

Incorporating Tiotropium Into a Respiratory Therapist-Directed Bronchodilator Protocol for Managing In-Patients With COPD Exacerbations Decreases Bronchodilator Costs

Gail S Drescher MA RRT, Bettye J Carnathan RRT, Susan Imus RRT, and Gene L Colice MD

BACKGROUND: Tiotropium is used in maintenance treatment of chronic obstructive pulmonary disease (COPD), but there are no guidelines on when to start tiotropium following an exacerbation. **OBJECTIVE:** To determine whether the addition of tiotropium to a respiratory-therapist-directed bronchodilator protocol affects bronchodilator costs for patients hospitalized for COPD exacerbation. **METHODS:** We retrospectively analyzed data on the number and type of bronchodilator treatments administered to all patients admitted for COPD exacerbation during the 3-month period (January through March 2006) after tiotropium was added to our bronchodilator protocol, and compared that data to a historical control period (January through March 2004) before tiotropium was available in our hospital. We compared the costs of bronchodilator treatments, baseline patient characteristics, comorbidities, concomitant medications, length of stay, adverse events, and in-hospital deaths. **RESULTS:** Baseline characteristics, comorbidities, and concomitant medications were similar in the 2004 control group ($n = 181$) and the 2006 intervention group ($n = 174$). The mean \pm SD number of bronchodilator treatments per admission was significantly higher in the control period (13.6 ± 15.6) than in the intervention period (10.6 ± 9.4). That difference correlated to a reduction in combination therapy (short-acting inhaled β_2 agonist plus ipratropium), which decreased from a per-admission average of 6.7 ± 14.2 in the control period to 1.9 ± 5.1 in the intervention period. Calculated bronchodilator costs were significantly lower in the intervention period than in the control period. Length of stay also significantly decreased, from 6.5 ± 5.0 d to 5.5 ± 4.0 d. There were no adverse events related to tiotropium. Pulmonary-related in-hospital deaths were not significantly different between the 2 periods. **CONCLUSIONS:** Early addition of maintenance-treatment tiotropium to a respiratory-therapist-directed bronchodilator protocol for patients hospitalized for COPD exacerbation reduced costs and produced no safety concerns. *Key words:* tiotropium bromide, chronic obstructive pulmonary disease, COPD exacerbation, respiratory therapist-directed bronchodilator protocol, costs, β_2 agonist, long-acting inhaled bronchodilator, anticholinergic. [Respir Care 2008;53(12):1678–1684. © 2008 Daedalus Enterprises]

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive disorder characterized by limitation of expiratory airflow, cough, sputum production, and dyspnea.¹ The vagal pathway is one of the primary reversible causes of

increased airway tone and bronchospasm in COPD. Consequently, anticholinergic medicines have been widely used to treat COPD, particularly since the introduction of specific muscarinic-receptor antagonists that have little systemic absorption, such as ipratropium.²

Gail S Drescher MA RRT, Bettye J Carnathan RRT, and Susan Imus RRT are affiliated with the Pulmonary Services Department, Washington Hospital Center, Washington DC. Gene L Colice MD is affiliated with the Department of Pulmonary, Critical Care, and Respiratory Services, Washington Hospital Center, and with the Department of Medicine, School of Medicine, George Washington University, Washington DC.

Gene L Colice MD has had relationships with GlaxoSmithKline, Boehringer Ingelheim, Pfizer, Eli Lilly, Abbott, Genentech, Almirall, Forrest, Adams, TEVA, OM Pharma, Nomura, and MedImmune. The authors report no other conflicts of interest related to the content of this paper.

Correspondence: Gail S Drescher MA RRT, Pulmonary Services Department, Washington Hospital Center, 110 Irving Street NW, Washington DC 20010. E-mail: Gail.S.Drescher@medstar.net.

Tiotropium is a long-acting inhaled anticholinergic bronchodilator that is more effective than ipratropium^{2,3} or salmeterol^{4,5} in COPD symptom control. The Global Initiative for Chronic Obstructive Lung Disease guidelines state that long-acting inhaled bronchodilators such as tiotropium are more effective and convenient than short-acting inhaled bronchodilators for the maintenance treatment of COPD.¹ Regular use of tiotropium can also decrease the use of health-care resources by reducing exacerbation frequency and severity, hospitalizations, and hospital days.⁶ Tiotropium is approved for maintenance treatment of COPD, but current guidelines do not provide recommendations for when to start regular use of tiotropium following the onset of a COPD exacerbation.

