Research Review
PRODUCT REVIEW

Tiotropium Bromide Monohydrate/Olodaterol Hydrochloride (Spiolto® Respimat®) in the Treatment of Chronic Obstructive Pulmonary Disease

About the Reviewer

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Conroy is a respiratory and general physician at Middlemore Hospital, Auckland and Honorary Clinical Senior Lecturer at the University of Auckland. His research is primarily focussed on clinical trials evaluating new treatment options for bronchiectasis. He also has research interests in pulmonary infections, asthma and COPD.

This review summarises evidence for the use of the fixed-dose combination bronchodilator tiotropium bromide monohydrate/olodaterol hydrochloride (Spiolto® Respimat®), hereafter referred to as tiotropium/olodaterol, in the treatment of chronic obstructive pulmonary disease (COPD). Also discussed is evidence favouring earlier treatment of COPD and the role of bronchodilators in this clinical setting. Tiotropium/olodaterol is registered with Medsafe and is fully funded by Pharmac (special authority criteria apply).

Chronic obstructive pulmonary disease (COPD) is a serious and progressive condition that limits airflow in the lungs and is typically characterised by a persistent cough with sputum (chronic bronchitis) with or without lung tissue destruction (emphysema).[1-3] People with COPD are also prone to shortness of breath and, in contrast to asthma, continue to lose lung function despite taking medication.

COPD and its health burden

COPD is a cause of considerable mortality and morbidity. In 2012, the mortality rate for COPD was 18.8 per 100,000 population, making it the fourth leading cause of death in New Zealand.[4] Māori had a mortality rate that was more than double the rate for non-Māori. In terms of morbidity, COPD was the third highest cause of health loss (% total disability-adjusted life years; DALYs) among males in 2012 and the fourth highest cause of health loss in females.[5] A recent study that analysed national hospital admissions for COPD estimated the cost of hospital admission at nearly $60 million (2012/13 financial year).[6] The overall admission rate was 2.82 per 1000 population, with rates for Māori and Pacific peoples being >3-fold higher than for European and others. High rates of admission were also strongly associated with advanced age and socioeconomic deprivation.

COPD and its clinical course

Although patients are less symptomatic earlier in the course of their disease, evidence from two studies suggests that the underlying progression of early COPD occurs at a faster rate than during the later stages of disease.[7,8] Tantucci et al. reviewed the spirometric data of COPD patients in the placebo arms of recent clinical trials, including TORCH and UPLIFT, to assess decline in lung function by stage of disease progression as defined by Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[9] They found that the mean rate of lung function decline was greatest during GOLD stage II, i.e. moderate disease (**Figure 1**). Similarly, Drummond et al. found a rapid rate of decline in lung function in COPD patients with only moderate disease in their analysis of longitudinal data from the Lung Health Study.[10]

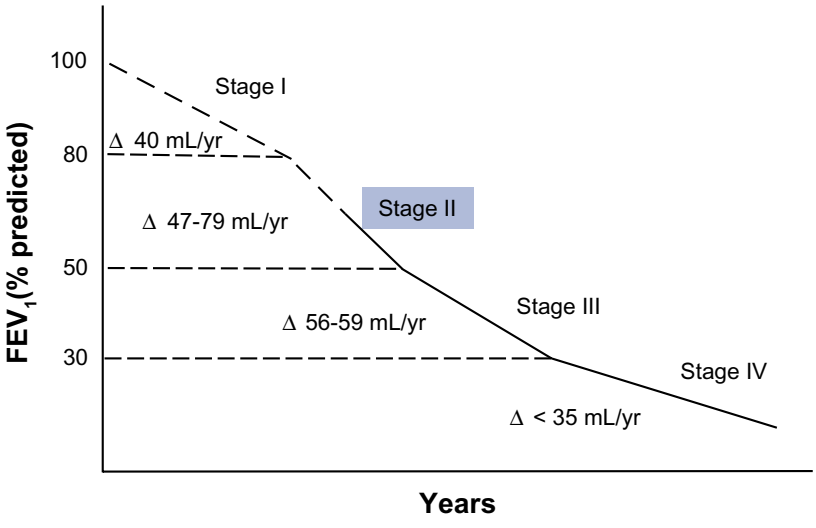

Figure 1. Annual average rate of decline in the forced expiratory volume in one second (FEV_1) in COPD patients according to initial severity of airflow obstruction as defined by the GOLD guidelines.[9] Dashed line indicates any stage or part of it where consistent data is lacking. Abbreviations: yr = year.

