Respiratory Medicine 109 (2015) 1312–1319

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Tiotropium + olodaterol shows clinically meaningful improvements in quality of life

Dave Singh [a, *], Gary T. Ferguson [b], Josef Bolitschek [c], Lars Grönke [d], Christoph Hallmann [d], Nathan Bennett [e], Roger Abrahams [f], Olaf Schmidt [g], Leif Bjermer [h]

[a] The Medicines Evaluation Unit, Manchester, UK
[b] Pulmonary Research Institute of Southeast Michigan, Livonia, MI, USA
[c] Krankenhaus der Elisabethinen, Linz, Austria
[d] Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany
[e] Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA
[f] Morgantown Pulmonary Associates, Morgantown, WV, USA
[g] Lungen- und Bronchialheilkunde, Koblenz, Germany
[h] Department of Respiratory Medicine and Allergology, Lund University, Lund, Sweden

ARTICLE INFO

Article history:
Received 15 April 2015
Received in revised form
27 July 2015
Accepted 7 August 2015
Available online 12 August 2015

Keywords:
COPD
Quality of life
Long-acting bronchodilator
Tiotropium
Olodaterol

ABSTRACT

Background: Tiotropium + olodaterol improves lung function and symptoms compared to monotherapies in chronic obstructive pulmonary disease (COPD). The OTEMTO 1 and 2 studies investigated the effects of tiotropium + olodaterol on lung function and health-related quality of life compared to placebo in patients with moderate to severe COPD.

Methods: In these two replicate, double-blind, parallel-group, placebo-controlled trials, patients were randomised to receive tiotropium + olodaterol 5/5 μg, 2.5/5 μg, tiotropium 5 μg or placebo for 12 weeks, via the Respimat® inhaler. Primary end points were St George's Respiratory Questionnaire (SGRQ) total score, forced expiratory volume in 1 s (FEV_1) area under the curve from 0 to 3 h (AUC_{0-3}) response and trough FEV_1 response.

Results: In OTEMTO 1 and 2, tiotropium + olodaterol 5/5 μg improved SGRQ total score by 4.89 (95% confidence interval [CI] −6.90, −2.88) and 4.56 (95% CI −6.50, −2.63) units versus placebo (both $p < 0.0001$), and 2.49 (95% CI −4.47, −0.51; $p < 0.05$) and 1.72 (95% CI −3.63, 0.19) units versus tiotropium 5 μg. Tiotropium + olodaterol 2.5/5 μg significantly improved SGRQ score compared to placebo. Both doses significantly improved FEV_1 AUC_{0-3} response compared to placebo and tiotropium 5 μg. Tiotropium + olodaterol 5/5 and 2.5/5 μg also significantly improved trough FEV_1 response compared to placebo (both studies) and separated from tiotropium 5 μg in OTEMTO 2. Adverse-event incidence was similar between treatment groups.

Conclusion: Tiotropium + olodaterol improved lung function and quality of life compared to placebo and tiotropium 5 μg.

Trial registration: ClinicalTrials.gov: NCT01964352 and NCT02006732.

1. Introduction

Tiotropium was the first once-daily long-acting muscarinic antagonist (LAMA) to be approved for the treatment of chronic obstructive pulmonary disease (COPD) and has now been developed in a fixed-dose combination with the once-daily long-acting β_2-agonist (LABA) olodaterol. Olodaterol is approved for the treatment of COPD and has an early onset of action and a 24-h effect on lung function [1–4]. The efficacy and tolerability of olodaterol was demonstrated in a large Phase III programme [1–5]. Combination

Abbreviations: AE, adverse event; AUC_{0-3}, area under the curve from 0 to 3 h; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; GOLD, Global initiative for chronic Obstructive Lung Disease; FVC, forced vital capacity; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; MCID, minimum clinically important difference; SGRQ, St George's Respiratory Questionnaire; TDI, Transition Dyspnoea Index.

* Corresponding author. The Medicines Evaluation Unit, The Langley Building, Southmoor Road, Wythenshawe, Manchester, M23 9QZ, UK.
E-mail address: dsingh@meu.org.uk (D. Singh).

http://dx.doi.org/10.1016/j.rmed.2015.08.002

therapies are commonly used in COPD and their use is supported by the Global initiative for chronic Obstructive Lung Disease (GOLD) report [6].

Data from the tiotropium + olodaterol Phase III studies have demonstrated significant improvements in lung function to a greater extent than tiotropium and olodaterol monocomponents, with no additional safety concerns [7,8]. The TONADO studies were two large replicate Phase III trials that demonstrated improvements in lung function and St George's Respiratory Questionnaire (SGRQ) total score over 52 weeks with tiotropium + olodaterol versus the monocomponents in patients with moderate to very severe COPD.

In the TONADO studies, it was not possible to include a placebo arm due to the 52-week duration and the inclusion of patients with very severe COPD. The effects of bronchodilator therapies on patient-reported outcomes are best investigated in placebo-controlled studies in order to understand whether the minimum clinically important difference (MCID) compared to placebo is achieved. The novelty of the OTEMTO studies was the inclusion of a placebo arm; the study design involved a shorter duration and the exclusion of patients with GOLD 4 disease in order to allow this. In addition, both the tiotropium + olodaterol 2.5/5 μg and 5/5 μg doses were included to investigate differences in effect size between the two doses.

