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CASE REPORT



Efficacy and safety of add-on tiotropium in the management of uncontrolled asthma: a patient case series

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ABSTRACT

Objective: Despite the availability of various treatment options, a large proportion of patients with asthma have uncontrolled asthma in the United States. Consequently, the economic burden of suboptimal asthma control is anticipated to substantially grow in the next 20 years, adversely impacting patients' quality of life. Therefore, there is an urgent need for effective treatments to achieve and maintain asthma control. The Global Initiative for Asthma recommends tiotropium as a controller medication for patients with asthma aged ≥ 6 years, based on evidence from several randomized controlled trials. However, more real-world data on the effectiveness of tiotropium are required to establish a broad picture of its use in everyday clinical practice.

Methods: Herein, we present 3 case reports of patients diagnosed with uncontrolled or fixed obstructive asthma not responding to inhaled corticosteroids (ICS) or ICS + long-acting β_2 -agonists (LABAs) and/or leukotriene receptor antagonists (LTRAs).

Results: All 3 patients were prescribed tiotropium, irrespective of their age. Tiotropium improved lung function and quality of life, as indicated by the forced expiratory volume in 1 s/forced vital capacity ratio and the Asthma Control Test score. Furthermore, the addition of tiotropium reduced the use of rescue medication.

Conclusions: Hence, the results from these case reports highlight that tiotropium could be an effective and safe add-on treatment option for patients across a range of age groups with uncontrolled or fixed obstructive asthma receiving prior ICS or ICS + LABA and/or LTRA therapy.

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Introduction

Persistent asthma, a heterogeneous disease characterized by chronic airway inflammation (1,2), is commonly treated with short-acting β_2 -agonists (SABAs), inhaled corticosteroids (ICS), or a combination of an ICS and a long-acting β_2 -agonist (LABA) (3). Additionally, other controller medications include oral corticosteroids (OCS); leukotriene receptor antagonists (LTRAs), long-acting muscarinic antagonists (LAMAs); and anti-immunoglobulin E, anti-interleukin 5/interleukin 5 receptor; and anti-interleukin 4 receptor agents (1). However, despite the availability of a number of treatment options, a 2016 report in the United States (US) highlighted that a large proportion (61.9%) of patients with asthma had uncontrolled asthma (4).

The economic burden of suboptimal asthma control is therefore substantial and anticipated to grow (5). Indeed, results from a recent study predicted that the 20-year (2019–2038) direct cost associated with uncontrolled asthma among adolescents and adults in the US would rise to \$300.6 billion, increasing to \$963.5 billion when indirect costs were included (5). Moreover, American adolescents and adults are estimated to lose 15.46 million quality-adjusted life-years

(QALYs) during this period owing to uncontrolled asthma (5). Consequently, there is a need for effective treatments that can improve lung function across the spectrum of patients with asthma.

Tiotropium Respimat[®] (Spiriva[®] Respimat[®] inhalation spray; Boehringer Ingelheim, Ridgefield, CT, US) 2.5 μ g (2 puffs of 1.25 μ g each, once daily) is the only Food and Drug Administration–approved LAMA for the long-term, once-daily maintenance treatment of asthma in patients aged ≥ 6 years in the US (6). Results from several randomized clinical trials have reported that tiotropium as an add-on treatment to ICS with or without other controller medications in patients with uncontrolled or symptomatic asthma improved lung function and asthma control, regardless of the baseline phenotype (7–11). A systematic review and meta-analysis of four randomized controlled studies of tiotropium added to low- to medium-dose ICS for adults with mild to moderate uncontrolled persistent asthma also found that lung function was significantly improved in patients receiving tiotropium plus ICS versus ICS monotherapy (12). Moreover, the incidence of serious adverse events was not significantly different between patients receiving tiotropium and ICS versus ICS alone (12). The efficacy

Table 1. Case report 1.

