus secretion, vasodilation and release of pro-inflammatory mediators by airway epithelial cells [Quizon *et al.* 2012]. Pretreatment with tiotropium results in prevention of allergen-induced airways smooth muscle thickening, mucous gland hypertrophy, interleukin (IL)-13-induced goblet cell metaplasia and eosinophilic inflammation in animal models [Kistemaker and

Correspondence to:
Christian Vogelberg, MD, PhD
University Hospital Carl Gustav Carus, Department of Pediatric Pulmonology and Allergology, Fetscherstr. 74, 01307 Dresden, Germany
christian.vogelberg@uniklinikum-dresden.de

Table 1. Effects of acetylcholine in the pathophysiology of asthma mediated by type 3 muscarinic receptors (modified from [Kistemaker and Gosens, 2015]).

Asthma relevant changes	Cells
Smooth muscle cell thickening	Smooth muscle cell
Mucus secretion	Epithelial cell, submucosal gland
Proliferation of fibroblasts	Fibroblast
Extracellular matrix production	Fibroblast
Th2 cytokine release	Macrophage, lymphocyte, neutrophil
Airway remodeling	Smooth muscle cell

Gosens, 2015]. This effect seems to be mediated primarily by blocking the type 3 muscarinic receptor (M3) (Table 1). While acknowledging these contributions to the pathophysiology of asthma, a long-acting anticholinergic agent might provide a more sustained therapeutic effect compared with the short-acting anticholinergic substances, and might therefore represent an alternative controller as an add-on to ICSs.

Actually, three long-acting anticholinergic substances are approved for the treatment of COPD: glycopyrrolate, umeclidinium and tiotropium. Glycopyrrolate prolonged bronchodilation and bronchoprotection compared with ipratropium and placebo in a proof-of-concept study [Hansel *et al.* 2005], but further studies are only in preparation. A recently published dose–effect study of umeclidinium in asthmatic patients not treated by ICS did not support a therapeutic benefit [Lee *et al.* 2015a]. However, another study investigating the effect of add-on umeclidinium to ICS *versus* ICS + LABA or ICS alone demonstrated an improvement of trough forced expiratory volume in 1 second (FEV₁) and morning and evening peak expiratory flow (PEF) compared with ICS alone [Lee *et al.* 2015b]. Patients with fixed bronchial obstruction showed the greatest benefit. Tiotropium has been approved for the indication of chronic obstructive pulmonary disease for more than 10 years. With a maximum effect after 30–60 minutes, cholinergic transmission is blocked for around 35 hours, which enables a once-daily admission. Although tiotropium also binds to M1 and M2 receptors, it dissociates more slowly from the M3 receptor. Within recent years, a systematic study program on the therapeutic effects of tiotropium with respect to the indication of asthma was added to preliminary studies. As a result of these studies, tiotropium bromide has recently been included into the revised Global Initiative for Asthma (GINA)

2015 strategy as an alternative add-on therapy, at steps 4 and 5, in adult patients with a history of exacerbations [GINA, 2016], and the label of tiotropium has been extended to include asthma by governing drug organizations. This article summarizes the major results of tiotropium in the treatment of asthma in adult patients.

Proof-of-concept studies

A first, preliminary, double-blind, placebo-controlled study investigated the duration of protection of three different single doses of tiotropium (10, 40, and 80 µg), inhaled with a dry powder inhaler, against methacholine-induced bronchoconstriction in 12 male asthmatic patients [O'Connor *et al.* 1996]. The main result was that the authors could demonstrate a significant dose-dependent protection against methacholine challenge lasting for 48 hours, and a mild bronchodilating effect for up to 25 hours.

A further placebo-controlled methacholine provocation study in 10 asthmatic patients confirmed the effect of a single inhalation of tiotropium. A dose of 18 µg of tiotropium inhaled with the Spiriva HandiHaler resulted in significant protection, even with a maximum methacholine dose of 1600 µg and only 30 minutes after administration [Terzano *et al.* 2004]. Although the number of patients was low in both preliminary studies, the results are important, because they demonstrated significant and sustained protection against methacholine challenge with once daily inhalation of tiotropium and an early onset of action. Compared with a pretreatment dose of 40 µg ipratropium, 18 µg of tiotropium led to a significantly higher bronchoprotective effect after standardized methacholine provocation in 44 patients with intermittent asthma 60 minutes after the time of inhalation; the effect of tiotropium was comparable with oxitropium in this study [Sposato *et al.* 2008].

