REVIEW

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The Role of Tiotropium+Olodaterol Dual Bronchodilator Therapy in the Management of Chronic Obstructive Pulmonary Disease

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Bronchodilator therapy is central to the management of chronic obstructive pulmonary disease and are recommended as the preferred treatment by the Global Obstructive Lung Disease Initiative (GOLD). Long acting anti-muscarinics (LAMA) and long acting β_2 agonists (LABA) are both more effective than regular short-acting drugs but many patients remain symptomatic despite monotherapy with these drugs. Combination therapy with LAMA and LABA increases the therapeutic benefit while minimizing dose-dependent side effects of long-acting bronchodilator therapy. The TOviTO programme has investigated the benefits of treatment with a combination of tiotropium and olodaterol administered via a single inhaler. Tiotropium+olodaterol 5/5 μg significantly improved forced expiratory volume in 1 second (FEV_1) area under the curve from 0 to 3 hours, trough FEV_1 health status and breathlessness versus the mono-components and placebo. Tiotropium+olodaterol 5/5 μg also increased endurance time and reduced dynamic hyperinflation during constant work rate cycle ergometry. On the basis of these and other studies the 2017 GOLD report recommends escalating to dual bronchodilator therapy in patients in groups B and C if they remain symptomatic or continue to have exacerbations and as initial therapy for patients in group D.

Keywords: Pulmonary Disease, Chronic Obstructive; Tiotropium; Olodaterol

Introduction

Although chronic obstructive pulmonary disease (COPD) is defined by the presence of persistent respiratory symptoms and airflow limitation[1] many people with COPD show a significant spirometric response to bronchodilators. For example, in both the Isolde and UPLIFT studies where patients were given 400 μg salbutamol and 80 μg ipratropium to assess the bronchodilator response at entry to the study, the mean increase in forced expiratory volume in 1 second (FEV_1) was around 200 mL with some patients showing increases in FEV_1 of over 500 mL[2,3]. As well as improving the FEV_1, which is largely a measure of large and medium airway caliber, bronchodilators have significant effects on small airway function (which is often reflected in changes in forced vital capacity [FVC]) and on static and dynamic hyperinflation[4-7].

Although the impact of COPD on patients' functional capacity and quality of life is affected by many factors not reflected in the degree of spirometric impairment, in large populations improvements in FEV_1 correlate with reductions in breathlessness (measured by the transitional dyspnea index [TDI]), health status (measured by the St George's Respiratory Questionnaire [SGRQ]), requirement for rescue medication use and the frequency of exacerbations[8,9].

Main Text

Bronchodilators are the mainstay of the pharmacologi-

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cal management of COPD and are recommended by the Global Obstructive Lung Disease Initiative (GOLD) as the preferred treatment for people with COPD[1]. Short acting bronchodilators, both β_2-agonists and anti-muscarinics taken either as needed or regularly improve both breathlessness and lung function[10] and greater effects are seen if drugs of both classes are combined[11,12]. However, many patients remain symptomatic despite the use of short acting drugs or have levels of symptoms that require treatment with more effective bronchodilators. The long acting anti-muscarinics (long-acting muscarinic antagonist [LAMA]) and long-acting β_2 agonists (LABA) are both more effective than regular short-acting drugs and more convenient. Long-acting bronchodilator monotherapy reduces airflow limitation[13-18] and dyspnoea[13,14,18] and improves physical activity/exercise capacity[19-22], and health status[13,14,16-18] as well as reducing the risk of exacerbations[23].

Tiotropium bromide was the first LAMA to be approved for maintenance treatment of COPD[24]. It is available in two formulations: dry powder (18 mg once daily) delivered via the breath-actuated HandiHaler, and aqueous solution (5 mg, two puffs 2.5 mg once daily) delivered via the Respimat Soft Mist Inhaler. It is effective when administered once daily as it has a long elimination half-life compared with other available LAMAs (27–45 hours following inhalation compared with, for example, just 2–3 hours with aclidinium)[25]. Tiotropium has occupied a central role in the management of COPD for the last decade.

Olodaterol is a once-daily LABA that is highly selective with nearly full intrinsic activity at β_2 receptors[26] and which has been shown to be effective at improving lung function over 24 hours in patients with COPD[27,28] and improving patient-reported outcomes[28].