In addition, the results of a systematic review that evaluated impairment levels with disease progression over time showed that even patients with mild or moderate COPD can have substantial limitations and physical impairment, which worsen over time.[11] Certainly, current data indicate that patients with COPD reduce their physical activity early in the course of the disease.[12-14] For example, a prospective study that measured physical activity in patients with COPD to identify the disease stage at which physical activity becomes limited demonstrated that activity levels start to decline dramatically from GOLD stage II (**Figure 2**).[14]

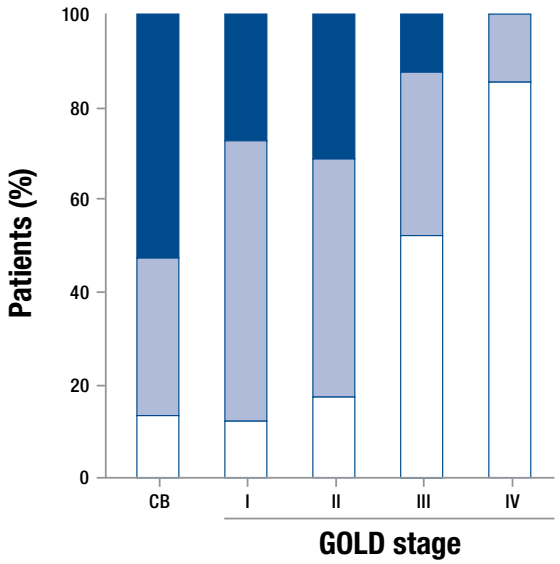

Figure 2. Percentage of COPD patients who were physically active (●), predominantly sedentary (◒) or very physically inactive (○), by GOLD stage.[14] CB = chronic bronchitis

Although lung function shows a weak-to-moderate association with physical activity, symptoms of dyspnoea and fatigue and disease exacerbations have been demonstrated to be more strongly associated with physical activity in patients with COPD.[15] Moreover, exertional dyspnoea often causes patients with COPD to unconsciously restrict their activities of daily living (ADLs) to reduce the intensity of their distress.[16] Reductions in ADLs lead to deconditioning which, in turn, further increases dyspnoea. Both dyspnoea and fatigue are important factors affecting health-related quality of life (HRQOL). The functional status of patients relates to how well they perform ADLs. Activities, however, may not be severely limited until the disease becomes advanced.

Because the rate of decline in lung function may be faster in the earlier stages of the COPD, early intervention may have the potential not only to control symptoms but also to slow disease progression and improve clinical outcomes. Post hoc analyses from two randomised controlled studies (UPLIFT and TORCH) have yielded data suggesting that early bronchodilator therapy may be beneficial in curtailing declines in lung function.[17,18] In the UPLIFT study, a small but statistically significant reduction (versus placebo) in the rate of decline of post-bronchodilator FEV_1 was identified in a subgroup of patients with GOLD stage II COPD using tiotropium.[17] Also, contributing evidence in support of a beneficial effect of bronchodilator therapy on patients with mild disease, the TORCH study demonstrated fewer exacerbations and mild lung function improvement (vs placebo) in a subgroup of patients with GOLD stage II disease during treatment with salmeterol plus fluticasone propionate.[18]

It should be noted that, to date, none of the existing medications for COPD has been conclusively demonstrated to modify the long-term decline in lung function when this is tested as a primary or secondary outcome in clinical trials.[1] Evidence from secondary analyses of such an effect with long-acting bronchodilators and/or inhaled corticosteroids (ICS) requires confirmation in clinical trials specifically designed and powered to assess such an effect.