SEE THE RELATED EDITORIAL ON PAGE 1657

Previous work by our group found that incorporating a long-acting inhaled β_2 agonist into a respiratory therapist (RT) directed protocol for administering bronchodilators to hospitalized patients with asthma or COPD reduced utilization of health-care resources.⁷ In that study we used formoterol as part of an early program of maintenance treatment, not as a rescue agent. In the present study we hypothesized that incorporating tiotropium into this protocol with patients hospitalized for COPD exacerbation and as part of an early maintenance program would further decrease costs.

Methods

Study Design

We retrospectively analyzed whether incorporating tiotropium into a standardized RT-directed protocol for administering bronchodilators would decrease treatment costs. Our primary objectives were to determine whether tiotropium reduced the number of bronchodilator treatments or the average cost of bronchodilator administration. Secondary objectives were to determine whether tiotropium impacted adverse events, stay, or pulmonary-related in-hospital deaths. Data from the intervention period (January through March 2006) were compared to a historical control period (January through March 2004), before tiotropium was available in our hospital.

Setting and Background

This study was conducted at the Washington Hospital Center, a not-for-profit teaching hospital with 907 beds, located in Washington DC. An RT-directed bronchodilator protocol has been used since 1997, and was developed through a consensus process that involved pulmonary/crit-

ical care physicians, RTs, and nurses. The protocol and all its revisions were approved by the institutional review board of Washington Hospital Center.

All patients with orders to receive bronchodilators are evaluated by an RT with standard criteria to determine whether inhaled bronchodilators are indicated. These criteria include previous or current diagnosis of pulmonary disease (eg, asthma or COPD), suspected pulmonary disease, or home use of inhaled bronchodilator, as indicated in the patient's medical record or via patient interview.

The initial bronchodilator medication is determined via diagnosis. Treatment frequency is determined via standard dosing recommendations for long-acting inhaled bronchodilators and the patient's response to short-acting agents. The severity of the patient's condition is established via vital signs and clinical evaluation. Evaluations and treatment plans are routinely reviewed by supervisors and the medical director of pulmonary services to ensure consistency and accuracy.⁷ Treatment plans are modified following any important change in patient status.

In 2004, non-intubated patients with COPD exacerbation received formoterol regularly and ipratropium and/or short-acting inhaled β_2 agonist for persistent symptoms. Tiotropium was added to Washington Hospital Center's formulary in 2005. That year we amended our protocol to include tiotropium, obtained administrative approval for the protocol change, and implemented an education program to train RTs in the use of tiotropium under our revised policy. In 2006 we implemented the revised protocol as the initial regular treatment for all COPD patients, with formoterol added if the patient did not show improvement. Short-acting inhaled β_2 agonists were administered when necessary.

If the patient could not perform the dry powder inhaler (DPI) maneuver (eg, because bronchoconstriction prevented the necessary inspiratory flow rate), we administered a nebulized short-acting β_2 agonist and/or anticholinergic until the patient was stable enough to perform the DPI maneuver. The HandiHaler (tiotropium) and Aerolizer (formoterol) DPIs are both designed to be used with low inspiratory flow (40–60 L/min).⁸ RTs also evaluate patients' DPI maneuvers, and then, with product delivery information, determine whether the medication was taken correctly. Patients do not self-administer their medications.

All protocol evaluations and treatments by RTs were documented in an electronic charting system (Clinivision, Tyco, Carlsbad, California). Adverse events were monitored during and immediately following treatment, according to departmental policy. Possible bronchodilator-associated adverse events were identified with product information and posted in the electronic charting system for easy RT access and classification.

Subjects

All general-care patients admitted to the medical floors with COPD exacerbation during the data-collection and historical control periods were included in the sample. Patients with stable COPD who were admitted for other medical conditions were excluded. Patients who were intubated or had a tracheostomy were also excluded, because DPI medications cannot be administered to these patients.

We used a 3-step process to identify patients with COPD exacerbations during the study periods. First, records of patients who received bronchodilator treatments for a COPD exacerbation on general medical units were obtained from the RT electronic charting system. Second, the discharge summaries of identified patients were reviewed to ensure that they met the Global Initiative for Chronic Obstructive Lung Disease criteria for a COPD exacerbation. Third, we reviewed information from the Washington Hospital Center clinical documentation database, including ICD-9 (International Classification of Diseases, 9th Revision, Clinical Modification) codes, medications, diagnostics, and RT notes, to further confirm the diagnosis of COPD exacerbation.