Again, 18 µg of tiotropium, added once daily to salmeterol and fluticasone in 25 severely asthmatic patients, provided significant improvement of lung function after reducing the ICS to half of the dose for 4 weeks. However, no influence on quality of life or symptoms could be demonstrated [Fardon *et al.* 2006]. Nevertheless, this preliminary study was important, because it demonstrated for the first time the potential of a combined add-on therapy of salmeterol and tiotropium to improve lung function despite a steroid-sparing treatment adjustment in severe asthmatic patients.

A few of these early proof-of-concept studies focussed on subgroups of severely asthmatic patients, who might benefit most from tiotropium inhalation. A Japanese study with a limited number of 17 asthmatic patients on high-dose ICS showed significant improvement of FEV₁ after 4 weeks of treatment. Those patients with predominantly neutrophilic-induced sputum responded better compared with those with a higher sputum eosinophilic level [Iwamoto *et al.* 2008]. Major limitations of this study were the small number of patients and the lack of a placebo arm. About 33% of 138 severely asthmatic patients from Korea, who inhaled 18 µg of tiotropium once daily for 12 weeks in addition to a high-dose ICS plus LABA, responded to the therapy (with an improvement of FEV₁ ≥ 15% or ≥200 ml for ≥8 weeks). Significantly, the presence of Arg16Gly polymorphism in ADRB2 was associated with a response to tiotropium [Park *et al.* 2009]. Again, as a consequence of the small sample size and the lack of a placebo arm, the effect of other confounding factors on the results, especially the ethnicity of the patients, is difficult to estimate.

Tiotropium add-on to ICS placebo-controlled studies

The Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid (TALC) study was the first larger and sufficiently powered study to test the add-on treatment effect of tiotropium in inadequately controlled asthmatic patients [Peters *et al.* 2010] (Table 2 displays the major results of all placebo-controlled and published trials). In this three-way, double-blind, triple-dummy crossover trial, 210 adult asthmatics (age 42.2 ± 12.3 yrs.) with uncontrolled asthma, who were uncontrolled despite having 160 µg of

beclomethasone administered daily, were included, and 174 finished the trial. Patients were eligible to proceed with the trial if, after the 4-week run-in period, the FEV₁ was 70% or less of the predicted value; or if, during the last two weeks of the run-in period, they had symptoms on ≥6 days/week, or needed rescue inhalation on ≥6 days/week, or on ≥2 nights/week with awakening due to asthmatic symptoms. Every patient completed three treatment periods, each for 14 weeks, followed by wash-out periods of 2 weeks in between. The add-on therapy with 18 µg of tiotropium, added to the ICS, was compared with doubling the dose of ICS and the add-on of 50 µg of salmeterol twice daily to the ICS. Add-on inhalation with tiotropium resulted in a higher increase in the morning PEF as the primary outcome parameter compared with doubling the dose of ICS (mean difference of 25.8 l/min, $p < 0.001$). Furthermore, tiotropium add-on therapy resulted in superiority in most secondary outcome parameters (evening PEF, mean difference of 35.3 l/min, $p < 0.001$; proportion of asthma control days, mean difference of 0.079, $p = 0.01$; FEV₁ before bronchodilation, mean difference of 0.10 l, $p = 0.004$; daily symptom scores, mean difference of -0.11 points, $p < 0.001$) compared with doubling the dose of ICS, and was non-inferior to add-on salmeterol. An analysis of the individual and differential responses of the asthmatic patients to salmeterol and tiotropium showed that an acute response, especially to albuterol, predicted a positive response to tiotropium for the improvement of FEV₁ and PEF [odds ratio (OR) 4.08, $p < 0.001$ and 2.12, $p = 0.021$, respectively] [Peters *et al.* 2013]. A decreased FEV₁/forced vital capacity (FVC) ratio and a higher cholinergic tone were further predictors of the clinical response to tiotropium, while other parameters such as sex, ethnicity, IgE level, sputum eosinophil count, fraction of exhaled nitric oxide, asthma duration, and body mass index showed no influence. The studies might be criticized because of the choice of PEF as the primary outcome parameter for asthma control, the relatively short treatment periods and therefore, the lack of long-term safety data. However, the two major findings, the superiority of add-on tiotropium compared with doubling the dose of ICS, and the non-inferiority to salmeterol are relevant for the grading of tiotropium within the different treatment options for asthma.

