

Tiotropium/olodaterol (Stiolto®): A new fixed-dose combination therapy for moderate-to-severe COPD

Emet Anceaume, PharmD Candidate

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death and major disability in the United States.¹ An estimated 12 million people in the U.S. are diagnosed with COPD, while an additional 12 million are unaware that they have the disease.² According to the World's Health Organization (WHO), >3 million people died of COPD in 2012, representing ~6% of all deaths globally that year.³ Current pharmacologic treatments are non-curative and focus primarily on delaying disease progression and relief of COPD symptoms, such as dyspnea, chest tightness, and exercise intolerance. These medications also decrease the incidence of exacerbations and hospitalizations, and improve quality of life.

The cornerstones of maintenance therapy for moderate-to-severe COPD include long acting β_2 -agonists (LABAs) and long acting muscarinic antagonists (LAMAs). These medications can be used separately; however, combination therapy with both a LABA and LAMA is recommended in patients who are not adequately controlled on a single long-acting bronchodilator. Currently, two fixed-dose LABA/LAMA combination products are available in the U.S. with approved indications for COPD: Breo Ellipta and Bevespi. In May 2015, the FDA granted an approved indication for tiotropium/olodaterol (Stiolto®) for long-term, once-daily maintenance therapy of airflow obstruction in patients with COPD. Stiolto® is not indicated to treat asthma or acute deterioration of COPD.⁴ The purpose of this article is to review the pharmacologic profile, clinical trials, side effects, dosing, and cost associated with tiotropium/olodaterol.

PHARMACOLOGY

Tiotropium is a long-acting, muscarinic antagonist with similar affinity for muscarinic receptors subtypes M_1 through M_5 . In the airways, tiotropium exhibits pharmacologic effects through



IN THIS ISSUE

Tiotropium/olodaterol (Stiolto®): A new fixed-dose combination therapy for moderate-to-severe COPD

inhibition of M_3 -receptors in smooth muscle, leading to bronchodilation. The LABA olodaterol exerts its pharmacological effects by binding and selectively activating β_2 -adrenoceptors in the airways. Activation of these receptors stimulates intracellular adenylyl cyclase, an enzyme that mediates the synthesis of cyclic-3', 5' adenosine monophosphate (cAMP).⁴ Elevated levels of cAMP induce bronchodilation by relaxation of airway smooth muscle cells. The pharmacokinetic properties of tiotropium and olodaterol are outlined in **Table 1**.⁴ Pharmacokinetic data on the combination product are reported to be similar to those of the individual monotherapies.

CLINICAL TRIALS

Two phase III trials (TONado 1 and 2) were conducted to assess the efficacy and safety of once-daily treatment with orally inhaled tiotropium/olodaterol (fixed dose combination [FDC], dosed at 5/5 mcg or 2.5/5 mcg), delivered *through* the Stiolto® Respimat inhaler, compared with its individual components in patients with moderate-to-very severe COPD (GOLD stage 2–4) over 52 weeks. The studies also included as part of the primary endpoint at week 24, the St. George's Respiratory Questionnaire (SGRQ) total score from baseline, and as part of secondary endpoints, the transition dyspnea index (TDI) total score. **Table 2** summarizes the pooled results of these trials.⁵

TONado 1 Trial

TONado 1 was a 52-week, randomized, double-blind, five-arm, incomplete-crossover study to determine the optimal once-daily dose of olodaterol (5 and 10 mcg) and tiotropium (1.25, 2.5,

Table 1 | Pharmacokinetics of olodaterol/ tiotropium.⁴

| Property | Tiotropium | Olodaterol |
|---------------------|---|---|
| Absorption | | |
| T_{max} | 5-7 minutes | 10-20 minutes |
| BA | 33% (inhaled), 2-3% (oral) | 30% (inhaled), <1% (oral) |
| Distribution | | |
| V_d | 32 L/kg | 1100 L |
| Metabolism | | |
| | CYP450-dependent oxidation & glutathione conjugation | CYP2C8, 2C9, 3A4; UGT1A1, 1A7, 1A9, 2B7 |
| Elimination | | |
| Route | 19% (urinary), ~80% (feces) | 7% (urinary), ~80% (feces) |
| $t_{1/2}$ | 25 hours | 7.5 hours |

BA = bioavailability; CYP = cytochrome P450; T_{max} = time to maximum (peak) serum concentration; UGT = glucuronosyltransferase; V_d = volume of distribution

