

Tiotropium Bromide/Olodaterol as Maintenance Treatment for Patients with COPD



Chihiro Nakano, Toru Yamagishi, Norio Kodaka, Yoshiyuki Kurose, Kayo Watanabe, Kumiko Kishimoto, Takeshi Oshio, Kumiko Niituma, Nagashige Shimada and Hiroto Matsuse

Division of Respiratory Medicine, Department of Internal Medicine, Toho University Ohashi Medical Center, Tokyo, Japan.

ABSTRACT: Chronic obstructive pulmonary disease (COPD) requires appropriate treatment regimens, since it is a major cause of morbidity and mortality worldwide. Recently, several clinical trials confirmed that compared with tiotropium monotherapy and combination therapy of long-acting β_2 agonist (LABA) plus inhaled corticosteroids (ICSs), maintenance therapy with once-daily dosing of a fixed-dose combination (FDC) of tiotropium plus olodaterol was safe and effective in improving the lung function, associated symptoms, and health status of patients with moderate to very severe COPD. Overall, tiotropium plus olodaterol FDC should be considered as an option for maintenance therapy in patients with moderately severe and severe COPD. Further studies will be required to show the effectiveness of this FDC in preventing COPD exacerbations and as maintenance therapy in patients with asthma–COPD overlap syndrome (ACOS).

KEYWORDS: COPD, long-acting muscarinic antagonist, long-acting β_2 agonist, tiotropium, olodaterol

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CORRESPONDENCE: hiroto.matsuse@med.toho-u.ac.jp

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Introduction

Chronic obstructive pulmonary disease (COPD) is a disease of the lungs, which involves chronic inflammation, particularly in the peripheral airways and parenchyma. Several cells, including macrophages, epithelial cells, dendritic cells, neutrophils, eosinophils, T-lymphocytes, and B-lymphocytes, are related to this inflammation. In patients with COPD, there is an increase in the total number of T-lymphocytes in the lung parenchyma and peripheral and central airways, with a greater increase in CD8⁺ than in CD4⁺ cells. The number of T-cells and the amount of alveolar destruction correlate with the severity of airflow obstruction.^{1,2} Furthermore, increased number of activated neutrophils in the sputum and broncho-alveolar lavage fluid in patients with COPD correlates with disease severity.³ Similar to cardiovascular disease and lung cancer, COPD slowly progresses and leads to death. The main cause of COPD is chronic cigarette smoking; however, only 25% of smokers develop COPD, suggesting that there may be genetic, epigenetic, or host factors that predispose to its development, although these have not been identified.⁴

In 2014, the Global Initiative for Asthma and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) issued a joint document describing asthma–COPD overlap syndrome (ACOS), which is characterized by persistent airflow limitation and several features that are usually associated

with both asthma and COPD.⁵ The clinical phenotypes and underlying mechanism of ACOS have attracted interest in the recent years. However, ACOS remains somewhat controversial and there is no consensus on the best definition of ACOS.^{6,7}

COPD is a major cause of morbidity and mortality worldwide. According to the World Health Organization estimates, six million people have moderate to severe COPD. In 2005, COPD was the cause of death in more than three million people, which corresponds to 5% of all deaths globally. Estimates show that in 2030, COPD will become the third leading cause of death worldwide.⁸ COPD is now the well-established terminology for what was historically known as chronic bronchitis or emphysema. It is characterized by airflow obstruction that does not change markedly over several months and is usually progressive. The primary cause of COPD is tobacco smoke, including second-hand or passive exposure, and it is diagnosed by spirometry. The goals of COPD management include control of symptoms, health status, and everyday activities; improvement in lung function; and prevention of future events by reducing exacerbations, slowing disease progression, and reducing mortality.

Current guidelines recommend maintenance therapy with either a long-acting muscarinic antagonist (LAMA) or a long-acting β_2 agonist (LABA) for symptomatic patients with moderate or more severe COPD.^{9,10} Phase II studies

demonstrated greater improvements in forced expiratory volume in one second (FEV_1) with once-daily fixed-dose combination (FDC) of tiotropium and olodaterol than either drug alone.^{11,12} Phase III trials hypothesized that combination therapy with tiotropium plus olodaterol FDC was the most effective strategy in improving lung function, quality of life, symptom scores, and rates of moderate to severe exacerbations. Moreover, it had similar effects on safety outcomes and severe exacerbations compared with monotherapy regimens. Recently, a once-daily maintenance bronchodilator FDC therapy has been approved to relieve symptoms of COPD.¹³

This paper reviews the available clinical trials to demonstrate the efficiency and safety of tiotropium plus olodaterol FDC in patients with COPD.