Age at the onset of asthma symptoms	• 4 years
History	• Diagnosed with seasonal allergic rhinitis at age 5 • Worsening of asthma symptoms at age 8, with increased nighttime coughing
Comorbidity	• Seasonal allergic rhinitis (allergy testing not performed) • Epilepsy
Treatment at referral	• Daily fluticasone propionate (44 µg, 1 puff BID)+oral montelukast (4 mg tablet)+albuterol (90 µg, 1–2 puffs as needed)+OCS (as needed) • Sodium valproate (25 mg/kg)
Treatment at the first follow-up (12 weeks)	• Daily fluticasone propionate (44 µg, 2 puffs BID)
Follow-up (12 weeks)	• Partial control of asthma symptoms (wheezing and breathlessness persisted) • Cough remained persistent (cough variant asthma excluded) • Prednisone 20 mg for 3 days followed by prednisone 10 mg for 3 days to alleviate asthma symptoms • Albuterol 2 puffs 3 times daily • Shortly after starting OCS, albuterol use was decreased to approximately 2–3 times per week • Albuterol was required 15 minutes after physical activity • The patient was not assessed for biologic therapy
Current treatment	• Daily fluticasone propionate (44 µg, 1 puff BID)+tiotropium 2.5 µg (2 puffs of 1.25 µg each, once daily)
Follow-up (4 weeks)	• Reduction in cough during PE and daily rescue inhaler use • OCS treatment was not required
Physical and clinical examination	Presentation: • Blood eosinophils=125 cells/µL • BMI=15.8 • ACT score=12 • FEV₁ (% predicted)=78 • FVC (% predicted)=95 • Post-BD ΔFEV₁%=19 • FEV₁/FVC=0.73 Follow-up (4 weeks): • Blood eosinophils=not measured • BMI=15.9 • ACT score=21 • FEV₁ (% predicted)=84 • FVC (% predicted)=95 • Post-BD ΔFEV₁%=No change • FEV₁/FVC=0.88

ACT, asthma control test; BD, bronchodilator; BID, twice daily; BMI, body mass index; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; OCS, oral corticosteroids; PE, physical education; Δ, change in value.

of tiotropium was demonstrated across age groups (children, adolescents, and adults) and asthma severities (mild, moderate, and severe asthma) (7–11). Furthermore, improvements in lung function observed with ICS+tiotropium were comparable to those observed with ICS+LABA or LTRA in other clinical trials in children with asthma (11,13,14), suggesting that tiotropium may be a viable alternative in patients aged 6–11 years (11). Tiotropium bromide delivered via the Respimat® inhaler has been approved by the US Food and Drug Administration since 2017 for the long-term, once daily maintenance treatment of asthma in patients aged 6 and older (6).

Moreover, the Global Initiative for Asthma (GINA) recommends tiotropium as an add-on therapy in step 4 (“other” controller treatment) and step 5 (“preferred” controller treatment) in patients with asthma aged ≥6 years (1). The National Asthma Education and Prevention Program (NAEPP) 2020 guidelines recommend that for patients aged ≥12 years with uncontrolled persistent asthma in whom a LABA cannot be used (e.g. the patient is unable to tolerate LABA treatment, LABA is contraindicated, the patient cannot use the inhaler device, or the LABA is unavailable), adding a LAMA to an ICS is an acceptable alternative (2). Furthermore, the NAEPP advocates that for patients in whom asthma is uncontrolled with an ICS-LABA combination, a LAMA may be added, as it offers a small potential benefit (2). However, more data are required on the effectiveness of tiotropium and its effect on patients’ day-to-day lives (15). Herein, we present 3 case reports highlighting the efficacy and safety of tiotropium in patients with uncontrolled asthma.

Methods

The case series includes 3 asthma patient cases experienced by the authors in their clinical practices. Electronic medical record data of patients were reviewed, and the individual patient data were evaluated for demographic and pathophysiologic characteristics, including age, sex, medical history, presence of comorbidities, treatment at the time of specialist referral, body mass index, Asthma Control Test (ACT) score, forced expiratory volume in 1 s (FEV₁), and forced vital capacity (FVC). Patients with uncontrolled asthma were prescribed add-on tiotropium and followed-up 4 weeks after the initiation of tiotropium. Each author consulted with his/her respective Institutional Review Board (IRB), and waiver of IRB approval was granted, as patient information was masked and demographic information modified to protect patient identity.