Table 2 | Select Efficacy Measures at 24 weeks (Combined Analysis of TOnado 1 and 2 trials).⁵

| Outcome | TIO/OLO 5/5 mcg vs. OLO 5 mcg | TIO/OLO 5/5 mcg vs. TIO 5 mcg | TIO/OLO 5/5 mcg vs. TIO/OLO 2.5/5 mcg |
|--|-------------------------------|-------------------------------|---------------------------------------|
| FEV ₁ AUC _{0-3h} (L) | 0.128 (0.111, 0.144) | 0.110 (0.093, 0.127) | 0.013 (-0.004, 0.030) |
| Trough FEV ₁ (L) | 0.085 (0.067, 0.102) | 0.060 (0.43, 0.077) | 0.022 (0.005, 0.039) |
| SGRQ total score | -1.693 (-2.778, -0.608) | -1.233 (-2.313, -0.153) | -0.662 (-1.73, 0.407) |
| TDI focal score | 0.420 (0.155, 0.684) | 0.356 (0.092, 0.619) | 0.003 (-0.259, 0.266) |
| Exacerbations ^a (Risk Ratio) | 0.834 (0.706, 0.986) | 0.925 (0.781, 1.095) | N/A |

^aexacerbation data over 52-weeks of treatment.

FEV₁ = forced expiratory volume in one second; OLO = olodaterol; SGRQ = St. George's respiratory questionnaire; TDI = transitional dyspnea score; TIO = tiotropium

and 5 mcg) in combination in patients with COPD.⁵ The study aimed to determine whether a FDC of tiotropium/olodaterol would provide improvements in lung function, health-related quality of life and other COPD disease parameters, with a comparable safety profile, compared to monotherapy with either component alone. Patients were randomly assigned to one of five arms: tiotropium/olodaterol FDC 5/5 mcg once daily; tiotropium/olodaterol FDC 2.5/5 mcg once daily; olodaterol Respimat 5 mcg once daily; tiotropium Respimat 5 mcg; or, tiotropium Respimat 2.5 mcg daily.

The study included men and women aged ≥ 40 years, with a diagnosis of COPD confirmed by spirometric criteria. Patients were required to have a post-bronchodilator FEV₁ $\geq 30\%$ and $< 80\%$, as well as a post-bronchodilator FEV₁/FVC ratio $< 70\%$. Current and former smokers with a smoking history > 10 pack-years were also enrolled. Concomitant respiratory medications included inhaled corticosteroids, inhaled short-acting β_2 -agonists, LABAs, and short-acting anticholinergics.⁵ Patients with a significant disease other than COPD were excluded. Other exclusion criteria were: clinically relevant abnormal baseline laboratory parameters or a history of asthma; myocardial infarction within 1 year of screening; unstable or life-threatening cardiac arrhythmia; known active tuberculosis; clinically evident bronchiectasis; cystic fibrosis or life-threatening pulmonary obstruction; hospitalization for heart failure within the past year; diagnosed thyrotoxicosis or paroxysmal tachycardia; previous thoracotomy with pulmonary resection; regular use of daytime oxygen if patients were unable to abstain during clinic visits; or current enrollment in a pulmonary rehabilitation program (or completed in the 6 weeks before screening). The study's primary efficacy endpoint was change from baseline to the end of treatment (day 29) in trough FEV₁ response. Secondary efficacy endpoints included FEV₁ area under the curve from zero to six hours (AUC_{0-6 hrs}) response after four weeks of treatment, trough FVC response, FVC AUC_{0-6 hrs} response after four weeks of treatment, and the incidence and severity of adverse events.⁵

A total of 232 patients with COPD (133 men and 99 women) were enrolled and received treatment with study medication. At enrollment, 39.6% of patients were aged 65 to < 75 years, 9.3% were aged 75 to < 85 years and 0.1% were aged ≥ 85 years, and approximately one-third were current smokers. Fifty percent of patients had GOLD 2 category COPD, 38.5% had GOLD 3, and 11.3% had GOLD 4. Approximately 21% had cardiac disorders, and 48% had vascular disorders.