COPD and its treatment

The primary aim of pharmacologic therapy for COPD is to ameliorate symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance.[1]

Long-acting bronchodilators, such as long-acting muscarinic antagonists (LAMAs) and long-acting β_2-adrenoceptor agonists (LABAs) are the foundation of maintenance therapy for patients with moderate-to-severe COPD whose symptoms are not adequately controlled by short-acting bronchodilators alone.[1,19] The GOLD classification of severity of airflow limitation in COPD defines moderate and severe COPD as follows:[1]

- Moderate (GOLD II): 50% ≤ FEV_1 < 80% predicted
- Severe (GOLD III): 30% ≤ FEV_1 < 50% predicted.

The GOLD guidelines recommend combining long-acting bronchodilators with differing mechanisms of action if a patient's COPD is insufficiently controlled with monotherapy,[1] and there has been growing interest in the additional benefits that combinations of LAMAs, typified by tiotropium, with LABAs might afford.[20]

Tiotropium/olodaterol

In line with current COPD guidelines recommending the concurrent use of long-acting bronchodilators with different mechanisms of action, the established LAMA tiotropium and the novel LABA olodaterol have been formulated as a fixed-dose combination (FDC) in a single inhaler that simultaneously delivers the two drugs, i.e. tiotropium/olodaterol (Spiolto Respimat).

Tiotropium is the most studied LAMA in COPD, with once-daily dosing leading to improvements in lung function and patient-orientated outcomes of COPD,[21,22] and for which secondary analyses suggest that tiotropium is associated with benefits in lung function decline in patients with early-stage disease.[17,23] Olodaterol is a LABA for which data from randomised controlled trials indicate that once-daily olodaterol produces symptomatic benefit and enhanced exercise capacity in patients with COPD.[24-26]

The Respimat delivery device is an active inhaler that operates on mechanical energy and, as such, does not require propellant.[27,28] It generates an aerosol with a high fine-particle fraction (approx. 65-80% of drug mass in aerosolized particles carried by particles with a diameter ≤5.8μm) delivered at reduced velocity (0.8 m/sec) and prolonged aerosol duration (1.5 sec) to enhance deposition within the lungs and minimise deposition in the oropharynx.[29,30] In a study that evaluated the deposition of a bronchodilator drug delivered from the Respimat inhaler versus a pressurized metered-dose inhaler, the amount of drug (as a proportion of the metered dose) deposited in the lungs of healthy volunteers was 39% versus 11% while oropharyngeal deposition was 37% vs 72%.[31] In a similar study, lung deposition was 53% versus 21% for the Respimat versus a metered dose inhaler while oropharyngeal deposition was 45% versus 56%.[32]

Studies have demonstrated high patient satisfaction with the Respimat inhaler,[28,33] with the long duration of the spray being of potential benefit in patients who have difficulty in co-ordinating inhalation with drug release.[27]

Tiotropium/olodaterol is indicated as a once-daily maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD (including chronic bronchitis and emphysema).[34]

Pharmacology

The following is an overview of the important clinical pharmacological properties of tiotropium/olodaterol. The Data Sheet should be viewed for full details of the pharmacodynamics and pharmacokinetics, drug interactions and precautions, and recommended dosage and administration for tiotropium/olodaterol.

Mechanism of action

Tiotropium and olodaterol are administered together to provide additive bronchodilation via their different modes of action and the different locations of the target receptors in the lungs.[34]

Tiotropium has similar affinity to the muscarinic receptor subtypes M1 to M5 (dissociation constant 5–41 pM).[34] In the airways, inhibition by

tiotropium of M3 receptors on the smooth muscle results in relaxation. The bronchoprotective effects of tiotropium have been demonstrated to be dose-dependent, lasting ≥24 hours in some *in vivo* studies. Its slow dissociation from M3 receptors is likely to account for the long duration of effect of tiotropium.

Olodaterol has a rapid onset of action (from 5min after the first dose) and duration of action of ≥24 hours.[34,35] It preferentially binds and activates β_2-adrenoceptors following inhalation. Activation of β_2-adrenoceptors in the airways results in stimulation of intracellular adenyl cyclase and synthesis of cyclic-3',5' adenosine monophosphate (cAMP).[34] Elevated levels of cAMP induce bronchodilation by relaxation of airway smooth muscle cells. The β_2-adrenoceptor is the predominant adrenergic receptor in the airway smooth muscle but is also present in the heart; therefore, even highly selective β_2-adrenergic agonists potentially have cardiac effects.