We included only patients with a history compatible with a COPD exacerbation, documented by a physician and defined by increased cough, sputum production, and dyspnea. We obtained data on the number and type of bronchodilator treatments, inhaled corticosteroids, supplemental oxygen, and adverse events from the RT electronic charting system. We obtained patient age, sex, length of stay (LOS), in-hospital deaths, and use of concomitant medications (eg, antibiotics, systemic corticosteroids, diuretics, β blockers, theophylline, and leukotriene inhibitors) from the hospital clinical database.

We also reviewed the medical records of 120 patients randomly selected (with a random numbers table) from 2004 and 2006, to collect information on comorbidities and concomitant medication use. We used the Charlson comorbidity index to obtain a standard measure of the severity of patient illness. This index was originally developed to predict mortality in chronic disease, but is a reliable and valid measure of multiple comorbidities.⁹

Statistical Analysis

We used the total number and type of bronchodilator treatments per admission as the primary outcome variables to assess health-care resource use. In addition, we compared the per-day use of short-acting combination bronchodilators over the first 6 days of hospitalization. The outcome variables we used to assess the safety of this regimen were adverse events, LOS, and in-hospital deaths. The variables we used to compare the baseline characteristics of the groups were age, sex, supplemental oxygen,

Table 1. Costs: Medications, Equipment, and Labor

	Unit Cost (2006 U.S. dollars)
Medication	
Albuterol	
Nebulized (2.5 mg/3-mL unit dose)	0.40
MDI (90 ug per puff)	18.75 for 17 g (0.09 per puff)
Levalbuterol (1.25 mg/3-mL unit dose)	2.70
Ipratropium	
Nebulized (0.5 mg/2.5-mL unit dose)	0.62
MDI (18 ug per puff)	73.00 for 200 \times 100 μ g (0.36 per puff)
Combivent (ipratropium bromide plus albuterol sulfate)	79.90 for 14.7 g (0.40 per puff)
Formoterol (12 ug/inhalation, unit dose)	2.19
Tiotropium (18 ug/inhalation, unit dose)	4.35
Equipment	
Spacer (AeroChamber)	9.50
Nebulizer kit (AeroEclipse)	5.00
Labor	
Hourly wage for respiratory therapist	28.20

MDI = metered-dose inhaler

Charlson comorbidity index, and concomitant medications (antibiotics, systemic steroids, diuretics, inhaled corticosteroid, β blockers, theophylline, and leukotriene inhibitors). We made statistical comparisons with the chi-square test and unpaired *t* test.

Costs are expressed per admission for bronchodilator therapy. Included in the cost analysis were prices for medication and equipment, relative value units for RT time in delivering bronchodilator therapy, and the average RT wage at Washington Hospital Center. Patients who receive nebulizer therapy are issued a nebulizer kit, and those who receive metered-dose-inhaler (MDI) therapy are issued a spacer (AeroChamber, Monaghan Medical, Plattsburgh, New York) that has a 1-way valve that prevents exhalation into the device. In our "common-canister" program the MDI (common canister) is shared among patients in the unit until the canister is empty. The cost per MDI puff is calculated on the price of the MDI and the total puffs available from the canister.

Patients prescribed formoterol received the Aerolizer DPI (Schering, Kenilworth, New Jersey), and those prescribed tiotropium received the HandiHaler DPI (Boehringer-Ingelheim, Ridgefield, Connecticut). The lowest average wholesale price of the medications and supplies were obtained from the 2006 edition of the Thomson *Physicians' Desk Reference*, which provides national pricing information (Table 1). Pricing information for the ipratropium MDI was obtained from the 2004 edition of the Thomson *Physicians' Desk Reference*, because this form

Table 2. Baseline Characteristics and Medications

Variable*	January Through March 2004 (<i>n</i> = 181)	January Through March 2006 (<i>n</i> = 174)
Age (mean ± SD y)	69.8 ± 11.2	68.6 ± 11.7
Male (<i>n</i> , %)	88 (48)	87 (50)
Oxygen (<i>n</i> , %)	138 (76)	130 (75)
Inhaled corticosteroids (<i>n</i> , %)	71 (39)	45 (25)
Comorbidity and concomitant medications (<i>n</i>)*	60	60
Charlson comorbidity index (mean ± SD)	2.7 ± 1.6	2.9 ± 1.9
Antibiotics (<i>n</i> , %)	48 (26)	38 (22)
Systemic corticosteroids (<i>n</i> , %)	49 (27)	33 (19)
Diuretics (<i>n</i> , %)	25 (14)	27 (15)
β blockers (<i>n</i> , %)	1 (< 1)	2 (< 1)
Miscellaneous medications (<i>n</i> , %) [†]	6 (< 1)	1 (< 1)

* Randomly chosen (with a random numbers table) from each study period.

