

What Does the TOVITO Programme Tell Us about How We Can Manage COPD?

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Cite this article as: Russell REK. What Does the TOVITO Programme Tell Us about How We Can Manage COPD?. Turk Thorac J 2018; 19(4): 216-9.

Abstract

Chronic obstructive pulmonary disease (COPD) patients suffer from a significant burden of disease which impairs their quality of life, exercise capacity and lung function. They also suffer from acute worsening of disease, called exacerbations. The role of drug treatment in the management of COPD is aimed at improving lung function, quality of life and reducing the risk of exacerbations. Bronchodilator drugs are the mainstay of therapy and the two classes, long acting beta2 agonists and long acting anti-muscarinics, are being combined together. The TOVITO programme of clinical research is a comprehensive and consistent set of studies investigating the role of Tiotropium and Olodaterol (Spiolto) on lung function, quality of life, exercise capacity and exacerbation frequency. The programme has included over 16 000 patients who have received the benefits of these two compounds when given together in a suitable inhaler. Safety data was collected with a focus on cardiovascular morbidity and mortality. The use of tiotropium/olodaterol combination resulted in significant gains in lung function, quality of life and exercise endurance. There was no difference between the arms in the Dynagito study which was designed to compare tiotropium/olodaterol combination with its constituent compounds. In all studies no safety concerns were raised. Tiotropium/Olodaterol (Spiolto) is an effective treatment for COPD with benefits to lung function, quality of life and exercise tolerance.

KEYWORDS: Tiotropium, olodaterol, COPD, exacerbations, quality of life

Received: 12.07.2018

Accepted: 19.07.2018

INTRODUCTION

The TOVITO programme is a series of clinical trials investigating the efficacy of the dual bronchodilators Olodaterol and Tiotropium (Spiolto). The studies investigated all aspects of efficacy including: lung function, exercise tolerance, quality of life and effect on exacerbations. They varied in sample size, length of study and comparators in accordance with the primary end point of the individual study. The programme has included over 16 000 participants.

Olodaterol is one of the super long acting beta agonists with a true sustained action allowing it to be used once a day. On its own it has a fast onset of action and a prolonged (24) duration of bronchodilation. In its registration studies Olodaterol demonstrated at both 5 and 10 microgram doses a significant improvement in FEV₁ area under the curve (AUC) of 140 ml which was sustained after 48 weeks of therapy when compared to placebo. When trough FEV₁ was measured there was a clear 80 mL improvement versus placebo which was sustained for 48 weeks. This makes Olodaterol a good choice of partner for Tiotropium [1–6].

Tiotropium was the first once daily long acting anti-muscarinic (LAMA) drug to be used in chronic obstructive pulmonary disease (COPD). It has a huge heritage of trials behind it and has been shown to provide sustained improvements in lung function, exercise capacity, quality of life and also impact exacerbation rates in COPD. The studies of tiotropium have varied in duration (up to 4 years) and in comparator. Tiotropium is generally used as the standard comparator for all new long acting bronchodilators in COPD trials [7–12].

We need better treatments for COPD. Patients present late in the course of the disease and by the time we treat them significant declines in lung function have already occurred [13,14]. Of great significance is the loss of function that has happened with the COPD patient developing increasing breathlessness with activity, which leads them adapting what they do. They often reduce activity and this in turn leads to deconditioning and so a rapid progressive downward spiral occurs [15]. For an individual by the time of presentation this process may already be established leading to a loss of quality of life. This needs to be addressed urgently and we need to give our patients the best evidence-based treatment

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we can to improve lung function, increase exercise capacity, reverse the deconditioning and improve quality of life. This requires effective bronchodilation coupled with behavioral change and pulmonary rehabilitation.

The TOVITO development programme was designed to address each aspect of this downward spiral and demonstrate that rapid, sustained bronchodilation could impact on each dimension of COPD. Each study also collected safety and side effect data.

Effect on Lung Function

The VIVACITO study was performed to measure the lung function effects of Spiolto measured for a 24-hour period for 6 weeks. Two hundred nineteen participants were enrolled in the study. The study demonstrated a 339 mL improvement in FEV₁ AUC (0-3 hr) and a 207 mL improvement in trough FEV₁ for Spiolto versus placebo and the monocomponents. The study also measured FVC and again demonstrated a clear superiority for the dual bronchodilator. Of great interest and perhaps significance is the full lung function data set that was also collected on a subgroup of participants. This demonstrated a large reduction in both functional residual capacity and residual volume. This reduction in gas trapping is a likely mechanism of possible improvements in exercise capacity and much of the quality of life benefits of these drugs [16,17].