Pharmacokinetics

When tiotropium and olodaterol were administered in combination by the inhaled route, the pharmacokinetic parameters for each component were similar to those observed when each mono-component was administered alone.[34]

Approximately 33% of the dose inhaled of tiotropium reaches the systemic circulation versus an absolute bioavailability of 2–3% when given as an oral solution.[34] Similarly, the absolute bioavailability of olodaterol following inhalation has been estimated to be approximately 30% versus <1% when given as an oral solution. Therefore, the systemic availabilities of tiotropium and olodaterol after inhalation are mainly determined by lung absorption, with any swallowed portion of the dose negligibly contributing to systemic exposure (as with inhaled corticosteroids[36]).

Potential safety concerns related to higher peak and overall tiotropium exposure following inhalation from the Respimat inhaler have been assessed. In a randomised double-blind study in patients with COPD, lower systemic exposure and availability ($C_{max,\ ss}$ 19% lower and $AUC_{0-6,\ ss}$ 24% lower) but similar bronchodilator efficacy and tolerability was demonstrated for tiotropium 5µg delivered via the Respimat versus tiotropium 18µg delivered via the HandiHaler® dry powder inhaler.[37]

Tiotropium shows a volume of distribution of 32 L/kg.[34] Although the local concentrations in the lung are unknown, the mode of administration suggests substantially higher concentrations in the lung. The volume of distribution of olodaterol is high (1,110 L), which suggests extensive distribution into tissues.

Metabolism of tiotropium is not substantial, as indicated by 74% renal excretion of unchanged drug after intravenous administration.[34] Hence, liver insufficiency is not expected to have any relevant influence on the pharmacokinetics of tiotropium. Olodaterol is substantially metabolised (unchanged drug in urine accounts for 5–7% of the dose after inhalation) by direct glucuronidation and by O-demethylation primarily via cytochrome P450 isozymes CYP2C9 and CYP2C8. However, mild to moderate hepatic impairment does not affect systemic exposure to olodaterol. The effect of severe hepatic impairment on systemic exposure to olodaterol has not yet been studied.

The half-life of tiotropium is 27–45 hours and that for olodaterol is about 45 hours following inhalation,[34] thus permitting tiotropium/olodaterol to be administered once-daily.

In patients with moderate to severe renal impairment (creatinine clearance <50 mL/min) intravenous administration of tiotropium resulted in a doubling of the total exposure (82% higher AUC_{0-4h} and 52% higher C_{max}) versus COPD patients with normal renal function.[34] In subjects with severe renal impairment (creatinine clearance <30 mL/min), systemic exposure to olodaterol was on average 1.4-fold increased. However, this magnitude of exposure increase does not raise any safety concerns given the safety experience of treatment with olodaterol in clinical studies of ≤1 year at doses of ≤2-fold the recommended therapeutic dose.

Precautions

Tiotropium/olodaterol should not be used in the treatment of asthma or acute episodes of bronchospasm, i.e. as rescue therapy, and nor should it be initiated in patients with acutely deteriorating COPD.[34] As with other inhaled medicines, use of tiotropium/olodaterol may result in life-threatening paradoxical bronchospasm; in which case, tiotropium/olodaterol should be discontinued immediately and substituted for an alternative therapy. Retrospective analyses of data from clinical trials in asthma and COPD patients have indicated a very low incidence of paradoxical bronchospasm with tiotropium and various short-acting bronchodilators delivered via the Respimat inhaler.[38-40] A review of adverse reaction reports for inhaled bronchodilators submitted to the FDA found that inhaler-induced paradoxical bronchospasm was infrequent; nonetheless, it was suggested that awareness of its possibility is essential given the potentially life-threatening nature of paradoxical bronchospasm.[41]

Due to the anticholinergic activity of its tiotropium mono-component, tiotropium/olodaterol should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia, or bladder-neck obstruction.[34]

Because tiotropium is predominantly excreted by the kidneys, use of tiotropium/olodaterol in patients with moderate to severe renal impairment (creatinine clearance ≤50 mL/min) should be closely monitored.[34]

LABAs should be used with caution in patients with cardiovascular disorders; hence, due to its LABA mono-component, tiotropium/olodaterol, should be used with caution in patients with cardiovascular disorders, including known or suspected prolongation of the QT interval.[34] Additionally, as with other β_2-adrenergic agonists, olodaterol may produce a clinically significant cardiovascular effect in some patients, in which case treatment with tiotropium/olodaterol may need to be discontinued.