The asthma studies that followed after the TALC study were all performed with the RespiMat

Table 2. Summary of placebo-controlled tiotropium studies in asthmatic patients.

Study	Design	Asthma severity	Standard therapy (µg) LABA	ICS	Tiotropium (µg)	Duration (week)	Randomized patients	Primary outcome parameter	Intervention	Results	Safety
[Fardon <i>et al.</i> 2006]	R, DB, PC, CO	Severe	2 × 125 FP BD	25 SM BD	18 od	4	18	N/A	FP 500 µg + SM versus FP 500 µg + SM + T10	Improvement of FEV ₁ , PEF, FVC, no change in symptoms or QOL	N/A
[Peters <i>et al.</i> 2010]	R, DB, PC, CO	Moderate	2 × 40 or 2 × 80 BM BD	50 BD	18 od	14	210	Morning PEF	BM 160 µg + T10 versus BM 160 µg + SM versus BM 320 µg	T10 superior to double dose BM, non-inferior to SM	AE/SAEs balanced across groups
[Kerstjens <i>et al.</i> 2011]	R, DB, PC, CO	Severe	≥800 BU or equiv.	yes	10 versus 5 od	8	107	Peak FEV ₁	≥800 µg BU + T10 5 µg versus ≥800 µg BU + T10 10 µg versus ≥800 µg BU	T10 both doses superior to PL	AE/SAEs balanced across groups
[Bateman <i>et al.</i> 2011]	R, DB, PC, PG	Moderate	400–1000 BU or equiv.	no	5 od	16	388	Morning PEF	ICS + T10 versus ICS + SM 25 bid versus ICS	T10 superior to PL and non-inferior to SM	AEs balanced across groups, most SAEs in SM group
[Kerstjens <i>et al.</i> 2012]	R, DB, PC, PG	Severe	≥800 BU or equiv.	yes	5 od	48	912	peak and trough FEV ₁	ICS + T10 versus ICS	T10 superior to PL, reduction of severe exacerbation, delayed first/severe exacerbation	AE/SAEs balanced across groups
[Beeh <i>et al.</i> 2014]	R, DB, PC, CO	Moderate	400–800 BU or equiv.	no	5 versus 2.5 versus 1.25 od	4	149	Peak FEV ₁	ICS versus ICS + T10	all T10 dosages superior to PL, 5 µg most superior	AE/SAEs balanced across groups
[Ohta <i>et al.</i> 2015]	R, DB, PC, PG	Moderate	400–800 BU or equiv.	yes	5 versus 2.5 od	52	285	Long-term safety	ICS versus ICS + T10 5 µg versus ICS + T10 2.5 µg	AE/SAEs balanced across groups, most of them mild-moderate; peak FEV ₁ superior to PL in T10 5 µg	AE/SAEs balanced across groups
[Timmer <i>et al.</i> 2015]	R, DB, PC, CO	Moderate	400–800 BU or equiv.	no	5 od versus 2.5 bid	4	94	FEV ₁ ; AUC from 0–24h	ICS versus ICS + T10 5 µg versus ICS + T10 2.5 µg bid	both T10 dosages superior to PL, no difference between both T10 dosages	AE/SAEs balanced across groups
[Kerstjens <i>et al.</i> 2015]	R, DB, PC, PG	Moderate	400–800 BU or equiv.	no	5 versus 2.5 od	24	2103	Peak and trough FEV ₁	ICS versus ICS + T10 5 µg versus ICS + T10 2.5 µg versus ICS + SM 50 µg bid	both T10 dosages and SM superior to PL, no difference between the treatment groups,	AE/SAEs balanced across groups

AE, adverse event; AUC, area under the curve; bid, twice daily; BM, beclomethasone; BU, budesonide; CO, crossover; DB, double blind; FEV₁, forced expiratory volume in 1 second; FP, fluticasone propionate; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting beta agonist; N/A, not applicable; od, once daily; PC, placebo controlled; PEF, peak expiratory flow; PG, parallel group; PL, placebo; QOL, quality of life; R, randomized; SAE, serious adverse event; SM, salmeterol; T10, tiotropium.

