Tiotropium for Adults with Inadequately Controlled Persistent Asthma

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OBJECTIVE: To review the literature evaluating the efficacy and steroid-sparing effect of tiotropium for inadequately controlled persistent asthma in adults.

DATA SOURCES: Information was obtained through a search of MEDLINE/PubMed (1966-October 2012), using the terms asthma and tiotropium. A further review of reference citations was performed to identify other relevant articles.

STUDY SELECTION AND DATA EXTRACTION: English-language case reports and clinical trials were reviewed. Publications evaluating the efficacy and steroid-sparing effect of tiotropium in adults with inadequately controlled persistent asthma were included in the review. One case report and 5 clinical trials met our criteria.

DATA SYNTHESIS: The ultimate goal for asthma management is to maintain disease control by preventing acute exacerbations while avoiding adverse medication effects. Inhaled corticosteroids (ICS) are part of all preferred maintenance regimens for persistent asthma. Unfortunately, persistent asthma remains inadequately controlled in some patients and concerns about serious adverse effects with long-term high-dose ICS treatment exist. Interest in the use of tiotropium to control asthma symptoms and reduce steroid requirements in inadequately controlled persistent asthma is emerging. Results of several trials indicate that tiotropium improves pulmonary function markers and reduces corticosteroid requirements. Moreover, the largest and longest published trial not only showed improvements in pulmonary function tests but also a reduction in corticosteroid use and an increase in the time to first exacerbation.

CONCLUSIONS: Although tiotropium use in treatment of persistent asthma appears to be promising, more robust clinical trials are needed to assess whether improved pulmonary function tests as well as a decrease in asthma exacerbations and corticosteroid requirements translate into improvements in quality of life. Additionally, the optimal patient population, long-term efficacy, and safety of tiotropium when delivered by various methods need to be determined before it can be recommended over current alternative asthma therapies.

Ann Pharmacother 2013;47:117-23.

Published Online, 16 Jan 2013, *theannals.com*, doi: 10.1345/aph.1R502

Request

Does tiotropium have a role in the management of inadequately controlled persistent asthma?

Response

BACKGROUND

Asthma is a chronic respiratory disease that affects approximately 17.5 million American adults.[1] It is characterized by episodes of impaired breathing as a result of upper airway inflammation, excess thickened mucus production within the bronchial tubes, and reversible bronchoconstriction of the surrounding airways. Symptoms of asthma include shortness of breath, wheezing, cough (often at night), and chest tightness, pain, or pressure. Other signs of asthma may include difficulty breathing during physical

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exertion or exercise, retractions, persistent coughing, rapid breathing, and sweating.[2] The severity of these symptoms and signs can vary among individuals and can range from mild (or even nonexistent at times) to persistent with severe symptoms that are inadequately controlled.[2,3]

The ultimate goal for asthma management is to maintain control of the disease by preventing acute exacerbations while avoiding adverse medication effects. Current US asthma guidelines for adults recommend a stepwise treatment approach that targets inflammation as well as bronchoconstriction to achieve optimal asthma control.[3] Inhaled corticosteroids (ICS) are part of all preferred maintenance regimens for persistent asthma. Unfortunately, systemic adverse effects in adults (hypothalamic-pituitary-adrenal axis suppression, osteoporosis, hyperglycemia) have been reported with use of chronic, high-dose ICS.[4-7] Because of the severity of these adverse effects, US asthma guidelines recommend adding a second agent (eg, long-acting β-agonist) to the treatment regimen and "stepping down" to the lowest dose of ICS that gives adequate control. Nonetheless, some patients with persistent asthma still require high-dose ICS or oral corticosteroids and the asthma remains inadequately controlled. For these patients, alternative medications with differing mechanisms of action (ie, leukotriene modifiers, theophylline, and anti-IgE monoclonal antibodies) can be considered to help control asthma symptoms and possibly allow for a reduced dose of corticosteroids.[3] Many of these alternatives have not been fully studied as adjunct therapy, have marginal efficacy, require laboratory monitoring, or are associated with serious adverse reactions. Because of these limitations, other treatment options are needed to help control asthma exacerbations while possibly reducing the corticosteroid dose in patients with inadequately controlled persistent asthma.