β_2-adrenergic agonists may produce significant hypokalaemia in some patients, which has the potential to produce adverse cardiovascular effects.[34] The decrease in serum potassium is usually transient and does not require supplementation. In patients with severe COPD, however, hypokalaemia may be potentiated by hypoxia and concomitant treatment with certain drugs, which may increase the susceptibility to cardiac arrhythmias.

Interactions

Tiotropium/olodaterol should not be used in conjunction with any other medication containing LABAs or LAMAs due to potential drug interactions.[34] The chronic co-administration of other anticholinergic drugs with tiotropium/olodaterol has not been studied and hence is not recommended. Concomitant administration of other adrenergic agents may potentiate the undesirable effects of tiotropium/olodaterol.

Cardiovascular disease (CVD) is a major comorbidity in COPD; it is probably both the most frequent and most important disease coexisting with COPD.[1] If concomitant administration of a β-adrenergic blocker and tiotropium/olodaterol is required in a COPD patient with co-existing CVD, use of a cardioselective β-blocker could be considered, although they should be administered with caution.[34] β-adrenergic blockers may weaken or antagonise the effect of olodaterol.

Concomitant treatment with xanthine derivatives, steroids, or non-potassium sparing diuretics may potentiate any hypokalaemic effect of adrenergic agonists.[34] Also, monoamine oxidase inhibitors, or tricyclic antidepressants or other drugs known to prolong the QTc interval may potentiate the action of tiotropium/olodaterol on the cardiovascular system.

Dosage and administration

The recommended dose is 5µg tiotropium and 5µg olodaterol given as two puffs from the Spiolto Respimat inhaler once daily, at the same time of the day.[34] Tiotropium/olodaterol should not be used more frequently than once daily.

Pivotal clinical trials

The following are individual summaries of the main features and findings of pivotal clinical trials of tiotropium/olodaterol delivered via the Spiolto Respimat inhaler in the treatment of COPD. Expert commentary on the clinical practice relevance or implications of these studies is provided by Conroy Wong.

Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2-4)[42]

Authors: Buhl R et al.

Summary: The efficacy and safety of tiotropium/olodaterol compared with the mono-components was evaluated in patients with moderate to very severe COPD (GOLD stage II-IV) in two replicate multicentre, randomised, double-blind, phase III trials (TONADO 1 and 2). Patients received tiotropium/olodaterol 2.5/5µg or 5/5µg, tiotropium 2.5µg or 5µg, or olodaterol 5µg over 52 weeks. In total, 5162 patients (2624 in TONADO 1 and 2538 in TONADO 2) received treatment. In terms of lung function, both FDCs significantly improved FEV_1 area under the curve from 0 to 3 hours (AUC_{0-3}) and trough FEV_1 response versus the mono-components in both studies. Statistically significant improvements in HRQOL, as measured by St George's Respiratory Questionnaire (SGRQ) total score at 24 weeks, versus the mono-components were only seen for tiotropium/olodaterol 5/5µg. The incidence of adverse events was comparable across the FDCs and the mono-components.

Comment: These two large randomized controlled trials confirm that a combination of tiotropium and olodaterol administered via a Respimat inhaler is superior to mono-component therapy in terms of improvements in FEV_1. The trial populations included moderate to very severe patients with post-bronchodilator FEV_1 <80%. Reassuringly, combination treatment was well tolerated and increased cardiac toxicity was not evident. The FEV_1 findings are similar to those from other LAMA/LABA combination studies. The effects on health-related quality of life as measured by SGRQ were statistically significant but the effects (compared to mono-component treatment; no placebo arm was included) were relatively small and less than the clinically-important threshold of 4 units. A limitation of the TORNADO studies is that they were not designed to assess the effects on the important clinical endpoint of COPD exacerbations.