Inhaler, which is characterized by the drug being released as a soft mist.

A total of 107 patients with uncontrolled, severe asthma were randomized in a double-blind, crossover study with three 8-week treatment periods, with either a tiotropium 5 µg, 10 µg, or placebo once daily add-on to a high-dose ICS plus LABA [Kerstjens *et al.* 2011]. The peak FEV₁ as the primary endpoint was significantly higher with both 5 and 10 µg of tiotropium compared with the placebo (a difference of 139 ml and 170 ml, respectively, $p < 0.0001$). The trough FEV₁ at the end of each treatment period was significantly higher in both dosage groups of tiotropium compared with the placebo group (86 ml and 113 ml, respectively, $p < 0.0004$), as were the average morning and evening PEFs of the second half of each treatment period. There were no significant changes in asthmatic symptoms or quality of life. Subgroup analysis did not reveal any significant association between treatment effects and sex, FEV₁ or reversibility at screening, smoking status, or asthma duration. The incidence of adverse events in the tiotropium and placebo groups was similar, with only dry mouth occurring more often in the 10 µg group. The study of Kerstjens and colleagues was the first of a series of further studies that used peak FEV₁ within three hours after dosing as outcome parameter [Kerstjens *et al.* 2011]. The differences of peak and trough FEV₁ were not only significantly higher in the tiotropium treated patients compared with placebo, but also clinically relevant. The lack of a wash-out period between the different treatments and the short treatment periods might on the other hand have limited changes in patient reported outcomes.

In a comparative study of uncontrolled asthmatic patients with the B16-Arg/Arg genotype, who are supposed to respond less to β_2 -agonists, 388 patients were randomized to a 16 week treatment with either 5 µg of tiotropium daily, 50 µg of salmeterol twice daily, or placebo; each as an add-on to 400–1000 µg of budesonide or its equivalent [Batemen *et al.* 2011]. Changes in the weekly PEF from the last week of the run-in to the last week of treatment were significantly greater for tiotropium and salmeterol compared with the placebo ($p < 0.05$). Again, tiotropium was non-inferior to salmeterol. The incidence of adverse events was similar in all groups, with only nasopharyngitis occurring more frequently in the placebo group. Although the concerns about the use of

LABAs in asthmatic patients with B16-Arg/Arg genotype for the use of LABAs have been relativized, this study demonstrated again the non-inferiority of tiotropium to salmeterol in moderate asthmatic patients and supports that tiotropium might be an alternative add-on to an ICS treatment option in asthmatic patients.

The first long-term study with an active treatment period of 48 weeks was performed with 912 severely asthmatic patients, who had symptoms despite a high dose of ICS plus LABA [Kerstjens *et al.* 2012]. A dose of 5 µg tiotropium once daily or placebo was added to the maintenance therapy. Peak FEV₁ response occurred within three hours of the administration of the maintenance and the study drugs, and the trough FEV₁ response, improved significantly from the baseline after 24 weeks in the tiotropium group, compared with the placebo group. Likewise, the time to the first severe asthma exacerbation increased (with a reduction of 21% in risk, and a hazard ratio of 0.79, $p = 0.03$). Further secondary endpoints (peak FVC and trough vital capacity; morning and evening PEF) improved significantly. The incidence of adverse events was comparable in both groups, with only higher rates of allergic rhinitis in the tiotropium group and higher rates of asthmatic episodes and insomnia in the placebo group. The patients that were included in this study were uncontrolled asthmatic patients despite high doses of an ICS plus LABA. Therapeutic alternatives are limited in these patients. Although the changes of the symptom and quality of life scores were low, this study demonstrates that an additional treatment with tiotropium significantly reduces the rate of asthma exacerbations and improves lung function in this difficult to treat patient group.