[†] Miscellaneous medication includes leukotriene inhibitors and theophylline.

of the drug was discontinued in 2006, although it was still available through the Washington Hospital Center pharmacy during the intervention period. Combination therapy is given with unit doses of albuterol and ipratropium, both of which cost approximately \$1 per treatment. DuoNeb (a combination of ipratropium bromide and albuterol sulfate) is not on our hospital formulary.

Results

Subjects

The intervention group comprised 174 patients. The historical control group comprised 181 patients. There were no significant differences in baseline characteristics between the 2 groups (Table 2). The Charlson comorbidity index was similar for the intervention group (2.9 ± 1.9) and the control group (2.7 ± 1.6). There were no significant differences in use of supplemental oxygen or concomitant medications between the 2 groups.

Treatments/Medication Use

2,488 bronchodilator treatments were given during the control period, and 1,731 bronchodilator treatments were given during the intervention period, which was a decrease of over 30% (Table 3). Bronchodilator treatments per admission was also significantly lower in the intervention period (Table 4). There was also a significant decrease in the use of combination therapy (ipratropium plus short-acting inhaled β₂ agonist): 6.7 ± 14.2 treatments per admission in the control period versus 1.9 ± 5.1 treatments per admission in the intervention period (*P* < .05). When analyzed on a per-day basis, significantly fewer combination-therapy treatments were administered over the first

6 days of hospitalization in the intervention period than in the control period (*P* < .05). There was also a significant decrease (approximately \$35/patient) in bronchodilator treatment costs per patient (*P* < .05).

Stay

LOS was shorter during each individual month and overall for the 3-month periods: 6.5 ± 5.0 d in the control period versus 5.5 ± 4.0 d in the intervention period (Fig. 1). The median stay was 6.0 d in the control period and 5.0 d in the intervention period.

Adverse Events/Deaths

There were 3 adverse events associated with bronchodilator therapy in the intervention period and 7 in the control period. In 2006, levalbuterol was related to 2 adverse events (tachycardia and tachypnea), and formoterol was related to one (anxiety). No adverse events were associated with tiotropium during the intervention period. During the control period 3 adverse events were related to combination therapy (hypoxia), 3 were related to ipratropium (hypertension), and 1 was related to levalbuterol (nervousness). The rate of adverse events was 4/100 admissions (7/181) in patients who received bronchodilators in the control period, versus 2/100 (3/174) in the intervention period (*P* < .05). In the intervention-period group there were 6 in-hospital deaths, 2 of which were related to COPD. In the control-period group there were 5 in-hospital deaths, 3 of which were pulmonary-related.

Discussion

In this retrospective analysis the incorporation of tiotropium into an RT-directed bronchodilator protocol as early

Tiotropium in an RT-Directed COPD Protocol

Table 3. Types and Frequency of Bronchodilator Treatments

Bronchodilator	January Through March 2004 <i>n</i> (%)	January Through March 2006 <i>n</i> (%)
Albuterol	84 (3)	71 (4)
MDI	52 (2)	15 (< 1)
Nebulizer	32 (< 1)	56 (3)
Levalbuterol	270 (11)	345 (20)
Formoterol	746 (30)	395 (23)
Ipratropium	146 (6)	25 (1)
MDI	71 (3)	5 (< 1)
Nebulizer	77 (3)	20 (1)
Combination ipratropium and short-acting inhaled β_2 agonist	1,242 (50)	354 (20)
MDI	147 (6)	87 (5)
Nebulizer	1,095 (44)	267 (15)
Tiotropium	NA	541 (31)
Total bronchodilator treatments	2,488 (100)	1,731 (100)

MDI = metered-dose inhaler

NA = not applicable because tiotropium was not available at our center at that time