Inhaled anticholinergic agents cause bronchodilation by antagonizing acetylcholine on muscarinic receptors, specifically M1, M2, and M3, within the respiratory system.[8,9] Animal models have also shown that inhaled anticholinergics may inhibit eosinophil accumulation in the lungs and decrease airway remodeling.[10,11] Because of their mechanism of action, it has been suggested that inhaled anticholinergics may be useful in the treatment of asthma. Yet, a Cochrane Database review focusing on the use of ipratropium bromide, a short-acting inhaled anticholinergic, as therapy in patients with persistent asthma reported no benefit with widespread routine use.[12] Moreover, US asthma guidelines do not recommend using ipratropium as maintenance therapy in adults with persistent asthma.[3] However, the guidelines do not address the use of long-acting inhaled anticholinergics as maintenance therapy in this population.

Tiotropium is an inhaled long-acting anticholinergic approved for once-daily maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), and for reducing COPD exacerbations.[13] It has a slower drug dissociation from the muscarinic M1 and M3 receptors compared with the M2 receptors, allowing for a longer half-life.[13] Since tiotropium is a bronchodilator that has a long duration of effect, it has been postulated that it may help control persistent asthma symptoms and exacerbations. In fact, results of initial investigations suggest patient factors for predicting a favorable response to tiotropium for certain populations with asthma (ie, those with concomitant COPD, a noneosinophilic phenotype, or an *Arg16Gly* and *Gly16Gly* in β_2 adrenergic receptor polymorphism).[14-16] Furthermore, it has been hypothesized that tiotropium may allow for a reduction in corticosteroid requirements. This review focuses on literature evaluating the efficacy and steroid-sparing effects of tiotropium in adults with inadequately controlled persistent asthma.

LITERATURE REVIEW

Literature evaluating tiotropium for inadequately controlled persistent asthma was accessed through a search of MEDLINE/PubMed (1966-October 2012). The search strategy used the terms asthma and tiotropium and was limited to English-language articles. A further review of reference citations was conducted to identify other relevant articles. Only publications evaluating the efficacy and steroid-sparing effect of tiotropium in patients with inadequately controlled persistent asthma were included. One case report and 5 clinical trials met these criteria.

Early interest for using tiotropium as a steroid-sparing agent came from a case report involving a 43-year-old male with severe, inadequately controlled persistent asthma despite treatment with prednisone 20 mg daily, fluticasone/salmeterol 500 µg/50 µg inhaled twice daily, montelukast 10 mg daily, and salbutamol as a rescue inhaler.[17] While being maintained on these medications, the patient's peak expiratory flow rate (PEF) was 450 L/min. His exercise capacity was limited because of asthma and he had acute asthma symptom flares, which occurred a few times per day. Since the patient was already on optimal persistent asthma treatment but the asthma remained inadequately controlled, tiotropium 18 µg daily was started. Over the course of a 6-month period, the patient had an increase in his PEF (range 520-740 L/min), improved exercise capacity, and a 90% reduction in his prednisone dose to 2 mg daily. Since this is a report of a single case, one cannot draw conclusions regarding cause and effect; however, the positive findings regarding improved PEF and decreased steroid requirements are hypothesis generating.