At day 29, the adjusted mean trough FEV₁ and FEV₁ AUC_{0-6 hrs} were increased from baseline with olodaterol 5-mcg and 10-mcg monotherapy, (0.071 L and 0.083 L, respectively, for trough

FEV₁ response, and 0.188 L and 0.198 L, respectively, for FEV₁ AUC_{0-6 hrs} response). Compared with olodaterol 5-mcg monotherapy, significantly greater FEV₁ responses were observed during treatment with combination tiotropium/olodaterol at doses of 1.25/5 mcg (+0.54 L with tiotropium/olodaterol), 2.5/5 mcg (+0.065 L) and 5/5 mcg (+0.084 L). The authors concluded that the addition of tiotropium to olodaterol resulted in improvements in lung function parameters compared with olodaterol monotherapy in this four-week study.⁵

Symptomatic benefit of the FDC was demonstrated by statistically significant improvements in mean SGRQ total score: compared with monotherapy, this improvement was observed with tiotropium+olodaterol FDC 5/5 mcg but not with 2.5/5 mcg. Improvements in SGRQ that exceeded the minimum clinically important difference of 4 units for this measure were seen in all treatment arms, but the difference between the FDCs and the monotherapies did not meet this threshold. 6 Since there was no placebo arm, further analysis of the relevance of these improvements is limited. Responder analyses have been proposed as an additional approach to assessing efficacy of treatments in COPD, particularly for studies in which second and third treatments are added to current therapy.⁶ The responder rates were defined as a reduction in SGRQ total score of ≥ 4 units from baseline. These were much greater for tiotropium+olodaterol FDC 5/5 mcg compared with its monotherapy components and for 2.5/5 mcg compared with olodaterol 5 mcg. The COPD exacerbation rate was significantly lower with tiotropium 5 μ g (RR =0.78; P=0.002) and tiotropium 10 μ g (RR =0.73; P=0.0008); the health-related quality of life and Mahler TDI coprimary endpoints were significantly improved with both doses (both P<0.0001).⁷

Table 3 | Adverse Event Summary

| Adverse Event | TIO/OLO 5/5 (n=1029) | TIO 5 (n=1033) | OLO 5 (n=1038) |
|-----------------|----------------------|----------------|----------------|
| COPD | 32.3 | 32.9 | 35.6 |
| Nasopharyngitis | 12.4 | 11.7 | 12.6 |
| Cough | 3.9 | 4.4 | 3.0 |
| Dyspnea | 3.8 | 4.9 | 3.7 |
| Back pain | 3.6 | 1.8 | 3.4 |
| Pneumonia | 3.3 | 2.5 | 3.5 |
| Bronchitis | 3.0 | 2.2 | 3.2 |

Data are presented as percentage of treated population. OLO = olodaterol; TIO = tiotropium

Table 4 | Approximate costs of Stiolto® and similar COPD medications in Gainesville, FL, 2016.⁸

| Drug | Cash Price (1-month supply) |
|--|--------------------------------|
| Stiolto Respimat (tiotropium bromide & olodaterol) | \$364 |
| Anoro Ellipta (umeclidinium & vilanterol) | \$340 |
| Incruse Ellipta (umeclidinium) | \$274 |
| Tudorza Pressair (aclidinium) | \$320 |
| Striverdi (olodaterol) | \$180 |
| Spiriva (tiotropium) | \$360 |

TONado 2 Trial

The positive results from the dose-ranging studies of tiotropium/olodaterol FDCs supported the evaluation of once-daily doses of tiotropium/olodaterol 2.5/5 mcg and 5/5 mcg in two 52-week, phase 3 confirmatory trials, known as TONado 2.⁴ These replicate, randomized, double-blind, active-controlled, parallel-group studies evaluated a total of 5,162 patients with COPD (1,029 receiving tiotropium/olodaterol 2.5/5 mcg or 5/5 mcg, 1,033 receiving tiotropium 2.5 mcg or 5 mcg, and 1,038 receiving olodaterol 5 mcg). All of the products were administered using the Respimat inhaler.⁴ The primary endpoints of both studies were the change from baseline in FEV₁ AUC_{0-3 hrs} and trough FEV₁ after 24 weeks of treatment.⁵

Most of the 5,162 patients were men (73%) and were either white (71%) or Asian (25%), with a mean age of 64 years. The mean post-bronchodilator FEV₁ was 1.37 L, and the mean β_2 -agonist responsiveness was 16.6% of baseline (0.171 L). Pulmonary medications, such as inhaled steroids (47%) and xanthines (10%), were allowed as concomitant therapy.⁵

In both studies, the two FDCs of tiotropium/olodaterol (2.5/5 mcg and 5/5 mcg) significantly improved FEV₁ AUC_{0-3 hrs} and trough FEV₁ compared with the individual components. FEV₁ AUC_{0-3 hrs} responses were 241 and 256 mL for tiotropium/olodaterol 2.5/5 mcg and 5/5 mcg, respectively, 148 and 139 mL for tiotropium 2.5 mcg and 5 mcg, respectively, and 133 mL for olodaterol 5 mcg, in the first study. In the second study, the corresponding FEV₁ AUC_{0-3 hrs} responses were 256 and 268 for tiotropium/olodaterol 2.5/5 mcg and 5/5 mcg, respectively, 125 and 165 for tiotropium 2.5 mcg and 5 mcg, respectively, and 136 mL for olodaterol 5 mcg. In both trials, the improvements in the adjusted mean FEV₁ AUC_{0-3 hrs} with tiotropium/olodaterol at both doses were statistically significantly greater ($p < 0.0001$ for all comparisons), versus those with the corresponding individual components.⁵