The TONADO study was a long term clinical trial which focused on lung function [18,19]. The trial lasted for one year and enrolled participants with GOLD stage 2, 3 and 4 COPD. There were also measurements of quality of life using the St George's Respiratory Questionnaire (SGRQ) as well as a high level of safety monitoring. The study really asked the questions: does Spiolto improve lung function in the longer term and do patients feel better because of it? Over the 52 weeks of the study there were significant improvements in spirometry as measured by trough fev1 and FEV₁ AUC versus the monocomponents. This was real-world patient population and the study also demonstrated improvements in quality of life. There were reductions in SGRQ score for those on Spiolto versus the mono-components and a 32% increase in the proportion of participant achieving the clinically significant 4-point reduction in SGRQ score (44.8% vs 57.5%, Olo-daterol versus Spiolto). The TONADO study also revealed a trend towards a difference in exacerbation rate between the dual therapy and the mono-components. The study was not designed or powered for this outcome.

The loss of lung function in COPD is not linear and recent studies have shown that patients with milder disease lose more lung function annually than those with more severe disease as measured by GOLD stage [20]. So, it is important to see how those with earlier stage disease (GOLD stage 2) respond to the dual bronchodilators. In the TONADO study the GOLD2 participants actually achieved greater improvements in lung function than the more severe, GOLD 3 and 4, participants and this difference was seen irrespective of prior long acting bronchodilator treatment.

Chronic obstructive pulmonary disease patients use prn rescue medication when they get breathless. This is a marker of subjective control of disease and a reduction in rescue

medication use implies that the patient is feeling less breathless. The TONADO study demonstrated that the participants treated with Spiolto used less rescue medication throughout the year of the study. The study also measured breathlessness using the transitional dyspnea index. The results consistently demonstrated a reduction in breathlessness if taking Spiolto with an increase in the proportion of patients achieving the minimal clinically important difference (48% vs 54.9%, Olo-daterol vs Spiolto).

The ENERGITO study compared Spiolto delivered in a Respi-mat with Salmeterol/Fluticasone delivered in an Accuhaler (Seretide) [17]. The doses given were 5/5 micrograms once a day and 50/500micrograms twice a day respectively. Two hundred and twenty-nine patients were studied for 6 weeks using a cross-over design. The primary outcome was lung function. The patient population contained GOLD stage 2 and 3 COPD patients. After 6 weeks of treatment the participants on Spiolto had a rapid, significant and sustained improvements in FEV₁ when measured over a continuous 24-hour period. The largest difference was seen in FEV₁ AUC for 0-12 hours 317 mL versus 192 mL, Spiolto and Seretide respectively. This result is to be expected given that the comparison is one bronchodilator against two with a lung function end point.

Effect on Quality of Life

The OTEMPTO studies were a pair of 12-week studies which studied the effects of Spiolto on quality of life in a very detailed manner [21,22]. 1621 subjects were studied, lung function changes were also measured with two comparators; placebo and tiotropium alone. The results show a significant improvement of 4.7 units in SGRQ versus placebo and 2.1 units against tiotropium. There was a striking increase in the SGRQ responder rate (those who achieved a 4 unit change) with this occurring in 52.4% for Spiolto, 41.4% for Tiotropium and 31.9% for placebo. As a physician having over 50% of patients on a treatment reporting that they feel significantly better is a very positively reinforcing factor. Breathlessness as measured by the TDI score was significantly reduced for the participants taking Spiolto versus tiotropium and placebo (1.73 vs 1.14 vs 0.11 respectively) with again a significant increase in responder rate (those who achieve the MCID od 1 point) 53.9% versus 41% versus 26.2% respectively. These changes were seen in subjects with both GOLD stage 2 and 3 disease. These studies give us confidence that the changes seen in lung function are then translated into changes in breathlessness and quality of life.

The TOVITO programme also looked at exercise capacity in the PHYSACTO, TORRACTO and MORACTO studies [23,24]. A variety of assessments were used including endurance shuttle walk tests (ESWT) in the PHYSACTO study. This demonstrated significant increases in endurance time for those on Spiolto versus tiotropium and placebo at both 8 weeks and 12 weeks.

Every study in the TOVITO programme included a safety analysis with a particular focus on cardiovascular events. In all assessments there were no significant signals by any measure [25].