The initial proof-of-concept trial evaluating the efficacy and steroid-sparing effect of tiotropium in adults with inadequately controlled persistent asthma was double-blind, randomized, placebo-controlled, and crossover in design.[18] Eligible patients (n = 26) were adults (age >18 years) with severe asthma (forced expiratory volume in 1 second [FEV_1] ≤65% predicted, forced vital capacity [FVC] <80% predicted), symptom reversibility by ipratropium and salbutamol, no upper respiratory tract infection, and who had used an oral corticosteroid 90 days prior to enrollment. Patients underwent a 28-day run-in period in which their first- and second-line asthma medications were replaced with a fluticasone metered-dose inhaler 1000 µg daily. Participants were then randomized to a stepped-down dose of fluticasone 500 µg plus salmeterol 100 µg plus tiotropium chlorofluorocarbon (CFC) 18 µg per day or fluticasone 500 µg plus salmeterol 100 µg plus placebo per day for 28 days. After the initial 28-day treatment period, patients were then crossed over to the other therapy for another 28 days. End points included changes from baseline in a number of pulmonary function measures (ie, FEV_1, morning and evening PEF, airway resistance, FVC, and exhaled nitric oxide [eNO], respiratory volume, total lung capacity) as well as quality of life and asthma symptoms. Of the patients who completed the study (n = 18), a significant difference from baseline was reported for improvement in mean morning PEF and airway resistance in both treatment groups (fluticasone/salmeterol/tiotropium: 55.3 L/min [$p < 0.01$] and 2.97 cm H_20/L/s [$p < 0.05$], respectively; fluticasone/salmeterol/placebo: 41.5 L/min [$p < 0.01$] and 2.96 cm H_20/L/s [$p < 0.05$], respectively). Only patients treated with fluticasone/salmeterol/tiotropium had a significant difference from baseline in FEV_1 (+0.17 L, $p < 0.05$), FVC (+0.24 L, $p < 0.05$), and eNO (–2.86 ppb, $p < 0.05$) compared with patients who received placebo (FEV_1, +0.11 L, $p > 0.05$; FVC, +0.13 L, $p > 0.05$; eNO not reported for placebo). There was no significant difference from baseline for respiratory volume, total lung capacity, quality of life, or asthma symptoms in either treatment group. When fluticasone/salmeterol/tiotropium and fluticasone/salmeterol/placebo groups were compared, no differences between any end points existed. Overall, the addition of tiotropium plus salmeterol allowed for a reduction in ICS requirements to 500 µg daily (mean equivalent maintenance dose of fluticasone at screening: 782 µg daily) as well as some improvement in physiologic parameters from baseline. This trial was limited by its small sample size, cohort design, and short treatment duration. There was no mention of a washout period between treatment regimens. Tiotropium has a long half-life; therefore, its carryover effect on end points may have skewed results when the treatment groups were compared. Approximately 31% of the patients did not complete the study because of asthma exacerbations, which is concerning since the ultimate goal for asthma control is to reduce exacerbations. No other adverse effects were reported.

Tiotropium as an alternative to increased ICS doses was further evaluated in a larger number of patients with inadequately controlled persistent asthma.[19] The purpose of the study was to assess whether the addition of inhaled tiotropium to ICS was superior in efficacy to doubling the dose of ICS and noninferior to a long-acting β-agonist and ICS. The TALC (Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid) study was a double-blind, 3-way, crossover trial that enrolled 210 adults (aged ≥18 years) with bronchodilator reversibility or bronchial hyperresponsiveness confirmed asthma. All recruited patients underwent a 4-week run-in phase that transitioned patients from their maintenance asthma medications to treatment with inhaled beclomethasone 80 µg twice daily. Patients eligible for randomization were nonsmokers who had a 75% or more adherence rate during the run-in phase and were classified as having moderate persistent asthma (FEV_1 ≤70% of predicted, symptoms or used a rescue inhaler ≥6 days per week, or nighttime asthma symptom awakenings ≥2 nights per week). Treatment groups received a 14-week course of beclomethasone 80 µg twice daily plus tiotropium CFC 18 µg daily, beclomethasone 80 µg twice daily plus salmeterol 50 µg twice daily, or beclomethasone 160 µg twice daily with matching placebos. For crossover, there was a 2-week washout period between each treatment during which participants received only beclomethasone 80 µg twice daily. The primary outcome was morning PEF. Other prespecified outcomes included FEV_1 before bronchodilation, proportion of symptom-free days, asthma symptoms, rescue bronchodilator use, asthma exacerbations, and results of validated questionnaires (Asthma Control Questionnaire-7 [ACQ-7], score range 0 [no impairment] to 6 [maximum impairment], with a minimal clinically important difference [MID] of 0.5 units[20]; Asthma Symptom Utility Index, score range 1-7, with a lower score reflecting a worse quality of life and a MID of 0.5[21]; and Asthma Quality-of-Life Questionnaire, score range 0-1, with a lower score reflecting worse asthma control).[22] A total of 210 patients were randomized and 174 completed the study. Reasons for dropouts included withdrawal of consent (n = 23), loss to follow-up (n = 7), medication-related adverse events (n = 2), ineligibility after randomization (n = 1), and other (n = 3). The intention-to-treat principle was used in all statistical analyses. For the primary outcome, tiotropium was considered superior to double-dose ICS. Tiotropium-treated patients had a morning PEF 25.8 L/min higher than those who received double-dose ICS (95% CI 14.4-37.1; $p < 0.001$). The results also favored tiotropium on many secondary outcomes compared with double-dose ICS, including prebronchodilator FEV_1 (difference 0.1 L; 95% CI 0.03-0.17; $p = 0.004$), proportion of symptom-free days (difference 0.079; 95% CI 0.019-0.140; $p = 0.01$), asthma symptoms (difference −0.11 points; 95% CI −0.16 to −0.06; $p < 0.001$) and the ACQ-7 (difference −0.18 points; 95% CI −0.34 to −0.03; $p = 0.02$). Patients who received tiotropium experienced fewer asthma exacerbations and fewer exacerbations requiring oral glucocorticoids than did those who received double-dose ICS (statistical values not reported). No significant difference was seen between tiotropium and double-dose ICS on rescue bronchodilator use or other validated questionnaires. Tiotropium was considered noninferior to salmeterol for morning PEF, prebronchodilator FEV_1, and proportion of symptom-free days. Additionally, the prebronchodilator FEV_1 favored tiotropium over salmeterol (0.11 L increase; 95% CI 0.04-0.18; $p = 0.003$) and postbronchodilator FEV_1 (0.07 L increase; 95% CI 0.05-0.1; $p < 0.001$). Asthma exacerbations occurred in patients from each treatment group (tiotropium, 9; double-dose ICS, 16; salmeterol, 5). Adverse events were reported as similar between groups for overall incidences and patterns. There are a number of limitations to this study. First, patients had to have a 75% adherence rate measured using peak flow, diary cards, and study medications after the run-in period to be included in the study, which implies possible selection bias for relatively good adherence. Second, it is unclear why the investigators chose to use a medium dose of beclomethasone in the treatment period and a low dose during the run-in and washout periods. The inclusion criteria selected for patients with moderate persistent asthma, who would have likely required higher corticosteroid doses. Third, using morning PEF as the primary outcome limits clinical applicability, as PEF is only a surrogate marker for asthma control. A better primary outcome may have been a reduction in asthma symptoms or exacerbations or the proportion of asthma-control days. Fourth, although a statistically significant difference was reported for the ACQ-7, only a difference of –0.18 points was reported, which is not considered clinically important by MID. Finally, a longer trial period is needed to explore tiotropium's efficacy as well as long-term safety in this patient population.