Results

Case report 1 (Table 1)

A 9-year-old male with epilepsy was diagnosed with asthma at the age of 4 years and seasonal allergic rhinitis at the age of 5 years. The patient enjoyed playing sports and participated in physical education (PE) 3 times a week. The patient struggled with a persistent cough during PE, although he rarely experienced difficulty in breathing while walking. Until the age of 7 years, the patient’s asthma symptoms were controlled with daily use of fluticasone propionate (44 µg, 1 puff twice daily; ICS), montelukast (4 mg tablet; LTRA) at night,

Table 2. Case report 2.

Age at the onset of asthma symptoms	• 40 years
History	• Worsening of asthma symptoms at age 72
Comorbidity	• Nonallergic rhinitis • Stage 2 hypertension
Treatment at referral	• Asthma: fluticasone propionate (110 µg, 2 puffs daily)+albuterol (180 µg; rescue medication) • Nonallergic rhinitis: fluticasone propionate (50 µg)+loratadine (10 mg) • Hypertension: enalapril (20 mg)
Current treatment	• Fluticasone propionate (110 µg, 2 puffs daily)+tiotropium (1.25 µg, 2 puffs daily)
Follow-up (4 weeks)	• Breathing improved and rescue medication was no longer required • The patient was not assessed for biologic therapy
Physical and clinical examination	Presentation: • Blood eosinophils=152 cells/µL • BMI=24 • ACT score=15 • FEV₁ (% predicted)=72 • FVC (% predicted)=93 • Post-BD ΔFEV₁%=13 • FEV₁/FVC=0.77 Follow-up (4-weeks): • Blood eosinophils were not evaluated at follow-up • BMI=24 • ACT score=21 • FEV₁ (% predicted)=89 • FVC (% predicted)=95 • Post-BD ΔFEV₁%=15 • FEV₁/FVC=0.94

ACT, asthma control test; BD, bronchodilator; BMI, body mass index; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; Δ, change in value.

Table 3. Case report 3.

Age at the onset of asthma symptoms	• Childhood
History	• Worsening of asthma symptoms at age 29 • Diagnosed with seasonal rhinitis
Comorbidity	• Seasonal allergies • Nasal polyposis
Treatment at referral	• Asthma: Budesonide (160 µg)+formoterol (4.5 µg), 2 puffs BID+albuterol (as needed)+OCS (as needed) • Allergies: fluticasone (50 µg)
Current treatment	• Budesonide (160 µg)+formoterol (4.5 µg), 2 puffs BID+tiotropium 2.5 µg (2 puffs of 1.25 µg each, once daily) • Mometasone nasal spray (400 µg) • The patient was assessed for suitability of biologic therapy
Physical and clinical examination	Presentation: • Blood eosinophils=610 cells/µL • Wheezing • BMI=20 • ACT score=8 • FEV₁ (% predicted)=42 • FVC (% predicted)=89 • Post-BD ΔFEV₁%=7 • FEV₁/FVC=0.47 Follow-up (6 weeks): • Blood eosinophils=420 cells/µL • BMI=20 • ACT score=20 • Spirometry was not performed at follow-up

ACT, asthma control test; BD, bronchodilator; BID, twice daily; BMI, body mass index; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; OCS, oral corticosteroids; Δ, change in value.