Similarly, the trough FEV₁ responses after 24 weeks were 111 and 136 mL for tiotropium/olodaterol 2.5/5 mcg and 5/5 mcg, respectively, 83 and 65 mL for tiotropium 2.5 mcg and 5 mcg, respectively, and 54 mL for olodaterol 5 mcg, in the first study. In the second study, the corresponding trough FEV₁ responses were 125 and 145 for tiotropium/olodaterol 2.5/5 mcg and 5/5 mcg, respectively, 62 and 96 for tiotropium 2.5 mcg and 5 mcg, respectively, and 57 mL for olodaterol 5 mcg. The improvements with tiotropium/olodaterol 2.5/5 mcg and 5/5 mcg over the corresponding individual components were statistically significant ($p < 0.05$ in both studies).

ADVERSE EFFECTS

Table 3 summarizes adverse events in the TONado 1 and 2 trials. In these studies, 74% of the patients treated with tiotropium/olodaterol reported any adverse event, compared with 76.6% and 73.3% of the olodaterol and tiotropium monotherapy groups, respectively. The most common adverse events were nasopharyngitis, cough, and back pain.⁵ In both studies, the most common serious adverse events were COPD exacerbation and pneumonia.

DOSING AND ADMINISTRATION

The recommended dose of tiotropium/olodaterol is two inhalations of 2.5/2.5 mcg per actuation once daily at the same time of the day. No more than two inhalations should be administered every 24 hours. The Respimat formulation can potentially allow patients to receive most of the medication through a mist, which aids those patients who are unable to forcibly inhale the drug out of the device. No dosage adjustment is required for geriatric patients, or in patients with hepatic or renal impairment. However, patients with moderate-to-severe renal impairment treated with tiotropium/olodaterol should be monitored closely for anticholinergic effects.⁵

COSTS

The average wholesale price (AWP) of one tiotropium/olodaterol inhalation device is \$379. Each device supplies 60 metered inhalations of 2.5/2.5 mcg, which is a 1-month supply when administered according to FDA-approved labeling. **Table 4** summarizes the cash price in Gainesville for Stiolto® and similar drugs used to treat COPD.⁸

CONCLUSION

Tiotropium/olodaterol (Stiolto® Respimat) is a recent FDC drug product indicated for the maintenance treatment of COPD.⁹ Recent studies have demonstrated that the combination of tiotropium bromide and olodaterol hydrochloride is more effective at improving FEV₁ AUC_{0-3 hrs} than either of the two agents used alone.⁹ Tiotropium/olodaterol is also one of the few combination products that includes a LABA and LAMA. Like olodaterol alone, the fixed-dose combination of tiotropium and olodaterol improves airflow within five minutes after the first dose.⁶ While the FDC product has been associated with various adverse events, the proportions of patients who withdrew from clinical trials because of such events were significantly lower for the tiotropium/olodaterol combination than for tiotropium or olodaterol alone.⁵ With these considerations in mind, tiotropium/olodaterol appears to offer COPD patients a suitable option for the maintenance treatment of COPD.

REFERENCES

- Centers for Disease Control and Prevention (CDC). Chronic obstructive pulmonary disease among adults. United States, 2012. MMWR Morb Mortal Wkly Rep 2012;61:938.
- Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2015. Available from: <http://www.goldcopd.org/>. Accessed September 2015

3. WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *American Journal of Respiratory & Critical Care Medicine*. 2001;163(5):1256–1276.
4. Mosley, Juan F., Lillian L. Smith, and Brittany N. Dutton. “Tiotropium Bromide/Olodaterol (Stiolto Respimat): Once-Daily Combination Therapy for the Maintenance of COPD.” *Pharmacy and Therapeutics* 41.2 (2016): 97–102. Print.
5. Buhl, Roland et al. “Tiotropium and Olodaterol Fixed-Dose Combination versus Mono-Components in COPD (GOLD 2–4).” *The European Respiratory Journal* 45.4 (2015): 969–979. PMC. Web. 23 June 2016.
6. Jones PW. Estimation and application of the minimum clinically important difference in COPD. *Lancet Respir Med* 2014;2:167-9.
7. Bateman E, Singh D, Smith D, et al. Efficacy and safety of tiotropium Respimat® SMI in COPD in two 1-year randomised studies. *Int J COPD*. 2010;5:197–208.
8. GoodRxprices2016. Available from: <http://www.goodrx.com/>. Accessed June 2016.
9. Boehringer Ingelheim FDA approves Boehringer Ingelheim's Stiolto Respimat as once-daily maintenance treatment for COPD. May 26, 2015. Available at: https://www.boehringeringelheim.com/news/news_releases/press_releases/2015/26_may_2015_copd.html. Accessed June 10, 2016.