Several dose-finding and therapy regimen studies followed the long-term treatment study by Kerstjens and colleagues [Kerstjens *et al.* 2012]. In a randomized, double-blind, placebo-controlled, four-way crossover study, 149 moderately symptomatic asthmatic patients treated with stable medium-dose ICS without LABA were randomized to three different tiotropium dosages *versus* placebo (1.25, 2.5 or 5 µg, administered once daily in the evening) [Beeh *et al.* 2014]. Each treatment was performed for a period of 4 weeks. The primary endpoint peak FEV₁ within the first 3 hours post-dose (0–3h) improved significantly in all three tiotropium dosage groups

($p < 0.0001$), with the largest difference from the placebo group being with 5 μg . Furthermore, a dose-dependent increase was also observed for the trough FEV_1 , the FEV_1 area under the curve (0–3h), the peak FVC (0–3h), the trough FVC and the FVC area under the curve (0–3h), with the largest increase with 5 μg . Although the treatment periods of only 4 weeks were very short, a superiority of the highest tested dose concerning changes in lung function could be demonstrated, while the safety profile was comparable between the different doses and placebo.

A Japanese study with 285 symptomatic asthmatic patients, who were treated with ICS and LABAs, compared the long-term safety and effect on lung function of two different doses of tiotropium (2.5 and 5 μg), administered for 52 weeks, with a placebo [Ohta *et al.* 2015]. The adjusted mean trough FEV_1 and the trough PEF were significantly higher with tiotropium 5 μg compared with the placebo, but not with 2.5 μg . ACQ-7 improved more in both tiotropium groups compared with the placebo. The incidence of adverse events was similar in the tiotropium and the placebo groups; however, bronchitis was more frequently reported in the tiotropium groups.

These results were supported by a randomized, double-blind, placebo-controlled crossover dose regimen study with 89 symptomatic asthmatic patients [Timmer *et al.* 2015]. Subjects received add-on treatment to medium-dose ICS with 5 μg tiotropium once daily, or 2.5 μg twice daily, compared with placebo. There were no significant differences between the 5 μg once daily and 2.5 μg twice daily groups in all investigated lung function parameters, but significant improvement compared with the placebo group with regard to the FEV_1 area under the curve from 0 to 24 h response, the peak FEV_1 (0–24h), the trough FEV_1 and the pre-dose PEF (am/pm).

Pooled data of two randomized, placebo-controlled, parallel-group studies with symptomatic asthmatic patients, who remained symptomatic despite the administration of a medium-dose ICS, confirmed the significant improvement of lung function during a 24 week treatment period [Kerstjens *et al.* 2015]. Patients were either treated with 5 or 2.5 μg tiotropium once daily, or with salmeterol 50 μg twice daily, or with a placebo, in addition to their maintenance ICS. Both the peak and trough FEV_1 responses and the ACQ-7 response were significantly greater in all

actively-treated patients compared with the placebo patients, with no relevant differences between the tiotropium groups and the salmeterol group. The safety profile was similar in all four treatment groups.

When summarizing the results of the dose-finding studies, all tested tiotropium dosages showed superiority to placebo in most lung function parameters. The highest dose of 5 μg resulted in the most significant improvement of lung function in some studies, but this was not consistent. The safety profile, however, was comparable with placebo without relevant differences between the different doses.

Tiotropium add-on to ICS non-placebo controlled studies

Results from the BELT study recently confirmed the non-inferiority of tiotropium add-on to ICS, compared with salmeterol in moderate-to-severe, black asthmatic patients [Wechsler *et al.* 2015]. No differences in the number of asthma episodes requiring an unscheduled visit, change of FEV_1 , symptom questionnaires, number of symptom-free days or the need for rescue medication could be seen between the two different treatment regimens. Allelic variation at the Arg16Gly locus of the β_2 -adrenergic receptor ('ADRB') gene locus did not affect the results.