Table 4. Health-Care Resource Use

	January Through March 2004	January Through March 2006
Bronchodilator treatments per admission (mean \pm SD)	13.6 \pm 15.6	10.6 \pm 9.4*
Formoterol per admission (mean \pm SD)	4.1 \pm 5.2	3.4 \pm 4.3
Short-acting, inhaled β_2 agonist treatments per admission (mean \pm SD)	1.8 \pm 3.9	2.3 \pm 4.4
Ipratropium treatments per admission (mean \pm SD)	0.8 \pm 3.0	0.2 \pm 0.6
Combination short acting inhaled β_2 -agonist plus ipratropium treatments per admission (mean \pm SD)	6.7 \pm 14.2	1.9 \pm 5.1*
Tiotropium treatments per admission (mean \pm SD)	NA	3.1 \pm 3.0
Bronchodilator cost per admission (mean \$)	107.85	88.97*

* $P < .05$ for 2006 versus 2004.

NA = not applicable because tiotropium was not available at our center at that time

maintenance therapy for patients with a COPD exacerbation was associated with significantly fewer bronchodilator treatments, significantly lower overall cost of bronchodilator administration, and significantly shorter LOS. No safety concerns were found with the use of tiotropium.

Previous work by our group found that the integration of formoterol (a long-acting inhaled β_2 agonist) into an RT-directed bronchodilator protocol lowered costs by decreasing the number of bronchodilator treatments and RT time administering bronchodilators.⁷ In the present analysis we extended those findings by assessing the addition of the long-acting inhaled anticholinergic tiotropium to the bronchodilator regimen for patients with a COPD exacerbation. Tiotropium is approved for COPD maintenance therapy, but not for rapid symptom relief, because it can take up to 2 hours to achieve peak effect. However, tiotropium can significantly improve lung function in COPD

within the first day of administration.^{10,11} Tiotropium also improves airflow within the first week of administration, even in patients who have a poor FEV₁ response to the initial dose.¹² Furthermore, the combination of formoterol and tiotropium provides greater bronchodilation than either individually.¹³ Preliminary work indicated that the combination of tiotropium and formoterol improves lung function more than either drug alone in mild-to-moderate COPD exacerbation.¹⁴

An important aspect of our protocol is that patients with a COPD exacerbation receiving long-acting inhaled bronchodilators might also receive short-acting inhaled agents, including ipratropium. There are several reasons for combining ipratropium and tiotropium in a COPD exacerbation. DiMarco and colleagues found that the bronchodilation effects of tiotropium do not last as long in patients with a COPD exacerbation as in patients with stable

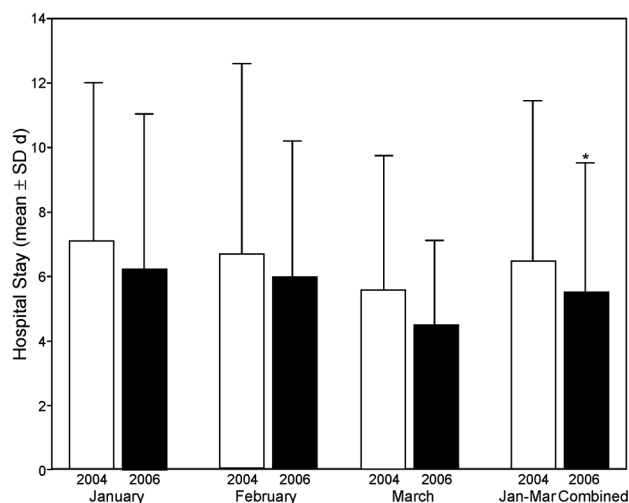


Fig. 1. Hospital stay of patients hospitalized for exacerbation of chronic obstructive pulmonary disease, by month and cumulative for January through March 2004 ($n = 181$) and January through March 2006 ($n = 174$). * $P < .05$ for 2004 versus 2006.

COPD.¹⁴ The dose-response curve of tiotropium suggests the potential for greater bronchodilation with additional doses, without substantial concern about adverse effects.² A recent study found that patients with COPD obtained significant additional bronchodilation when ipratropium was added to tiotropium.¹⁵

As expected, in the present study the addition of tiotropium significantly decreased bronchodilator treatments per admission, largely because of the decreased use of combination therapy (short-acting inhaled β_2 agonist plus ipratropium). Although albuterol and ipratropium are both substantially less expensive than tiotropium, the reduction in RT time and nebulizer supplies for administering short-acting inhaled bronchodilators offset the higher cost of tiotropium. The cost savings might have been greater if we had been able to accurately calculate the time needed to administer tiotropium. Our department allocates the same amount of relative-value-unit time for administering a DPI treatment as we do for giving bronchodilators via nebulizer or MDI. Administering a DPI can take less than several minutes, but administering a nebulizer treatment can take 10–30 min, depending on the amount of medication in the reservoir cup. Anecdotally, our RTs reported that patients were generally able to operate the tiotropium DPI without difficulty.