Efficacy of tiotropium + olodaterol in patients with chronic obstructive pulmonary disease by initial disease severity and treatment intensity: a post hoc analysis[43]

Authors: Ferguson GT et al.

Summary: This aim of this post hoc efficacy analysis of the combined TONADO study 1 and 2 results was to determine the effectiveness of tiotropium/olodaterol across COPD disease severities, with or without prior maintenance therapy, and according to patients' age and sex. Pooled data were assessed for the following subgroups: GOLD II and GOLD III/IV stages of disease, sex, age, prior maintenance treatment with LAMA or LABA, and prior use of ICS. Tiotropium/olodaterol improved lung function (FEV_1 AUC_{0-3} and trough FEV_1) versus the mono-components in patients with GOLD II and III/IV disease, irrespective of prior LAMA or LABA maintenance therapy, prior ICS use, sex, and age; most comparisons between FDCs and their respective mono-components were statistically significant ($p<0.05$). In addition, FEV_1 AUC_{0-3} (**Figure 3**) and trough FEV_1 responses for the individual treatments were generally greater in patients with GOLD II than with GOLD III/IV disease.

Comment: Post hoc analyses are inevitably limited in providing reliable data for clinical use. However, this post hoc analysis is reassuring in showing that tiotropium/olodaterol appears to be effective in COPD patients irrespective of age, gender, previous inhaler (LAMA, LABA, or ICS) use, and disease severity.

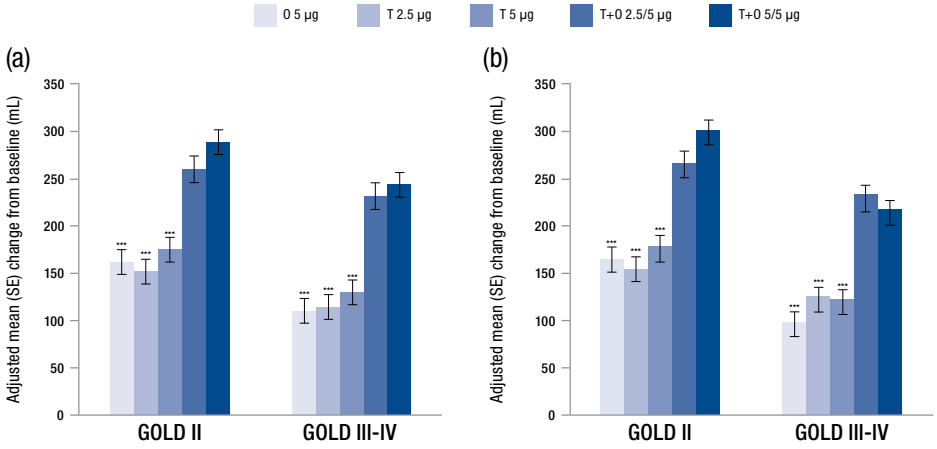

Figure 3. Lung function change (change from baseline in adjusted mean FEV_1 AUC_{0-3} responses at 24 weeks) by disease severity with tiotropium/olodaterol treatment based on pooled data from TONADO 1 and TONADO 2 studies.[43] ***p<0.0001 versus T + O combined. (a) Patients without prior LAMA or LABA use; (b) patients with prior LAMA or LABA use.
FEV_1 = forced expiratory volume in 1 second; AUC_{0-3} = area under the curve from 0 to 3 hours; LAMA = long-acting muscarinic antagonist; LABA = long-acting β_2-agonist; SE = standard error; O = olodaterol; T = tiotropium; GOLD = Global initiative for chronic Obstructive Lung Disease

Tiotropium + olodaterol shows clinically meaningful improvements in quality of life[44]

Authors: Singh D et al.