Pharmacologic Properties of Tiotropium and Olodaterol

Tiotropium is an established once-daily LAMA that is effective in improving lung function and patient-reported symptoms and is effective in reducing exacerbations of patients with COPD.^{14,15} Tiotropium bromide is kinetically selective for M_3 receptors, which mainly results in bronchodilation.¹⁶ It is available in two formulations: (1) dry powder delivered via a HandiHaler device (Boehringer Ingelheim) at 18 μg once daily and (2) an aqueous solution delivered via Respimat Soft Mist Inhaler (SMI) (Boehringer Ingelheim) at 5 μg once daily. The Respimat SMI deposits the drug in the lungs more efficiently than the HandiHaler device. In addition, the mass of the aerosol particle is 1–5 μm in diameter, with a high proportion of the droplets in the aerosol cloud falling into fractions of fine particles. Notably, particle size and the dose of delivered drug are not dependent on a patient's inspiratory effort.¹⁷ The deposition pattern within the lungs is more peripheral for Respimat SMI than for the HandiHaler device; therefore, the Respimat SMI is more effective than the HandiHaler device.¹⁸ Drug deposition in the oral cavity is also less with the Respimat SMI in comparison with that by the HandiHaler.¹⁹

Olodaterol is a LABA with high selectivity for β_2 -adrenergic receptors and provides 24-hour bronchodilation and symptomatic benefits in patients with COPD. Data on the pharmacokinetic properties of olodaterol and the other once-daily LABAs are presented in Table 1. Several clinical trials that compared olodaterol with the other once-daily LABAs found that the clinical efficacies were comparable.²⁰ The recommended dose of olodaterol is 5 μg once daily via Respimat inhaler. Tiotropium plus olodaterol FDC is available via the Respimat device. The chemical structures and data on the pharmacokinetic properties of tiotropium and olodaterol^{21,22} are presented in Figure 1 and Table 1, respectively.

The Efficiency of Tiotropium Plus Olodaterol in Clinical Trials

Lung function. Three phase III trials demonstrated that tiotropium plus olodaterol FDC was significantly more effective than monotherapy with either drug. The ENERGITO study showed that tiotropium plus olodaterol FDC was significantly more effective than salmeterol plus fluticasone propionate, which is a LABA plus inhaled corticosteroid (ICS) combination, in improving lung function of COPD. The TONADO studies were two replicate, randomized, double-blind, parallel-group, multicenter, phase III trials that demonstrated that, compared with monotherapy with either agent, once-daily tiotropium plus olodaterol FDC for over one year significantly improved lung function and health-related quality of life of COPD patients with GOLD severity groups 2, 3, and 4.²³ There were three endpoints evaluated after 24 weeks of treatment: area under the curve of FEV_1 response from 0 to 3 hours (AUC_{0-3}) in each individual trial, trough FEV_1 response in each individual trial, and St. George's Respiratory Questionnaire (SGRQ) score. Response was defined as change in mean values at 1 hour and 10 minutes prior to the first dose of the study medication compared with baseline. The adjusted mean FEV_1 AUC_{0-3} improvements with tiotropium plus olodaterol were significantly different from those of the corresponding individual studies and the combined analysis.

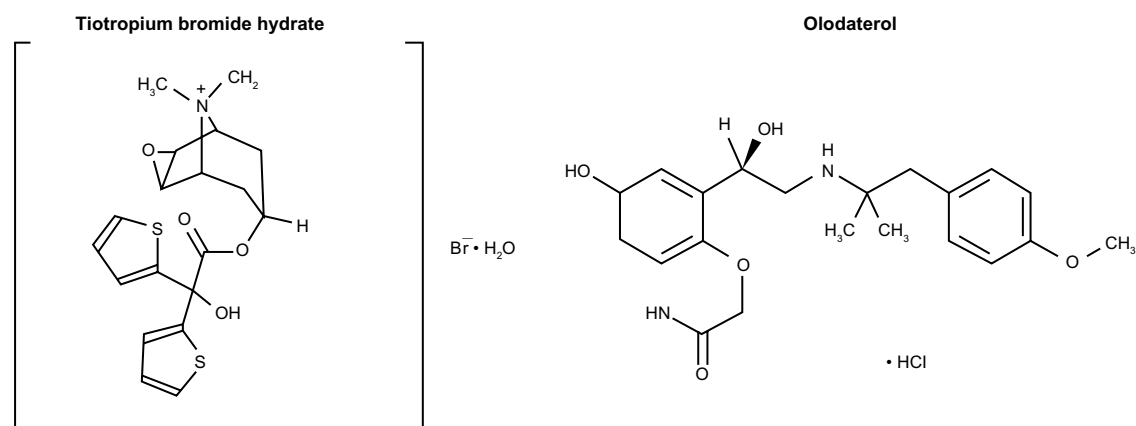


Figure 1. Chemical structures of tiotropium and olodaterol.