Adverse events related to bronchodilator administration are routinely monitored by RTs under our bronchodilator protocol. Tiotropium is well tolerated and has a safety profile similar to ipratropium.¹⁶ No adverse events were associated with tiotropium use in the present retrospective analysis. We previously found 3–7 bronchodilator-associated adverse events reported for every 100 patients treated with inhaled bronchodilator,⁷ and in the present analysis

we found a similar rate. Our earlier work found that incorporating formoterol into the RT-directed bronchodilator protocol was associated with fewer adverse events, probably by decreasing the number of short-acting inhaled bronchodilators administered per admission. We found a similar, but not significant, trend in the present study. In the control period there were 4 adverse events per every 100 patients who received bronchodilators, but in the intervention period there were only 2 adverse events per every 100 patients. Presumably, if there were a safety advantage with tiotropium use in the intervention period, it was due to the decrease in per-admission bronchodilator treatments.

COPD is a major cause of morbidity and mortality in the United States and other developed countries, and has an enormous economic impact. The direct costs of COPD, including diagnosis and medical management, topped \$18 billion in 2002;¹ up to 70% of that cost related to hospitalizations.¹⁷ Maintenance treatment with tiotropium reduces the frequency and severity of exacerbations¹⁸ and reduces hospitalization days.^{19,20} The results of the present study add to the latter findings and suggest that tiotropium might reduce LOS in patients hospitalized for a COPD exacerbation. These results are encouraging but should be viewed cautiously. Although our finding on LOS is similar to average values reported by the Centers for Medicare and Medicaid Services, multiple factors influence LOS in a COPD exacerbation. However, if tiotropium reduces LOS, there should be important economic benefits from the early introduction of tiotropium during hospitalization for COPD exacerbation.

Limitations

The treatment group was compared to a historical control group. However, the same RT-directed bronchodilator protocol was used during both study periods, which ensured consistency in care through standardization of patient assessment, bronchodilator ordering practices, and medication administration. Also, by comparing patients admitted in January through March of 2004 and 2006 we controlled for seasonal variations in hospital admissions and infectious disease rates. The control and intervention groups had similar sample sizes and baseline characteristics. Most patients hospitalized for a COPD exacerbation suffer from one or more comorbid conditions.²¹ The Charlson comorbidity index scores showed no difference in illness severity between the 2 groups.

The use of antibiotics and systemic corticosteroids was similar in the control and intervention periods, and surprisingly less frequent than advocated by guidelines.²² Therefore, the reduction in bronchodilator treatments and LOS cannot be attributed to more aggressive care in 2006. Lindenauer and colleagues conducted a retrospective co-

hort study of almost 70,000 patients hospitalized for COPD exacerbation, to determine whether providers were following peer-reviewed clinical guidelines,²³ and, as in the present study, there was widespread under-use of systemic corticosteroids and antibiotics.

Objective data on changes in lung function during hospitalization were not available and should be obtained in a future randomized prospective study of early introduction of tiotropium in COPD exacerbations. However, if use of short-acting inhaled bronchodilators is accepted as a surrogate marker of lung function, the decreased use of short-acting inhaled bronchodilators in the intervention period suggests more sustained bronchodilation with the regular use of long-acting inhaled bronchodilators.

Conclusions

The addition of tiotropium as early maintenance treatment in an RT-directed bronchodilator protocol is cost-effective and safe in patients hospitalized for COPD exacerbation. Tiotropium reduced bronchodilator administration costs by decreasing the need for short-acting inhaled bronchodilators. No safety concerns were found with tiotropium in this patient population. Our preliminary information also suggests that tiotropium may have contributed to shorter LOS, but this finding requires careful future assessment.