Although long acting bronchodilators provide adequate control of symptoms for some patients, significant numbers of patients treated with long acting bronchodilator monotherapy continue to experience significant breathlessness. For example, in a study of nearly 700 patients in both primary care and specialist centers in the United States over half had a modified Medical Research Council breathlessness score (mMRC) of 2 or more despite treatment with a single long-acting bronchodilator[29].

LABAs and LAMAs act via different mechanisms; when used together in patients with COPD, they exert additional bronchodilating effects[30-32]. By targeting different receptors using an anti-muscarinic and a β agonist it is possible to increase the therapeutic benefits while minimizing dose-dependent side effects. The complementary pharmacological profiles of tiotropium and olodaterol make them ideal partners and data from studies using them in separate inhalers support the benefits of combing them[33,34]. Following on from these studies, an extensive clinical trial programme (The TOviTO programme) has investigated the benefits of treatment with a combination of tiotropium and olodaterol administered via a single inhaler. Consolidating treatments into single devices ought to decrease the complexity of usage, improve compliance and improve outcomes, particularly if the device is a Respimat Soft Mist which is easy to use and gives good pulmonary deposition[35,36]. The TOviTO program consists of ten phase 3 studies evaluating the potential benefits and safety profile of the fixed-dose combination (FDC) of olodaterol and tiotropium through the Respimat inhaler. The program has studied over 15,000 patients with moderate-to-very-severe COPD in more than 50 countries[37].

The two replicate TONADO trials were randomised, double-blind, parallel-group, multicentre trials which compared the efficacy and safety of tiotropium+olodaterol FDC administered via the Respimat device compared with the mono-components in patients with moderate to very severe COPD[38]. Current or ex-smokers aged 40 or more with at least a 10 pack year history of smoking and a post-bronchodilator FEV_1 of less than 80% of their predicted value and a post-bronchodilator FEV_1/FVC less than 70% were randomized to receive tiotropium+olodaterol FDC 2.5/5 μg or 5/5 μg, tiotropium 2.5 μg or 5 μg, or olodaterol 5 μg delivered once-daily via Respimat inhaler over 52 weeks. The primary end points were the FEV_1 area under the curve from 0 to 3 hours (AUC_{0-3}) response, trough FEV_1 response and SGRQ total score at 24 weeks.

Both tiotropium+olodaterol fixed dose combinations significantly improved FEV_1 AUC_{0-3} and trough FEV_1 response versus the mono-components in the two replicate studies. FEV_1 AUC_{0-3} responses for tiotropium+olodaterol FDC 2.5/5 μg, 5/5 μg, tiotropium 2.5 μg, 5 μg, and olodaterol 5 μg were 241, 256, 148, 139, and 133 mL, respectively, in one study, and 256, 268, 125, 165, and 136 mL, respectively, in the other study. Improvements in the adjusted mean FEV_1 AUC_{0-3} with tiotropium+olodaterol FDC 5/5 μg and 2.5/5 μg over the corresponding individual components in the individual studies and the combined analysis were statistically significant ($p<0.0001$ for all comparisons)[38].

After 24 weeks, the pre-specified analysis of the adjusted mean SGRQ total score showed statistically significant improvements for tiotropium+olodaterol FDC 5/5 μg over corresponding individual components (vs. olodaterol 5 μg: –1.693 [0.553], $p<0.01$; vs. tiotropium 5 μg: –1.233 [0.551], $p<0.05$) but not for tiotropium+olodaterol FDC 2.5/5 μg versus the individual components. An analysis of responder rates examining the proportion of patients who achieved a decrease in SGRQ total score by at least the minimum clinically important difference of 4.0 units was also performed. Over half of patients treated with the FDCs responded: the responder rates were 57.5% for tiotropium+olodaterol 5/5 μg and 53.2% for 2.5/5. This compared to responder rates of 49.6%, 48.7%, and 44.8% for tiotropium 2.5 μg, 5 μg, and olodaterol 5 μg, respectively. The increases in the responder rates for tiotropium+olodaterol

FDC 5/5 μg over its individual components was statistically significant[38].