**Table 1.** Pharmacokinetics of LABA and tiotropium.

	TIOTROPIUM	OLODATEROL	INDACATEROL	VILANTEROL
T _{max} (min)	5	10–20	15	5–15
Time to steadystate (days)	7	8	12–15	6
T _{1/2} (hr)	–	7.5	45.5–126.0	11.0
Bioavailability (%)	33	~30	43–45	27
Clearance (ml/min)	880	872	–	–
Distribution volume	32 L/kg	1110 L	–	–
Absorption (%)	76	70.4	–	–
Protein binding after i.v.	72	60	95	94
Administration (%)				
Metabolism	CYP2D6, CYP3A4	CYP2C8, CYP2C9	CYP2D6, CYP3A4	CYP3A4
Elimination	Urine	Feces	Feces	Feces, urine

Abbreviations: T_{max}, time to maximum concentration; T_{1/2}, half-life.

In each of the 52-week studies, improvements in FEV₁ values were observed on all test days. Tiotropium plus olodaterol improved FEV₁ and trough FEV₁, regardless of concomitant ICS use. The VIVACITO studies investigated the effects of a once-daily tiotropium plus olodaterol FDC on 24-hour lung function and lung volume. The primary endpoint was FEV₁ AUC_{0–24} response after 6 weeks of treatment; the key secondary endpoints were FEV₁ AUC from 0 to 12 hours and AUC from 12 to 24 hours.²⁴ This study showed improvements in FEV₁ for more than 24 hours with tiotropium plus olodaterol FDC compared with tiotropium or olodaterol alone, with no observed intolerability. There were also significant improvements in residual volume (RV) response and inspiratory capacity (IC) with the tiotropium plus olodaterol FDC versus placebo and monotherapy regimens at 2:30 hours and 22:30 hours after dose administration. These two trials demonstrated the efficacy of tiotropium plus olodaterol FDC in patients with severe COPD. The OTEMTO studies showed that in different COPD subgroups of lung function (GOLD 2 or 3), 12 weeks of tiotropium plus olodaterol FDC was more effective than tiotropium monotherapy and placebo in improving FEV₁ AUC_{0–3} and trough FEV₁. Moreover, lung function outcomes were generally greater in patients who had been receiving LABA and/or ICS maintenance treatment.²⁵ These data suggested that tiotropium plus olodaterol FDC should be considered as an initial option for maintenance therapy in patients with moderate or more severe COPD. The ENERGITO studies showed that after 6 weeks of treatment, tiotropium plus olodaterol FDC over a full 24-hour dosing interval improved FEV₁ values compared with salmeterol plus fluticasone propionate.²⁶ The primary endpoint was response of FEV₁ AUC_{0–12} after six weeks of treatment. The key secondary endpoint was response in terms of FEV₁ AUC_{0–24}. Tiotropium plus olodaterol FDC was superior to salmeterol plus fluticasone propionate in the secondary endpoints of lung function, including FEV₁ AUC_{0–24}.

Health-related quality of life and symptom scales.

Five trials demonstrated the effectiveness of tiotropium and olodaterol FDC in improving symptoms, health status, and everyday activities of COPD patients. The clinical results are summarized in Table 2.

The TONADO studies demonstrated that compared with monotherapy with either component, 24 weeks of tiotropium plus olodaterol FDC significantly improved the SGRQ total score when given at a dose of 5/5 µg, but not when given at a dose of 2.5/5 µg.²³ The incidence of adverse events was comparable between the FDCs and monotherapy with either component.

One of the endpoints of the OTEMTO study was comparison of SGRQ total score at 12 weeks among four treatment regimens.²⁵ In this study, improvement of SGRQ total score after tiotropium plus olodaterol FDC was most evident in the GOLD B subgroup (ie, severe symptoms, but with mild airway obstruction). Furthermore, the improvement in SGRQ total scores with tiotropium plus olodaterol FDC compared to tiotropium or placebo was greater in patients who were not receiving ICS at baseline. The objective of the PHYSACTO trial was to confirm whether LAMA therapy and LAMA/LABA combined therapy, with or without exercise training, improved exercise endurance therapy. In addition, it aimed to evaluate the extent to which pharmacotherapy alone and pharmacotherapy with exercise training can enhance the effects of a behavioral change intervention on physical activity levels.²⁷ The primary outcome was improvement in exercise capacity after eight weeks, which was measured by endurance time during shuttle walk test. The secondary outcomes were improvement in physical activity, including objective accelerometer assessment and patient-reported activity level, based on the functional performance inventory.

Improvement in symptoms and decrease in COPD mortality with tiotropium plus olodaterol FDC will be evaluated by the ongoing MORACTO and TORRACTO clinical studies.