REFERENCES

- Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GINA executive summary. *Eur Respir J* 2008;31(1):143-178.
- Gross NJ. Tiotropium bromide. *Chest* 2004;126(6):1946-1953.
- Sin DD, McAlister FA, Man SFP, Anthonisen NR. Contemporary management of chronic obstructive pulmonary disease: scientific review. *JAMA* 2003;290(17):2301-2312.
- Donohue JF, van Noord JA, Bateman ED, Langley SJ, Lee A, Witek TJ, et al. A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. *Chest* 2002;122(1):47-55.
- Brusasco V, Hodder R, Miravittles M, Korducki L, Towse L, Kesten S. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. *Thorax* 2003;58(5):399-404.
- Vincken W, van Noord JA, Greefhorst APM, Bantje TA, Kesten S, Korducki L, Cornelissen PJG. Improved health outcomes in patients with COPD during 1 year's treatment with tiotropium. *Eur Respir J* 2002;19(2):209-216.
- Colice GL, Carnathan B, Sung J, Paramore LC. A respiratory therapist-directed protocol for managing in-patients with asthma and COPD incorporating a long-acting bronchodilator. *J Asthma* 2005;42(1):29-34.
- Weuthen T, Roeder S, Brand P, Mullinger B, Scheuch G. In vitro testing of two formoterol dry powder inhalers at different flow rates. *Journal of Aerosol Medicine* 2002;15(3):297-303.
- Fortin M, Hudon C, Dubois MF, Almirall J, Lapointe L, Soubhi H. Comparative assessment of three different indices of multimorbidity for studies on health-related quality of life. *Health Qual Life Outcomes* 2005;3:74.
- Casaburi R, Mahler DA, Jones PW, Wanner A, San Pedro G, Zupallack RL, et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002;19(2):217-224.
- van Noord JA, Smeets JJ, Custers FLJ, Korducki L, Cornelissen PJG. Pharmacodynamic steady state of tiotropium in patients with chronic obstructive pulmonary disease. *Eur Respir J* 2002;19(4):639-644.
- Tashkin D, Kesten S. Long-term treatment benefits with tiotropium in COPD patients with and without short-term bronchodilator responses. *Chest* 2003;123(5):1441-1449.
- van Noord JA, Aumann JL, Janssens E, Verhaert J, Smeets JJ, Mueller A, Cornelissen PJG. Effects of tiotropium with and without formoterol on airflow obstruction and resting hyperinflation in patients with COPD. *Chest* 2006;129(3):509-517.
- Di Marco F, Verga M, Santus P, Morelli N, Cazzola M, Centanni S. Effect of formoterol, tiotropium, and their combination in patients with acute exacerbation of chronic obstructive pulmonary disease: a pilot study. *Respir Med* 2006;100(11):1925-1932.
- Kerstjens HA, Bantje TA, Luursemma PB, Sinninghe Damste HE, de Jong WJ, Lee A, et al. Effects of short-acting bronchodilators added to maintenance tiotropium therapy. *Chest* 2007;132(5):1493-1499.
- Kesten S, Jara M, Wentworth C, Lanes S. Pooled clinical trial analysis of tiotropium safety. *Chest* 2006;130(6):1695-1703.
- Niewoehner DE. The impact of severe exacerbations on quality of life and the clinical course of chronic obstructive pulmonary disease. *Am J Med* 2006;119(10 Suppl 1):S38-S45.
- Niewoehner DE, Rice K, Cote C, Paulson D, Cooper JA Jr, Korducki L, et al. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator. *Ann Intern Med* 2005;143(5):317-326. Summary for patients in: *Ann Intern Med* 2005;143(5):120.
- Oostenbrink JB, Molken R, Al MJ, van Noord JA, Vincken W. One-year cost-effectiveness of tiotropium versus ipratropium to treat chronic obstructive pulmonary disease. *Eur Respir J* 2004;23(2):241-249.
- Friedman M, Menjoge SS, Anton SF, Kesten S. Healthcare costs with tiotropium plus usual care versus usual care alone following 1 year of treatment in patients with chronic obstructive pulmonary disorder. *Pharmacoeconomics* 2004;22(11):741-749.
- Groenewegen KH, Schols AMWJ, Wouters EFM. Mortality and mortality-related factors after hospitalization for exacerbation of COPD. *Chest* 2003;124(2):459-467.
- Bach PB, Brown C, Gelfand S, McCrory DC; American College of Physicians; American Society of Internal Medicine; American College of Chest Physicians. Management of acute exacerbations of chronic obstructive pulmonary disease: a summary and appraisal of published evidence. *Ann Intern Med* 2001;134(7):600-620.
- Lindenauer PK, Pekow P, Gao S, Crawford AS, Gutierrez B, Benjamin EM. Quality of care for patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 2006;144(12):894-903.