Effect on Exacerbations

Exacerbations of COPD are important. They lead to morbidity, mortality and consume enormous amounts of healthcare resource world-wide [26]. They are classed into mild, moderate and severe depending upon which treatment is given and where they are given as a surrogate for physiological and systemic severity [27]. The final study of the TOVITO programme was the DYNAGITO study. This was the final piece in the puzzle designed to assess the effect of Spiolto on the exacerbation rate in a 1-year study in 7800 participants with the comparator of tiotropium alone. The study background and design are important. Previous studies had demonstrated the potential for Tiotropium to reduce exacerbation rate and the TONADO studies had demonstrated a trend towards a reduction in exacerbations in those taking Spiolto [10,18]. The DYNAGITO study is the largest of the TOVITO programme as required by the power calculation which set a significance rate of 1% (as this was single study and not a paired study) as required by regulators, with an anticipated reduction in exacerbation rate of 10% [28]. DYNAGITO was a double blind randomised study with a primary endpoint of rate of moderate or severe exacerbation, with secondary endpoints of time to first moderate-to-severe exacerbation, annualized rate and time to first exacerbation leading to hospitalization, and time to all-cause mortality. Given the size and duration of the study a large amount of safety data was collected. The inclusion criteria included those with a FEV₁ less than 60% and a history of one or more moderate or severe exacerbation in the year prior to study entry. It was designed to be as real world as possible and there was no pre-planned statistical adjustment for relevant co-variables. If a participant was taking inhaled cortico-steroids (ICS) at entry, then they stayed on the steroid throughout. 70% of the participants were taking ICS throughout the study. 50% of the participants were GOLD stage 3 COPD patients with 48% being in the GOLD category B and 39% being GOLD category D. Patients were 27% less likely to drop out of the study if taking the dual bronchodilator suggesting that they were more stable on this therapy. This study did not reach the pre-set level of statistical significance and demonstrated a 7% reduction in exacerbation rate for Spiolto versus Tiotropium ($p=0.0498$). When analysed considering baseline therapy it was clear that there was a significant effect of dual therapy versus tiotropium alone (relative rate of exacerbation 0.91 (95% CO 0.84-0.99). There was a significant reduction (20%) in those exacerbations needing treatment with oral corticosteroids in those receiving Spiolto. The meaning of this finding for clinical practice is unclear and deserves further study. This may help our understanding of the nature of exacerbations and why physicians choose treatments. When a post-hoc analysis of the DYNAGITO data included adjustment for co-variables which may affect the baseline exacerbation rate (sex, disease severity, baseline therapy, smoking status or baseline exacerbation rate) the exacerbation rate ratio was significantly different between Spiolto and tiotropium at the 1% level (0.89, 95% CI 0.84-0.96, $p=0.001$). The health status of the participants, as measured by CAT (COPD assessment test), was significantly better for those taking Spiolto versus those taking Tiotropium. There was no difference in adverse event rate between either of the treatment arms. And a detailed assessment of major cardio-

vascular events showed no difference for the duration of the DYNAGITO study.

The DYNAGITO study was an attempt to take a very real-life approach to treatment aimed at reducing exacerbations of COPD. It was well designed and appropriately powered to achieve an answer based upon the predicted effect rate. Perhaps the effectiveness of Tiotropium on exacerbation rate was unexpectedly good. In taking a very clear and statistically clean approach and not including any adjustments for co-variables was brave but potentially weakened the ability of the study to demonstrate the effect of dual therapy on exacerbation rate. It will be interesting to see more data as it emerges especially with regard to the effect of blood eosinophils in this study and, given the number of participants, duration of the study and level of data collected, much more will come out of the DYNAGITO study which will enhance our understanding of the nature of COPD exacerbations.

CONCLUSION

Taking the TOVITO programme as a whole there is no doubt that treatment using a dual bronchodilator approach has consistent and significant effects on COPD patients of all disease severity. There are improvements in lung function, with a particular benefit on measures of gas trapping. Exercise capacity is improved, and patients feel less breathless and have an improved quality of life. In my opinion, there is adequate evidence to recommend that the optimal baseline therapy for our patients with COPD should be the use of dual bronchodilators given in an effective device designed specifically for patients with COPD.

Peer-review: This manuscript was prepared by the invitation of the Editorial Board and its scientific evaluation was carried out by the Editorial Board.

Conflict of Interest: The author has received Honoria and travel grants to attend advisory boards, speak at conferences and attend conferences for Boehringer Ingelheim, Glaxosmithkline, Astrazeneca, Teva, Chiesi and Novartis.

Financial Disclosure: The author has no financial interest in the products in this article or associated companies.

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