**Table 2.** Summary of clinical trials for tiotropium and olodaterol fixed-dose combinations.

TRIAL	OBJECTIVE	ENDPOINT	TREATMENT	P-VALUE
TONADO	GOLD severity groups 2,3 and 4.	FEV ₁ AUC ₀₋₃	T+O 5/5 µg vs:	
		Trough FEV ₁	O 5 µg	<0.0001
		SGRQ total score	T 2.5 µg	<0.0001
			T 5 µg	<0.0001
			T+O 2.5/5 µg	<0.0001
VIVACITO	GOLD severity groups 2,3 and 4.	FEV ₁ AUC ₀₋₂₄	T+O 5/5 µg vs:	
			O 5 µg	<0.0001
			T 2.5 µg	<0.0001
			T 5 µg	<0.0001
			T+O 2.5/5 µg	0.8238
ENERGITO	GOLD 2,3.	FEV ₁ AUC ₀₋₂₄	T+O 5/5 µg vs:	
			Salmeterol+olodaterol	<0.0001
			50/500 µg	
			Salmeterol+olodaterol	<0.0001
			50/250 µg	
OTEMTO	GOLD 2,3.	FEV ₁ AUC ₀₋₃	T+O 5/5 µg vs:	
		Trough FEV ₁	T 5 µg	<0.0001
		SGRQ total score	placebo	<0.0001
			ICS use at baseline	<0.0001

Abbreviations: GOLD, Global Initiative for Chronic Obstructive Lung Disease; FEV₁, forced expiratory volume in one second; SGRQ, St. George's Respiratory Questionnaire; T+O, tiotropium and olodaterol; O, olodaterol; T, tiotropium.

COPD exacerbations. Consistent exacerbations have major implications for COPD management, especially among patients with prior history of exacerbations. The FLAME study showed that indacaterol–glycopyrronium, which is another LABA plus LAMA FDC, was more effective than salmeterol–fluticasone, which is an ICS plus LABA combination, in preventing COPD exacerbations among patients with prior history of exacerbations in the previous year.²⁸ ICS plus LABA as an option for maintenance treatment is recommended only for individuals who are at high risk for exacerbation, but prospective studies showing improved outcomes are lacking. Clinical guidelines recommended ICS plus LABA or LAMA alone as treatment for COPD patients who have high risk for exacerbations.

The TONADO study demonstrated a trend of improvement in moderate/severe COPD exacerbations after tiotropium plus olodaterol FDC,²⁷ whereas the ongoing DYNAGITO study will determine the effectiveness of this FDC for COPD exacerbations.

Safety. Phase I trials confirmed the safety of olodaterol and tiotropium FDC in healthy subjects (Boehringer Ingelheim; unpublished data). In all the clinical trials on patients with COPD, the incidence of adverse events was similar among tiotropium and olodaterol FDC (2.5/5 and 5/5 µg) and monotherapy with either drug. The most common individual adverse events were worsening of COPD in 6.5%–10.1% and cough, particularly due to nasopharyngitis, in 5.1%–12.3%.²²

No significant abnormalities in vital signs or laboratory parameters were observed in that study. Tiotropium and olodaterol FDC appeared to have no increase in the risk of cardiac events compared with monotherapy with either agent.

In the ENERGITO study, use of tiotropium and olodaterol 5/5 µg FDC resulted in two serious adverse events leading to death; one was due to cerebral hemorrhage in a predisposed patient and the other occurred 19 days after the last dose of the study treatment, with unknown cause.²⁶ Collectively, tiotropium plus olodaterol FDC had similar effects on safety outcomes compared with monotherapy with either agent.

Conclusion

Several studies confirmed that, compared with tiotropium monotherapy and combination therapy with ICS plus LABA, once-daily dosing maintenance therapy with tiotropium plus olodaterol FDC was safe and effective in improving lung function, with associated symptomatic and health status benefits, in patients with moderate to very severe COPD. Overall, tiotropium plus olodaterol FDC should be considered as an option for maintenance therapy in such patients. Further studies will be required to show the effectiveness of this FDC in preventing COPD exacerbations and as maintenance therapy in patients with ACOS.

Author Contributions

Wrote the first draft of the manuscript: CN. Contributed to the writing of the manuscript: TY, NK, YK, KW, KK,



TO, KN, NS, HM. Confirmed the manuscript results and conclusions: TY, NK, YK, KW, KK, TO, KN, NS, HM. Made critical revisions and approved the final version of the manuscript: HM. All the authors reviewed and approved the final manuscript.

Abbreviations

ACOS: asthma–chronic obstructive pulmonary disease overlap syndrome

COPD: chronic obstructive pulmonary disease

FEV₁: forced expiratory volume in one second

FDC: fixed-dose combination

GOLD: Global Initiative for Chronic Obstructive Lung Disease

ICS: inhaled corticosteroid

LAMA: long-acting muscarinic antagonist

LABA: long-acting β 2 agonist

RV: residual volume

SGRQ: St. George's Respiratory Questionnaire

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