The objective of the OTEMTO studies was to evaluate the effect of tiotropium + olodaterol on lung-function improvement and health-related quality of life after 12 weeks of treatment compared to placebo and tiotropium 5 μg in patients with moderate to severe COPD.

2. Methods

2.1. Study design

These were two replicate, multinational, double-blind, parallel-group, placebo-controlled studies (OTEMTO 1, 1237.25, NCT01964352; OTEMTO 2, 1237.26, NCT02006732) in which patients were randomised to receive one of four treatments once daily for 12 weeks, all delivered via the Respimat® inhaler: placebo, tiotropium 5 μg, tiotropium + olodaterol 2.5/5 μg and tiotropium + olodaterol 5/5 μg (Fig. 1).

After completing an initial screening visit, patients entered a 2-week screening period prior to randomisation. A follow-up visit took place ~3 weeks after last dose of study medication.

2.2. Patients

Patients aged ≥40 years with moderate to severe COPD (GOLD 2–3; post-bronchodilator forced expiratory volume in 1 s [FEV_1] ≥30% and <80% of predicted normal), FEV_1/forced vital capacity (FVC) <70% predicted and a smoking history of >10 pack-years were included. Patients were excluded if they had a history of asthma, another significant disease, COPD exacerbation or symptoms of lower respiratory tract infection within the previous 3 months, unstable or life-threatening cardiac arrhythmia, hospitalisation for heart failure within the past year, a history of myocardial infarction within 1 year of screening or a history of life-threatening pulmonary obstruction.

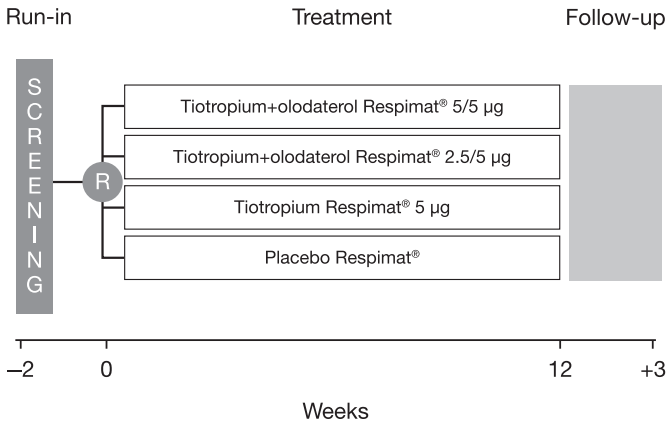

Fig. 1. OTEMTO study design. R, randomisation.

Patients were allowed to continue their inhaled corticosteroid therapy (if they were on a stable dose for 6 weeks prior to screening). LAMAs or LABAs other than study medication were prohibited during the screening or treatment periods, and short-acting muscarinic antagonists were permitted only during the screening period. Open-label salbutamol was provided as rescue medication for use throughout the study.

2.3. Study outcomes

The three primary end points, measured at 12 weeks, were SGRQ total score, FEV_1 area under the curve from 0 to 3 h (AUC_{0-3}) response (change from baseline) and trough FEV_1 response. Trough FEV_1 was defined as the mean of the FEV_1 values at 23 h post-dose and 23 h 50 min post-dose.

The secondary end points were Mahler Transition Dyspnoea Index (TDI) focal score and, trough FVC and FVC AUC_{0-3} responses. All adverse events (AEs) and serious AEs were reported, vital signs were monitored and 12-lead electrocardiogram recordings were taken for all patients at screening and at Week 12, with any abnormalities reported as AEs.

2.4. Assessments

Pulmonary function testing was performed according to American Thoracic Society/European Respiratory Society guidelines [9] and tests were performed in triplicate, with the highest FEV_1 and FVC being reported. Pulmonary function tests were performed at 1 h pre-dose, 10 min pre-dose, 5, 15 and 30 min post-dose and 1, 2 and 3 h post-dose at baseline and Week 12, and at 10 min pre-dose only after 2 and 6 weeks of treatment. The final trough FEV_1 measurement was taken the day after the Week 12 visit (at 23 h and 23 h 50 min post-dose). Further information about the spirometry methodology is provided in the Supplementary material.

Patients completed the SGRQ at baseline and at Weeks 6 and 12, before any other assessments at that visit. The questionnaire consists of 16 questions about patients' recollections of their symptoms over the past month (Questions 1–8) and their current state, including activity levels and impact on functioning (Questions 9–16). Patients completed the questionnaire in the clinic.

The Mahler Baseline Dyspnoea Index was administered at baseline and used as the baseline value for analyses of TDI score. The TDI was administered at Week 6 and Week 12 and consists of an interview to measure the level and extent of activities patients can perform before feeling breathless, relative to their baseline performance. The interviews were conducted by trained clinic staff.

2.5. Statistical analysis

The pre-specified analyses of the study were designed to test tiotropium + olodaterol versus placebo for all of the primary end points; the hypothesis testing strategy is presented in Supplementary Fig. S1. Assuming standard deviations of 0.226 L for FEV_1 AUC_{0-3} and 0.225 L for trough FEV_1, and a two-sided alpha of 0.05, a sample size of 200 patients per group per trial was required