albuterol (90 µg, 1–2 puffs, as needed; SABA) as rescue medication, and OCS as required. However, at 8 years of age, his asthma symptoms worsened, and he required albuterol over 7 times a week. Subsequently, his ICS dose was increased (44 µg, 2 puffs twice daily); however, his cough remained persistent, and he still required albuterol (2 puffs, thrice daily) and frequent courses of OCS (prednisone 20 mg for 3 days followed by prednisone 10 mg for 3 days). The patient presented with typical symptoms of asthma including shortness of breath and wheezing; hence, a diagnosis of cough variant asthma was excluded. Following concerns from his mother and grandmother, the patient was prescribed tiotropium (2.5 µg, 2 puffs of 1.25 µg, once daily; LAMA), and his ICS dose was reduced (44 µg, 1 puff twice daily). The addition of tiotropium decreased asthma symptoms and improved asthma control, indicated by an improved ACT score and FEV₁/FVC ratio at the 4-week follow-up consultation.

Case report 2 (Table 2)

A 72-year-old female with non-allergic rhinitis and stage 2 hypertension, who lived in a hot and humid climate and enjoyed gardening for 4–5 h every day in the early afternoon, was diagnosed with asthma at the age of 40 years. She presented with worsening of asthma symptoms over the past 4–6 weeks. The patient was receiving a daily dose of fluticasone propionate (110 µg, 2 puffs once daily; ICS) and using albuterol (180 µg; SABA) rescue medication as needed. She demonstrated good inhaler technique and was adherent to ICS therapy. The patient was reluctant to take albuterol before gardening because it made her feel anxious and she experienced palpitations; however, she would then require 2 puffs mid-afternoon and again after gardening owing to worsening of symptoms. Therefore, her physician prescribed tiotropium (1.25 µg, 2 puffs once daily) and recommended

early-morning gardening instead. At the 4-week follow-up, her asthma was under control, indicated by an improvement in lung function and ACT score. Furthermore, she no longer required rescue medication while gardening.

Case report 3 (Table 3)

A 29-year-old female, who worked in the restaurant industry and smoked marijuana occasionally, was diagnosed with asthma in childhood. She presented to the clinic with nasal polyposis, persistent wheezing, shortness of breath and cough, and had received 3 courses of OCS in the past 6 months.

The patient was diagnosed with poorly controlled, fixed obstructive asthma, as indicated by a low ACT score and no change in her postbronchodilator FEV₁%, despite taking budesonide (160 µg, 2 puffs twice daily; ICS)+formoterol (4.5 µg, 2 puffs twice daily; LABA) and as-needed albuterol and OCS. Therefore, her physician decided to add tiotropium (2.5 µg, 2 puffs of 1.25 µg each, once daily) to her treatment regimen, trained her on proper inhaler use, and developed a written action plan. At the 6-week follow-up, the patient reported feeling better, with no exacerbations since the initiation of tiotropium.

Discussion

The 3 case reports presented here describe the authors' experience with specific asthma patients regarding the efficacy and safety of tiotropium across a range of age groups in patients with uncontrolled or fixed obstructive asthma despite regular treatment with ICS or ICS+LABA or LTRA and as-needed SABA, good inhaler technique, and adherence to therapy. Overall, the addition of tiotropium (2 puffs of 1.25 µg each, once daily) improved symptom control and lung function and enhanced patients' quality of life, as indicated by improvements in the FEV₁/FVC ratios and ACT scores.

Notably, the 9-year-old male patient benefited from the addition of tiotropium over an increase in the ICS dose. This finding is consistent with results from previous clinical trials in adults and children with uncontrolled asthma, where the addition of tiotropium was superior to increasing the ICS dose in terms of improvements in lung function and asthma control (16,17). The observed improvement in this 9-year-old male patient following the addition of tiotropium to his treatment regimen is of particular importance since results from a Cochrane review concluded that the current evidence does not support increasing the ICS dose to treat exacerbations in adults and children with mild to moderate asthma (18). Furthermore, potential adverse events are associated with regular ICS use, and very high doses of ICS are not recommended in children owing to a lack of safety information (19). LTRAs are less effective than ICS, particularly for exacerbations (1), but may be effective in patients who do not tolerate ICS due to side effects or in patients with concomitant allergic rhinitis, the latter being present in this 9-year-old male patient. However, the US Food and Drug Administration recently required a boxed warning