A single-centre Chinese study comparing the effect of add-on treatment with tiotropium 5 μg or LTRA and the effect of doubling the dose of ICS in uncontrolled asthmatic patients using inhaled salmeterol/fluticasone 50/250 μg demonstrated no significant difference between the tiotropium group and the 'doubling of the dose of ICS' group with regard to the PEF variability or the ACT score after 16 weeks of treatment [Wang *et al.* 2015]. Fractionated exhaled nitric oxide (FeNO) concentration was significantly higher in the tiotropium group compared with the double-dose ICS group, but the risk of pneumonia was lower.

A recently published, double-blind, two-way crossover study investigated the total tiotropium exposure, expressed as area under the plasma concentration versus time curve over 24 hours, in asthmatic patients, who were symptomatic despite receiving a medium dose of ICS [Beeh *et al.* 2016]. The study participants were either treated with tiotropium 5 μg once daily or 2.5 μg twice daily, as an add-on to their maintenance

therapy, for 4 weeks. The total tiotropium exposure did not differ significantly between the two dosage groups, thus supporting 5 µg as a suitable dosage.

The limited number of studies that compared different treatment strategies demonstrated a non-inferiority of an add-on treatment with tiotropium to ICS compared with a combination of salmeterol and ICS. These data might indicate the potential of tiotropium as a safe and effective steroid-sparing treatment alternative. However, more studies, especially investigating the treatment effect on asthmatic inflammation are needed to assess the best treatment combination.

Real-life studies

Only a few studies investigating tiotropium in asthmatic patients under real-life conditions have been published so far. Abadoglu and Berk reported the effect of add-on treatment with tiotropium in severely asthmatic patients, comparing the number of exacerbations, emergency department visits, hospitalizations and changes of lung function in the 12 months before and after the onset of the treatment [Abadoglu and Berk, 2016]. All endpoints improved significantly; asthma control improved in 42.2%, the number of emergency department visits decreased in 46.9%, and the number of hospitalizations decreased in 50% of the patients. The FEV₁% and FVC % rates also improved significantly.

These results are supported by a recently published real-life care study [Price *et al.* 2015]. Records from the UK's Optimum Patient Care Research Database from 2001–2013 revealed a significant decrease of asthma exacerbation and acute respiratory events in the 2042 study patients, leading to significantly reduced antibiotic prescription and oral corticosteroid courses. In this study, no significant changes of lung function were documented; however, the usage of short-acting β₂-agonists increased significantly.

Although randomized, controlled trials are essential to evaluate the efficacy and limits of a new therapy, comparative observational studies are important to verify these data in a real-life setting. On this note, more observational studies are needed to better estimate the therapeutic potential of tiotropium in different patients and to better understand which kind of asthma patients benefit more or less from tiotropium.

Conclusion

Only recently has tiotropium been included as the first long-acting anticholinergic agent in the GINA guidelines. Compared with other long-acting anticholinergic substances, there is substantial clinical evidence for the therapeutic benefit of an add-on therapy with tiotropium in adult patients with insufficiently controlled asthma. Most of the studies in adults included patients aged 18–75, but there is also a rising body of paediatric studies with similar results [Vogelberg *et al.* 2014, 2015; Hamelmann *et al.* 2016]. Thus, tiotropium might extend treatment options both in children starting at age of 6 years and adults. Both the relevant lung function parameters and the indicators for asthma control improve with add-on treatment with tiotropium. The first preliminary studies also demonstrate non-inferiority compared with the add-on treatment with salmeterol, and all studies report an excellent safety profile of the drug. The pharmacological properties of tiotropium suggest that relevant effects in asthma therapy include not only bronchodilation but also anti-inflammatory impact. This again might explain the changes of lung function but also the increase of time until the first exacerbation and the reduction of severe exacerbation [Kerstjens *et al.* 2012]. Although tiotropium is presently recommended as an alternative add-on treatment option in steps 4 and 5, further studies will be needed to finally evaluate the potential of the drug with respect to asthma treatment. This also includes the need for additional head-to-head studies to define the position that tiotropium ought to have in asthma guidelines. Further real-life studies might help to identify asthmatic patients who would benefit most from tiotropium.

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