Bateman and colleagues explored the efficacy of tiotropium in a subset of patients with inadequately controlled moderate persistent asthma.[23] This randomized, double-blind, placebo-controlled, parallel-group study enrolled 388 patients who were aged 18-67 years, with the *B16-Arg/Arg* genotype and reversible airway obstruction and who were receiving inhaled corticosteroids (400-1000 μg budesonide or equivalent). Eligible patients had a prebronchodilator FEV_1 90% or more of the predicted level if the patient was taking salmeterol or formoterol or 80% or more for those only taking ICS at baseline. All participants continued treatment with their pre-enrollment ICS dose and received salmeterol 50 μg twice daily during an open-label 4-week run-in period. Patients were then randomized to tiotropium 5 μg daily (delivered by a Respimat inhaler), salmeterol 50 μg twice daily, or placebo for 16 weeks. The primary outcome was change from the last week before randomization to week 16 in mean weekly morning predose PEF. Other outcomes included weekly means of daily morning and evening predose PEF, morning and evening FEV_1, asthma symptoms, and use of rescue medications. When tiotropium and salmeterol were compared with placebo, each was superior to placebo for the primary end point (–3.9 ± 4.87 L/min, –3.2 ± 4.64 L/min, and –24.6 ± 4.84 L/min, respectively; $p < 0.05$ for both comparisons). Tiotropium was noninferior to salmeterol in the mean weekly morning predose PEF (difference –0.78 L/min; 95% CI –13.096 to 11.53; $p = 0.002$), in mean weekly evening predose PEF (difference 3.353 L/min; 95% CI –9.882 to 16.59; $p = 0.001$), and in mean weekly evening predose FEV_1 (difference 0.052 L; 95% CI –0.027 to 0.13; $p = 0.011$). Parameters for noninferiority were not defined for the other prespecified secondary end points. Asthma exacerbations occurred in patients from each treatment group (tiotropium 12.5% [16/128], salmeterol 12.7% [17/134], placebo 13.5% [17/126]). Additionally, adverse events were reported as similar between groups for overall incidences and patterns, with the most common adverse effect reported as nasopharyngitis or bronchitis. Limitations of this trial include its short duration and lack of evaluation of asthma exacerbation rates. Although this trial did examine the effects of tiotropium and salmeterol on asthma symptoms and quality of life, no noninferiority change values were defined for those end points; therefore, the treatments cannot be adequately compared. Additionally, as this trial only included patients with the *B16-Arg/Arg* polymorphism of *ADBR2*, the application of the results to other populations may be limited.