There was also a statistically significant improvement in the key secondary end point of the Mahler TDI focal score at 24 weeks in the combined data set for both tiotropium+olodaterol FDCs versus their mono-components (nominal p<0.05). Fifty-four point nine percentage of patients treated with tiotropium+olodaterol FDC 5/5 μg achieved the minimal clinically important difference of 1 unit improvement in the TDI compared to 50.6% with 5 μg tiotropium and 48.2% with 5 μg olodaterol.

With both tiotropium+olodaterol FDC 5/5 μg and 2.5/5 μg there was a reduction in adjusted weekly mean daily (24-hour) rescue medication use compared to the monotherapy components throughout the 52-week treatment period. Such reductions in rescue medication are important indicators of whether patients notice a benefit from their maintenance therapy[39].

The TONADO studies were not designed to examine the effects of tiotropium+olodaterol FDC on exacerbation rates but data on exacerbations were collected and there was a trend for improvement in exacerbations with the FDCs versus the monotherapy components. The incidence of adverse events was comparable between the FDCs and the mono-components.

Post-hoc analysis of the TONADO studies showed tiotropium+olodaterol FDC improved lung function over the mono-components in patients with GOLD 2 and 3–4 disease, irrespective of prior LAMA or LABA maintenance therapy and most comparisons between the FDCs and their respective mono-components were statistically significant (p<0.05)[40]. There was also no difference in the relative responses to tiotropium+olodaterol 5/5 μg compared to the mono-therapies in different age groups[41].

Adverse event incidence was generally balanced across all treatment groups, with the majority being mild to moderate in severity and the incidence of adverse events was comparable between the FDCs and the mono-components.

Because the TONADO studies ran for 52 weeks, it was considered unethical to include a placebo group, but it is important to be able to assess the effects of mono-therapy and the FDCs on patient reported outcomes (PRO) compared to placebo and the OTEMTO studies were designed to do this. These again comprised two randomized, double-blind, parallel-group, multicentre trials which compared the efficacy and safety of tiotropium+olodaterol FDC administered via the Respimat device compared with the mono-components and placebo over 12 weeks in patients with moderate to severe COPD[42]. The three primary end points, measured at 12 weeks, were SGRQ total score, and FEV_1 AUC_{0-3} and trough FEV_1 changes from baseline.

In OTEMTO 1 and 2, after 12 weeks tiotropium+olodaterol 5/5 μg significantly improved FEV_1 AUC_{0-3} response compared to placebo by 0.331 L and 0.299 L, respectively and improved trough FEV_1 response by 0.162 L and 0.166 L compared to placebo (p<0.0001).

Tiotropium+olodaterol 5/5 μg improved SGRQ total score at 12 weeks by 4.89 units and 4.56 units versus placebo (p<0.0001) in OTEMTO 1 and 2, respectively and the improvement compared to tiotropium 5 μg was 2.49 units (p=0.0136) and 1.72 units (p=0.0780), respectively[42]. After 12 weeks of treatment 52% of patients receiving tiotropium+olodaterol 5/5 μg were classed as SGRQ responders compared to 41% receiving tiotropium 5 μg (p<0.01) and 32% in the placebo group (p<0.0001)[43].

Changes in TDI were assessed as a secondary endpoint. Tiotropium+olodaterol 5/5 μg improved TDI score at 12 weeks by 2.05 units and 1.20 units versus placebo (p<0.0001) in OTEMTO 1 and 2. At week 12, 54% of patients receiving tiotropium+olodaterol 5/5 μg were classed as TDI responders compared to 41% receiving tiotropium (p<0.001) and 26% of patients receiving placebo (p<0.0001)[43].

Post-hoc analysis of the OTEMTO studies showed tiotropium+olodaterol fixed dose combination improved lung function, SGRQ and TDI compared to tiotropium and placebo in patients with GOLD 2 and 3–4 disease[44]. There was also no difference in the relative responses to tiotropium+olodaterol 5/5 μg compared to tiotropium and placebo in different age groups[41]. When analysed by baseline breathlessness assessed using the mMRC, the difference between SGRQ scores achieved by tiotropium+olodaterol 5/5 μg compared to tiotropium 5 μg was greatest in patients with an mMRC of 2 or more compared to those with an mMRC less than 2[45]. This shows that the greatest benefit of combination bronchodilator therapy is seen in the more symptomatic patients where it is most needed.

