Efficacy of Tiotropium/Olodaterol Compared with Tiotropium in Patients Naïve to LAMA, LABA and ICS: Pooled Analysis of Four Clinical Trials

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RATIONALE

The efficacy of tiotropium/olodaterol (T/O) compared with tiotropium (Tio) has been demonstrated in a large Phase III program. This subgroup analysis investigated the treatment effect in patients who, at study entry, were not receiving maintenance treatment with long-acting muscarinic antagonists (LAMAs), long-acting β_2-agonists (LABAs) or inhaled corticosteroids (ICS).

METHODS

TONADO 1&2 (NCT01431274/NCT01431287) included patients with COPD with post-bronchodilator forced expiratory volume in 1 second (FEV_1) <80% predicted; OTEMTO 1&2 (NCT01964352/NCT02006732) included patients with post-bronchodilator FEV_1 30–<80% predicted. This post hoc analysis examined the treatment differences between T/O 5/5µg and Tio 5µg in trough FEV_1 response, St. George's Respiratory Questionnaire (SGRQ) total score change from baseline and Transition Dyspnea Index (TDI) score at 12 weeks, in patients not receiving LAMA, LABA or ICS, at baseline in all four studies.

RESULTS

We included 1,078 patients who were not receiving LAMA, LABA or ICS at entry. The pooled analysis shows a significantly greater increase in trough FEV_1 from baseline with T/O compared with Tio at

Week 12 (0.056 L [95% CI 0.033, 0.079]) (Table). There were also significant improvements with T/O versus Tio in SGRQ total score (–1.780 [–3.126, –0.434]) and TDI score (0.409 [0.077, 0.741]) at Week 12. There was a greater chance of being an SGRQ responder (≥4-unit improvement) with T/O treatment (59.6%) than Tio (48.8%; odds ratio 1.54 [1.20, 1.99]), and of being a TDI responder (≥1 unit improvement) with T/O (63.3%) than with Tio (55.0%; odds ratio 1.43 [1.11, 1.85]).

CONCLUSIONS

Overall, there were greater improvements in lung function, health status and breathlessness with T/O compared with Tio in patients who were not receiving LAMA, LABA or ICS at baseline. Dual bronchodilation with T/O may be an effective first-line option for treatment-naïve patients with COPD who have poor lung function and/or a high symptom burden.

Word count: 300

Table. Treatment differences in trough FEV_1, SGRQ total score and TDI score after 12 weeks in TONADO and OTEMTO combined

	n T/O / Tio	T/O vs Tio, mean difference (95% CI)	P value
Trough FEV_1, L			
	510/548	0.056 (0.033, 0.079)	<0.0001
SGRQ total score			
	488/521	–1.780 (–3.126, –0.434)	0.0096
TDI score			
	494/525	0.409 (0.077, 0.741)	0.0158

Mixed effect model repeated measures including fixed effects of treatment, study, planned test day, treatment-by-test day interaction, baseline and baseline-by-test day interaction; patient as a random effect (trough FEV_1 analysis only); spatial power covariance structure for within-patient errors and Kenward−Roger approximation for denominator degrees of freedom.
CI, confidence interval; FEV_1, forced expiratory volume in 1 second; SGRQ, St. George's Respiratory Questionnaire; T/O, tiotropium/olodaterol; TDI, Transition Dyspnea Index; Tio, tiotropium.

Benefits of tiotropium/olodaterol compared with tiotropium in patients with COPD receiving only LAMA at baseline: pooled analysis of 4 clinical trials

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Background

TONADO and OTEMTO were large, randomised, double-blind, Phase III trials that demonstrated the efficacy of tiotropium/olodaterol (T/O) compared with tiotropium (tio) in COPD.

Aim

We pooled data from TONADO and OTEMTO to investigate the effect on symptoms and lung function of stepping up treatment from tio to T/O in patients who received only tio at baseline.

Methods

TONADO 1+2 (NCT01431274/NCT01431287) were 52-week studies and OTEMTO 1+2 (NCT01964352/NCT02006732) were 12-week studies in patients with COPD with FEV_1 <80% predicted in TONADO and ≥30% and <80% predicted in OTEMTO. In this post hoc analysis, we examined the treatment differences between T/O 5/5 µg and tio 5 µg at 12 weeks in patients who received LAMA monotherapy at baseline. 98% of patients treated with LAMA received tio.

Results

At Week 12, T/O increased trough FEV_1 from baseline compared with tio (0.074 L; 95% CI 0.033, 0.115; Table). Improvements with T/O versus tio were seen in SGRQ total score (–2.68; 95% CI –5.06, –0.29) and TDI score (1.15; 95% CI 0.56, 1.73). There was a greater likelihood of being a TDI responder and a trend towards a greater likelihood of being an SGRQ responder with T/O compared with tio.

Conclusions

In patients with COPD, optimising lung function by stepping up to T/O from tio led to significant improvements in lung function, health status and breathlessness.

Table: Pooled data from TONADO and OTEMTO showing treatment differences in trough FEV_1, SGRQ total score, TDI score and responder analyses after 12 weeks

	n, T/O / tio	T/O vs tio, mean difference (95% CI)	P value	% responders, T/O / tio	T/O vs tio, responder analysis odds ratio (95% CI)	P value
Trough FEV_1, L	144/147	0.074 (0.033, 0.115)	0.0004	NA		
SGRQ total score	141/142	−2.68 (−5.06, −0.29)	0.0280	57.4/47.9	1.49 (0.93, 2.40)	0.0980
TDI score	140/143	1.15 (0.56, 1.73)	0.0001	57.1/31.5	2.81 (1.71, 4.60)	<0.0001

An SGRQ responder is defined as ≥4-unit improvement of SGRQ total score from baseline; a TDI responder is defined as ≥1-unit improvement of TDI score from baseline.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; NA, not applicable; SGRQ, St. George's Respiratory Questionnaire; T/O, tiotropium/olodaterol; TDI, Transition Dyspnoea Index; tio, tiotropium.