A companion study[24] to the previously detailed study[23] evaluated the use of tiotropium in patients with inadequately controlled severe asthma. This randomized, double-blind, placebo-controlled crossover study enrolled adults (aged 18-75 years) with severe persistent asthma (postbronchodilator FEV_1 ≤80% predicted) who were already receiving at least a high-dose ICS and a long-acting β-agonist. Patients were randomized to tiotropium 5 μg by Respimat inhaler daily, tiotropium 10 μg by Respimat inhaler daily, or placebo in a crossover fashion, with each crossover period lasting 8 weeks. Stable doses of theophylline, leukotriene modifiers, or oral glucocorticoids were continued. The primary end point was peak FEV_1 at the end of each treatment period. One hundred seven participants were randomized and 100 completed the study; 54.2% were female, with a mean age of 54.8 years and mean prebronchodilator FEV_1 58% predicted. The peak FEV_1 was significantly improved with both tiotropium 5 μg (difference 139 mL; 95% CI 96-181; $p < 0.01$) and 10 μg (difference 170 mL; 95% CI 128-213; $p < 0.01$) compared with placebo, although there was no difference seen between the 5- and 10-μg doses of tiotropium (difference 32 mL; 95% CI –11 to 75; $p = 0.40$). Tiotropium was superior to placebo in all spirometric measures, including average morning PEF (tiotropium 5 μg, difference 7.9 L/min; 95% CI 1.2-14.7; $p = 0.02$; tiotropium 10 μg, difference 15.3 L/min; 95% CI 8.6-22.0; $p < 0.001$) and evening PEF (tiotropium 5 μg, difference 14.7 L/min; 95% CI 6.8-22.5; $p < 0.001$; tiotropium 10 μg, difference 23.2 L/min; 95% CI 15.4-31.1; $p < 0.001$). Adverse effects occurring more frequently in the active treatment groups included dry mouth, cough, and headache. Study limits include the short duration of each treatment period and lack of a washout period between crossovers, making it difficult to draw conclusions for individual treatments. Moreover, the trial end points focused only on surrogate markers of lung function rather than exploring the efficacy of tiotropium on quality of life measures or asthma exacerbation rates.

Because of the positive effects of tiotropium on pulmonary function tests as well as its steroid-sparing effects in patients with inadequately controlled asthma, Kerstjens and colleagues set out to evaluate its efficacy for the more important outcome of reduction of asthma exacerbations. They conducted 2 replicate, randomized, controlled, 48-week trials that evaluated the efficacy of tiotropium in 912 adults with poorly controlled severe asthma.[25] Eligible patients were nonsmoking adults (aged 18-75 years) who had asthma that was diagnosed before the age of 40 for 5 or more years, ACQ-7 scores of 1.5 or more, persistent airflow limitation that was defined as having a FEV_1 80% or less of predicted, and 70% or less of FVC after use of a short-acting β-agonist at screening visit, despite the use of daily ICS (≥800 μg budesonide or equivalent) and long-acting β-agonists, and 1 or more asthma exacerbation treated with systemic corticosteroids over the past 12 months. Enrolled patients (trial 1, $n = 459$; trial 2, $n = 453$) were randomized to tiotropium 5 μg daily or placebo, administered by a Respimat inhaler. Patients were continued on their maintenance high-dose ICS and long-acting β-agonists. Additionally, pretrial asthma medications (eg, sustained-release theophylline, leukotriene modifiers, anti-IgE antibody, and 5 mg or less of oral corticosteroids) were allowed if the patient was stable on the medication 1 month prior to study entry and throughout the 48-week trial. The 3 coprimary outcomes were changes from baseline in peak FEV_1 (measured within 3 hours of study drug administration) at week 24, trough FEV_1 (measured at the end of the dosing interval) at week 24, and time to first severe asthma exacerbation (defined as an exacerbation requiring the initiation or at least a doubling of the dose of systemic corticosteroids for 3 or more days). Study results were reported on data from 907 patients as a modified intention-to-treat population (patients who were randomized received 1 or more dose of study drug and had 1 or more on-treatment efficacy measurement). At week 24, a significant difference between tiotropium and placebo in the mean (SE) change from baseline for improvements in peak FEV_1 (trial 1, 86 [34] mL; $p = 0.01$; trial 2, 154 [32] mL; $p < 0.001$) and trough FEV_1 (trial 1, 88 [31] mL; $p = 0.01$; trial 2, 111 [30] mL; $p < 0.001$) was reported. Additionally, an increase in the time to first severe exacerbation was reported when tiotropium-treated patients were compared with placebo-treated patients (282 days vs 226 days, respectively), which translated into a 21% overall risk reduction for severe exacerbations (hazard ratio 0.79; 95% CI 0.62-1.00; $p = 0.03$). By increasing the time to severe exacerbation in patients treated with tiotropium, one can infer from the definition of this end point that patients were exposed to fewer systemic corticosteroids. Overall, adverse events were similar between groups. Of the events considered to be drug-related, dry mouth was reported more often in tiotropium-treated patients (1.8%) compared with placebo-treated patients (0.7%). The results of this trial seem promising; however, limitations to the data do exist. Patients enrolled in this study had to have persistent airflow restrictions with postbronchodilator ratio of FEV_1 to FVC of <0.7, which limits the external validity of the results. Also, improvements in FEV_1 were less than 10%, which is small. However, this was still considered an improvement since patients were already on maximum asthma regimens with fixed airflow limitations. Finally, when looking at the individual trials, an unexplained larger placebo response was found in trial 1 compared with trial 2.