Summary: The effects of tiotropium/olodaterol on lung function and HRQOL, as measured by the SGRQ, compared with placebo in patients with moderate to severe (but not very severe) COPD was assessed in two replicate, randomised, double-blind trials (OTEMTO 1 and OTEMTO 2). Patients were assigned to receive tiotropium/olodaterol 5/5µg, 2.5/5µg, tiotropium 5µg, or placebo for 12 weeks. A total of 812 patients in OTEMTO 1 and 809 patients in OTEMTO 2 were randomised and treated. In OTEMTO 1 and 2, respectively, tiotropium/olodaterol 5/5µg improved SGRQ total score by 4.89 (95% CI -6.90 to -2.88) and 4.56 (95% CI -6.50 to -2.63) units versus placebo (both $p<0.0001$) [**Figure 4**]. Compared with tiotropium 5µg, tiotropium/olodaterol 5/5µg improved SGRQ total score by 2.49 (95% CI -4.47 to -0.51; $p<0.05$) units in OTEMTO 1 and by 1.72 (95% CI -3.63 to 0.19; NS) units in OTEMTO 2. Tiotropium/olodaterol 2.5/5µg also significantly ($p<0.001$) improved SGRQ score versus placebo (**Figure 4**).

Comment: These studies were designed specifically to address the issue of health-related quality of life as measured by the SGRQ (primary end-point). Importantly, they include a comparison against placebo. Tiotropium/olodaterol 5/5µg treatment improved SGRQ total score more than the minimal clinically-important difference of 4U relative to placebo. By contrast, tiotropium alone did not. These studies show that combination tiotropium/olodaterol provides clinically meaningful improvements in quality of life in patients with moderate and severe COPD.

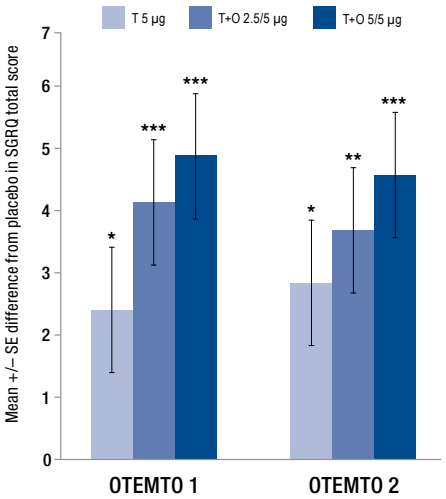

Figure 4. St George's Respiratory Questionnaire (SGRQ) total score difference from placebo after 12 weeks' treatment with tiotropium/olodaterol or its tiotropium mono-component in the OTEMTO 1 and 2 studies.[44] *p<0.05; **p<0.001; p<0.0001 vs placebo.
T = tiotropium; O = olodaterol; SE = standard error Disease

The 24-h lung-function profile of once-daily tiotropium and olodaterol fixed-dose combination in chronic obstructive pulmonary disease[45]

Authors: Beeh K-M et al.

Summary: The objective of this randomised, double-blind, phase III trial with an incomplete crossover design (VIVACITO) was to investigate the effects on 24-hour lung function and lung volume of tiotropium/olodaterol in patients with COPD. Patients received four of the following six treatment options for 6 weeks each: placebo, olodaterol 5µg, tiotropium 2.5µg, tiotropium 5µg, tiotropium/olodaterol 2.5/5µg and tiotropium/olodaterol 5/5µg. A total of 219 patients were randomised and treated. The 24-hour FEV_1 time profiles showed a consistent improvement in FEV_1 with all active treatments compared with placebo after 6 weeks of treatment and with tiotropium/olodaterol showing a greater improvement than the mono-components (**Figure 5**). This was quantified by the greater responses in FEV_1 $AUC_{0–24}$ observed with tiotropium/olodaterol 5/5µg and 2.5/5µg versus placebo and mono-components after 6 weeks of treatment; mean response with tiotropium/olodaterol 5/5µg versus placebo was 0.280L (p<0.0001). Differences versus mono-components with tiotropium/olodaterol 5/5µg were 0.115L versus olodaterol 5µg, 0.127L versus tiotropium 2.5µg, and 0.110L versus tiotropium 5µg (p<0.0001 for all comparisons). The incidence of adverse events was similar across the treatment groups and no safety concerns were identified.