EDITOR'S CORNER

Cardiovascular Safety of Nonsteroidal Anti-inflammatory Drugs for Arthritis

A recent study published in the *New England Journal of Medicine* investigated the cardiovascular (CV), gastrointestinal (GI), and renal outcomes with celecoxib, a selective COX-2 inhibitor, compared with two non-selective nonsteroidal anti-inflammatory drugs (NSAIDs), naproxen and ibuprofen, for treatment of arthritis.¹

The study included adult patients with rheumatoid arthritis or osteoarthritis, who required daily treatment with an NSAID for pain. Patients were required to have established CV disease or an increased risk for CV disease. Twenty-four thousand two-hundred twenty-two patients were randomized in 1:1:1 fashion to receive celecoxib (100 mg twice daily), ibuprofen (600 mg three times daily), or naproxen (375 mg twice daily) with matching placebo. Primary composite outcome was the first occurrence of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke. Other outcomes included significant GI and clinically significant renal events.

At study end, the incidence of the primary composite outcome occurred at similar rates in the celecoxib group compared to the naproxen group (2.3% vs 2.5%; HR 0.93, $p < 0.001$ for noninferiority). Celecoxib was also found to be noninferior to ibuprofen for the primary composite outcome (2.3% vs 2.7%; HR 0.85, $p < 0.001$ for noninferiority). Serious GI events were lower in the celecoxib group compared to both the naproxen and ibuprofen group. Additionally, serious renal events occurred less frequently in the celecoxib group compared to the ibuprofen group, but in similar rates compared to the naproxen group.

The results of this study indicate that the potential CV risks associated with celecoxib may not be greater than that seen with naproxen or ibuprofen. Concerns for CV safety with celecoxib stem from the withdrawal of rofecoxib, another selective COX-2

inhibitor, which was found to increase the risk of acute myocardial infarction.² Though the results from the current study appear to placate some concerns surrounding CV risk with celecoxib, several considerations should be kept in mind. First, only about 25% of patients in the study had established CV disease. Thus, the results of this study may not be completely generalizable to patients with overt CV disease. Second, approximately 46% of the patients were taking concurrent aspirin therapy. The antiplatelet effects of aspirin could have been attenuated in patients taking the non-selective NSAIDs, naproxen and ibuprofen, thereby biasing the results in favor of celecoxib. Third, a large proportion of patients (68.8%) discontinued the study drug and roughly 30% were lost to follow-up, both of which could have potentially undermined the statistical validity of the study.³

This study attempted to provide clearer evidence in regards to the CV safety profile of celecoxib. However, due to concerns regarding interpretation of the results, it is difficult to determine the clinical implications of this study. The results of the study highlight the CV safety profile of NSAIDs in the low to moderate CV risk population, and whether NSAIDs are safe to use from a CV perspective in high risk patients still remains to be seen.

References

1. Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. *N Eng J Med* 2016; DOI:10.1056/NeJMoa1611593.
2. Food and Drug Administration. FDA public health advisory: safety of Vioxx. September 30, 2004 (<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm106274.htm>).
3. FitzGerald GA. IMPRECISION: Limitations to interpretation of a large randomized clinical trial. *Circulation* 2016; DOI:10.1161/CIRCULATIONAHA.116.026324.

PHARMANOTE®

Published by the UF Family Practice Residency Program and the Departments of Community Health & Family Medicine and Pharmacotherapy & Translational Research

University of Florida

Editor-in-Chief

John G. Gums, PharmD, FCCP

Managing Editor

Steven M. Smith, PharmD, MPH, BCPS

Associate Editor

R. Whit Curry, MD

Assistant Editor

Andrew Y. Hwang, PharmD, BCPS

The material contained in this newsletter has been prepared for informational purposes only. The articles are the work product of the individual authors to whom each article is attributed. The articles contained herein should not be used without proper permission or citation. Should you have questions about any of the content in this newsletter please contact the [Editor](#).