Discussion

Evidence on tiotropium's efficacy and steroid-sparing effects for patients with uncontrolled persistent asthma is emerging. In the detailed case report[17] and clinical trials that we reviewed,[18,19,23-25] when tiotropium was compared with or added to asthma regimens, reductions in steroid requirements were reported and PEF and FEV_1 did improve when tiotropium was compared with placebo. Yet, PEF and FEV_1 are only measures of lung function and these effects have not translated into clinical improvements in quality of life. The largest and longest trial to date evaluated symptom control and exacerbation rates as primary end points and showed positive outcomes.[25]

Collectively, the trials reviewed here are heterogeneous. All patients enrolled in the clinical trials had uncontrolled persistent asthma; however, the severity of disease differed. Also, different treatments were used in the trials. Some trials compared tiotropium with a long-acting β-agonist while others added tiotropium to ICS and long-acting β-agonist regimens. The delivery of tiotropium in these trials was not consistent. In some trials, tiotropium 18 μg was delivered using the CFC metered-dose inhaler (MDI), while other trials delivered tiotropium 5 μg by the Respimat inhaler. A dose of tiotropium 5 μg delivered by the Respimat inhaler is considered to be equivalent to 18 μg delivered by CFC MDI. The Respimat inhaler releases the tiotropium as a fine-particle soft mist allowing for increased lung deposition of drug[26] and possibly increased plasma concentrations.[26-28] Because of the length of the trials (4-48 weeks), long-term efficacy and safety in this population with a chronic disease are still unknown.

Summary

In adults with inadequately controlled persistent asthma, the addition of tiotropium to standard therapies often resulted in improved pulmonary function test results as well as decreases in asthma exacerbations and corticosteroid requirements. Although these results are promising, more robust clinical trials are needed to assess whether these changes translate into clinical improvements in quality of life. Additionally, the optimal patient population, long-term efficacy, and safety of tiotropium when delivered by various methods need to be determined before it can be recommended over current alternative asthma therapies.

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Reprints/Online Access: www.theannals.com/cgi/reprint/aph.1R502

Conflict of interest: Authors reported none

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EXTRACTO

Tiotropio Para Adultos con Asma no Controlada Adecuadamente

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Ann Pharmacother 2013;47:117-23.

OBJETIVO: Revisar la literatura publicada recientemente donde se evaluó la eficacia y el efecto moderado de esteroide de tiotropio para asma persistente no controlada adecuadamente en adultos.

FUENTES DE INFORMACIÓN: Revisión bibliográfica de artículos publicados en MEDLINE/PubMed entre 1966 y octubre de 2012. La estrategia de búsqueda usó los términos asma y tiotropio. Las referencias de los artículos fueron revisadas para identificar otras referencias relevantes.

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE DATOS: Informes de casos y estudios clínicos fueron revisados. Las publicaciones donde se evaluó la eficacia y el efecto moderado de esteroide de tiotropio en adultos con asma persistente no controlada adecuadamente fueron incluidas en la revisión. Un estudio de caso y 5 estudios clínicos cumplieron con los criterios de selección.