Multiple studies have assessed whether other LABA/LAMA combinations result in similar improvements in lung function, reductions in exacerbation rates, and achievement of minimal clinically important differences in TDI and SGRQ scores compared to monotherapy[46].

Clinically, it is important to know if there is additional benefit of dual bronchodilator therapy in patients who have a good response to either LAMA or LABA monotherapy as well as those who do not. One study has examined the efficacy of dual bronchodilatation (umeclidinium+vilanterol 62.5/25 μg) in patients identified as responsive or non-responsive to mono-bronchodilatation (umeclidinium 62.5 μg, vilanterol 25 μg)[47]. Umeclidinium+vilanterol significantly increased lung function versus umeclidinium in umeclidinium-responders and versus vilanterol in vilanterol-responders. In umeclidinium and vilanterol non-responders, lung function was still significantly increased by dual therapy, but by a smaller amount.

The CRYSTAL study examined directly switching from various treatments to glycopyrronium (50 μg) or indacaterol+glycopyrronium (110/50 μg) in terms of lung function and

symptoms in symptomatic patients with moderate COPD[48]. This was a prospective, multicentre, 12-week, randomized, pragmatic, open-label trial designed to mimic clinical practice. Indacaterol+glycopyrronium significantly improved lung function and dyspnea after direct switch from LAMA or LABA.

The effects of dual bronchodilator therapy on exercise capacity were examined in the TORRACTO study[49]. This was a randomized, double-blind, placebo-controlled study to determine the effect of 12-week treatment of inhaled tiotropium+olodaterol FDC at two different doses (2.5/5 μg and 5/5 μg) delivered by the Respimat inhaler on exercise endurance time during constant work rate cycle ergometry in 390 patients with COPD. The geometric mean endurance time during constant work rate cycle ergometry was 527.51 seconds with tiotropium+olodaterol 5/5 μg (14% increase vs. placebo, p=0.021). Tiotropium+olodaterol 5/5 μg increased pre-exercise inspiratory capacity versus placebo at 12 weeks by 234 mL (p<0.0001) and at week 12, the slope of the intensity of breathing discomfort (Borg scale) during exercise decreased with tiotropium+olodaterol 5/5 μg (p=0.060).

Tiotropium monotherapy is effective at reducing the risk of exacerbations[23] and LABA/inhaled corticosteroid (ICS) was not more effective than tiotropium at preventing exacerbations in the INSPIRE study[50]. Recently, the FLAME study showed that dual bronchodilator therapy with indacaterol+glycopyrronium was more effective than LABA/ICS at reducing exacerbation rates[51]. Currently, there are no data comparing tiotropium+olodaterol with tiotropium from studies with exacerbation rates as the primary outcome. The DYNAGITO study (registered as NCT02296138 at ClinicalTrials.gov) comparing the annualized rate of moderate-to-severe COPD exacerbations over 1 year in patients treated with tiotropium+olodaterol 5/5 μg or tiotropium 5 μg will provide these data. The study is still on going, but results are expected in late 2017 or early 2018.

Conclusion

The GOLD report emphasises the fact that bronchodilators are central to the management of COPD[1]; however, many patients remain symptomatic despite mono-therapy with a LABA or LAMA. Dual bronchodilator therapy improves lung function and PRO compared to the mono-components, and reduces exacerbation rates compared to LABA/ICS.

Once-daily dosing of COPD therapy translates into significantly higher adherence than other dosing frequencies, thereby leading to reductions in healthcare resource utilization and cost[52].

On the basis of the evidence for the effectiveness of dual bronchodilator therapy, the 2017 GOLD report recommends escalating to dual bronchodilator therapy in patients in group B (higher symptoms but low risk of exacerbations) if they have persistent breathlessness on monotherapy. It also states that for patients with severe breathlessness initial therapy with two bronchodilators may be considered.

The GOLD report also recommends that patients in group C (low symptoms but high risk of exacerbations) with persistent exacerbations despite treatment with a LAMA may benefit from escalation to dual bronchodilator therapy. For patients in group D (high symptoms and high risk of exacerbations) the GOLD report recommends starting treatment with dual bronchodilators.

Conflicts of Interest

Professor Halpin has received sponsorship to attend international meetings, and honoraria for lecturing, attending advisory boards and preparing educational materials from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Pfizer & Sandoz. He is a member of the GOLD Board of Directors and the GOLD Science Committee.

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