about the risks of serious mental health adverse effects with montelukast and that patients should be counseled regarding the risk of neuropsychiatric events (1). It is also important to highlight that seasonal allergic rhinitis may have contributed to the worsening of symptoms in this patient; allergic rhinitis is well documented as a comorbidity of asthma (20). However, the improvement in symptom control seen with the addition of tiotropium rather than further increasing the ICS dose is significant, as children with severe asthma have a 32-fold higher risk of developing chronic obstructive pulmonary disease (COPD) by the age of 50 years compared with children with intermittent and mild persistent asthma (21). One of the greatest unmet needs is in patients with uncontrolled asthma despite treatment with ICS+LABA. Indeed, it has been reported that ICS+LABA only achieves well-controlled asthma in approximately 70% of patients (22,23).

In our second case report of a 72-year-old female patient taking a high dose of ICS, the patient received a prescription of tiotropium instead of a LABA. The patient did not tolerate adrenergic drugs, reporting symptoms of anxiety and palpitations following albuterol administration, a common observation in clinical practice, which led to the consideration of an alternative approach. The addition of tiotropium resulted in asthma control and normalized lung function, as indicated by follow-up spirometry test results. Therefore, tiotropium may serve as an equivalent alternative to LABAs in this group of patients (24). Indeed, when added to ICS, the effects of tiotropium in terms of peak expiratory flow, asthma control days, and daily symptoms were reportedly equivalent to those achieved with the addition of salmeterol to the treatment regimens of patients with uncontrolled asthma (9,16). Furthermore, tiotropium has been reported as a cost-effective option for add-on therapy (25).

The degree of obstruction is measured by a positive bronchodilator response, which is defined as an increase of ≥12% and ≥200 ml in FEV₁ or FVC from baseline (26). Our final case report of a 29-year-old female patient had a post-bronchodilator change in FEV₁ of 7% at presentation and indicated a patient subtype with fixed obstructive asthma. Such patients have severe airway obstruction (27), indicated by an FEV₁/FVC ratio of <0.7 and no change in postbronchodilator FEV₁% (1). These patients may exhibit characteristics of an asthma-COPD overlap. Given the efficacy of tiotropium in COPD, tiotropium could be an effective add-on therapy in this subset of patients (28). It is important to note that tiotropium bromide when administered for the treatment of COPD in 5 µg (2 puffs of 2.5 µg per puff, once daily (6)) differs from the dosage approved for asthma (2.5 µg; 2 puffs of 1.25 µg per puff, once daily (6)). Moreover, tiotropium has not specifically been studied in a randomized controlled trial for patients with asthma and COPD overlap (ACO).

It is also important to consider the patient phenotype when assessing the response to high-dose ICS treatment and whether the patient has type 2 airway inflammation. The 29-year-old female patient demonstrated characteristics of eosinophilic asthma, as signified by high baseline blood eosinophil levels and the presence of nasal polyposis (a

common comorbidity of type 2 airway inflammation) (1,29). The patient may have been a candidate for add-on type 2 biologic therapy (1), and this was discussed with the patient as part of the treatment consultation. However, the high acquisition price of biologic therapy was not acceptable to this patient (30), and, consequently, tiotropium add-on therapy was prescribed along with treatment of the patient's comorbidities and management of other modifiable risk factors (1). Add-on tiotropium therapy is associated with an incremental cost-effectiveness ratio of \$34478/QALY (31) versus standard therapy and is consequently recommended before the use of biologic agents in the GINA report owing to various cost considerations (1). Emerging novel therapies for asthma present new treatment options, but assessing the cost-effectiveness of such treatments (1,31) is also important.

Conclusion

Taken together, the results from the case reports presented here complement the efficacy and safety of add-on tiotropium therapy beyond the constraints of a randomized controlled clinical trial and across a range of age groups in patients with uncontrolled or fixed obstructive asthma receiving prior therapy.

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