SÍNTESIS: La meta del manejo de asma es mantener la enfermedad bajo control previniendo exacerbaciones agudas mientras se evitan los efectos adversos a medicamentos. Los corticoesteroides inhalados (ICS) forman parte del régimen preferido de mantenimiento para el asma persistente. Desafortunadamente, algunos pacientes no están controlados adecuadamente y existen preocupaciones sobre efectos adversos serios con el tratamiento a largo plazo con ICS en dosis altas. El interés en usar tiotropio para controlar los síntomas de asma y de reducir los requisitos de esteroide es asma persistente pobremente controlada ha tomado auge. Los resultados de diferentes estudios han reportado que tiotropio mejora los marcadores de función pulmonar y reduce los requisitos para el uso de costicoesteroides. El estudio más largo y grande publicado hasta el momento no solo demostró mejoras en las pruebas de función pulmonar pero también en la reducción en el uso de costicoesteroides y un aumento en el tiempo en que ocurre la primera exacerbación.

CONCLUSIONES: Aunque prometedor, es necesario realizar estudios clínicos más robustos para determinar si las mejoras en las pruebas de función pulmonar así como las disminuciones en exacerbaciones de asma y requisitos de corticoesteroides se traducen en mejoras en calidad de vida. Además, es necesario determinar la población óptima de pacientes, la eficacia a largo plazo y el perfil de seguridad de tiotropio cuando se administra de diversas maneras antes de que pueda ser recomendado sobre otras alternativas de tratamiento de asma actualmente disponibles.

Traducido por Homero A Monsanto

RÉSUMÉ

Est-ce Que le Tiotropium est Efficace dans le Traitement de l'Asthme Persistant non Contrôlé?

KS Adams, DK Lowe

Ann Pharmacother 2013;47:117-23.

OBJECTIF: Revoir la littérature publiée évaluant l'efficacité et l'effet d'épargne des stéroïdes du tiotropium dans le traitement de l'asthme persistant insuffisamment contrôlé chez l'adulte.

SOURCES DES DONNÉES: L'information a été obtenue par une recherche dans MEDLINE/PubMed (1966-octobre 2012) avec les mots-clés asthma et tiotropium. Un examen plus approfondi des références a été réalisé afin d'identifier d'autres articles pertinents.

SÉLECTION DES ÉTUDES ET EXTRACTION DES DONNÉES: Les rapports de cas et les essais cliniques en langue anglaise ont été examinés. Les publications évaluant l'efficacité et l'effet d'épargne des stéroïdes du tiotropium chez l'adulte souffrant d'asthme persistant insuffisamment contrôlé ont été inclus dans l'étude. Un rapport de cas et de 5 essais cliniques répondaient aux critères.

SYNTHÈSE DES DONNÉES: Le but ultime du traitement de l'asthme est de maintenir le contrôle de la maladie par la prévention des exacerbations aiguës, tout en évitant les effets indésirables aux médicaments. Les corticostéroïdes inhalés (CSI) font partie de tous les traitements chroniques privilégiés pour l'asthme persistant. Malheureusement, certains patients restent insuffisamment contrôlés et des préoccupations demeurent concernant les effets indésirables à long terme avec des doses élevées de CSI. Le tiotropium pourrait aider à maîtriser les symptômes d'asthme et à réduire les besoins en stéroïdes. Les résultats de plusieurs essais cliniques rapportent que le tiotropium améliore les marqueurs de la fonction pulmonaire et réduit les besoins en corticostéroïdes. En outre, l'essai clinique de plus longue durée a démontré non seulement des améliorations de la fonction pulmonaire, mais aussi une réduction de l'utilisation de corticostéroïdes et une augmentation du temps pour la première exacerbation.

CONCLUSIONS: Bien que prometteur, des essais cliniques plus robustes avec le tiotropium sont nécessaires pour évaluer si l'amélioration des tests de fonction pulmonaire ainsi que la réduction des exacerbations et de l'usage des CSI se traduit par une amélioration de la qualité de vie. En outre, la population-cible, l'efficacité à long terme et l'innocuité du tiotropium doivent être déterminées avant qu'il ne puisse être recommandé comme traitement alternatif aux thérapies actuelles.

Traduit par Nicolas Paquette-Lamontagne