Comment: This study confirms the superior effect of tiotropium/olodaterol over mono-component treatment on FEV_1 over 24 hours. An interesting aspect of this study was the evaluation functional residual capacity (FRC) and residual volume (RV) by body plethysmography in a subgroup of 143 participants. Tiotropium/olodaterol improved FRC and RV at 2.5 hours and the effect was sustained over 24 hours. This study suggests that the mechanism by which symptoms improve in patients is prolonged bronchodilation leading to reduced hyperinflation and gas trapping.

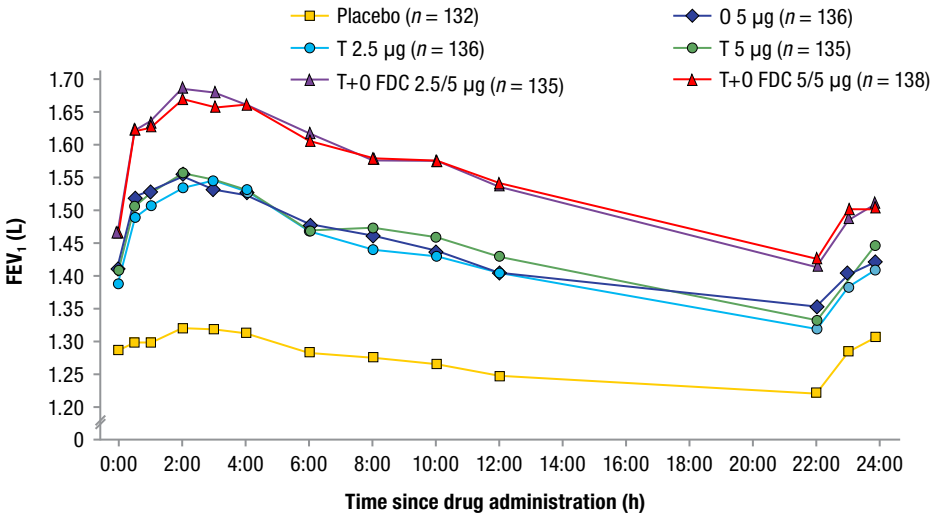

Figure 5. Adjusted mean 24-hour FEV_1 profile after 6 weeks of treatment with tiotropium/olodaterol or its mono-components in the VIVACITO trial.[45] FEV_1 = forced expiratory volume in one second; T = tiotropium; O = olodaterol; FDC = fixed-dose combination.

EXPERT'S CONCLUDING COMMENTS

GOLD recommends the use of a LAMA/LABA combination in patients with COPD who are not fully controlled on one long-acting bronchodilator. Tiotropium/olodaterol delivered via a soft mist inhaler (Respimat) is a valuable new option for treatment of these patients and provides improvements in symptoms, lung function, and quality of life. No head-to-head randomized trials have compared tiotropium/olodaterol with other LAMA/LABA combinations but it appears that they all have similar efficacy and safety. It is therefore important to personalise inhaler therapy and select the device that best suits each patient. The role of tiotropium/olodaterol in the treatment of frequent exacerbators is unclear at present but an ongoing large clinical trial (DYNAGITO) will answer this question in the near future.

TAKE-HOME MESSAGES

- COPD is a costly medical condition, with high-risk groups, including Maori and Pacific peoples, being over-represented in terms of morbidity and mortality.
- Healthcare interventions, especially those targeting high-risk groups, are required to reduce the burden of COPD.
- The airflow obstruction in COPD is due to several factors including smooth muscle constriction. This bronchoconstriction is the aspect of airflow obstruction that is most easily corrected; hence, bronchodilators are the primary drugs used in the management of COPD.
- Recent research suggests that the most rapid declines in lung function and activity levels may occur earlier rather than later in the disease course.
- In pivotal clinical trials, tiotropium/olodaterol produced improvements in lung function that translated into clinically-relevant improvements in symptoms and quality of life.
- In a post hoc analysis, tiotropium/olodaterol produced improvements in lung function that were greater in patients with less severe disease, adding support for the use of combination bronchodilation earlier in the course of COPD.

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