Benefits of tiotropium + olodaterol over tiotropium at delaying clinically significant events in patients with COPD classified as GOLD B

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Background

Two large clinical studies (TONADO® 1 + 2) demonstrated the benefits of treatment with a combination of once-daily tiotropium (T), a long-acting muscarinic antagonist, and olodaterol (O), a long-acting (β₂) agonist, compared to treatment with the monocomponents in patients with moderate to very severe chronic obstructive pulmonary disease (COPD) over 52 weeks.1

Until recently, the focus of treatment had been on improving the single outcome of lung function. However, it is becoming clear that many factors come into play as COPD deteriorates, and it is of interest to determine whether these clinically significant events can also be delayed with optimized bronchodilation, which, in turn, could lead to longer-term disease stabilization.

A post hoc analysis of the UPLIFT study demonstrated that composite end points, which included clinically significant events as part of a Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2 and GOLD stage B COPD, can be sensitive to treatment effects, with T delaying clinically significant events compared to placebo.2

The two composite end points in the UPLIFT analysis evaluated the time to first clinically important deterioration (in 2.5 years) for the percentage of decline in forced expiratory volume in 1 second (FEV1) and St. George’s Respiratory Questionnaire (SGRQ) score, severe exacerbation, or death, or (2) trough FEV1, SGRQ score, or moderate or severe exacerbation. The first composite end point showed limitations, with the second end point generating composite results that are difficult to interpret.3

Methods

Study design

A total of 5162 patients were randomized to T 2.5 µg or 5 µg, T 5 µg, or O 5 µg (delivered via Respimat® inhaler) in the 52-week, parallel-group, double-blind studies (TONADO® 1 [NCT01315274] and TONADO® 2 [NCT01315287] (Figure 1)).

• Assessment of trough FEV1 was performed on Day 1 and at Weeks 2, 12, 24, 32, 40, and 52.

• SGRQ was completed on Day 1 and after 12, 24, and 52 weeks.

Analyses

Post hoc analysis of time to first clinically important deterioration in patients classified as GOLD stage B using combined TONADO study data.

Results

• Patient demographics and disease characteristics were comparable for GOLD stage B patients in the T 2.5 µg and 5 µg treatment groups included in the analysis. (Table 1)

• Using composite point 1 time to first trough FEV1, SGRQ total score increase, or severe exacerbation, death, or moderate or severe exacerbation was achieved using a composite end point that includes time to first trough FEV1 <75% of predicted, time to first decrease in trough FEV1 from baseline of 100 mL, increase in SGRQ total score from baseline of 4 units, or time to first severe (hospitalized) exacerbation, or death.

• The time to first occurrence of one of these events was recorded as the time to clinically important deterioration.

• Data are presented for comparisons of the licensed doses of T 2.5 µg and 5 µg.

Statistics

• Time to first clinically significant event (individual components of composite end points) and time to first clinical deterioration (composite end points) were calculated for all 2.5 years and reported for the 24th percentile (midtime not reached for most events) for each treatment group.

• Hazard ratios (HRs) for treatment comparisons were obtained from fitting a Cox proportional hazard regression model with treatment as the only covariate.

• Kaplan-Meier estimates of probability of clinical deterioration based on the composite end points were generated for each treatment group.

• For the individual clinically significant events included in composite end point 1, time to trough FEV1 decline (HR [95% CI] 0.66 [0.51, 0.87]; p = 0.0016) and time to SGRQ score increase (HR [95% CI] 0.71 [0.52, 0.96]; p = 0.021) were significantly longer with T+O 5/5 µg than T 5 µg (Table 2).

• For the individual clinically significant events included in composite end point 2, time to trough FEV1 decline (HR [95% CI] 0.65 [0.52, 0.91]; p = 0.0032) and time to SGRQ score increase (HR [95% CI] 0.77 [0.60, 0.98]; p = 0.0332) were significantly longer with T+O 5/5 µg than T 5 µg (Table 3).

• Event rates for time to severe exacerbation and time to death were very low (one death and 16 patients with severe exacerbations across both treatment groups) and 25th percentiles were non-estimable.

Conclusions

• In the TONADO® studies, T+O increased time to clinically important deterioration compared to T alone in patients with GOLD stage B COPD, suggesting that T+O is more effective at preventing these significant events in this patient population.

• Based on these results, T+O not only significantly improves lung function but may also have a slower clinical deterioration of the disease through its effects beyond lung function.

• For this patient population with less severe exacerbations and deaths occur infrequently, it appears that comparing the effectiveness of different treatments in delaying clinically important deterioration can be achieved using a composite end point that includes time to first trough FEV1, SGRQ score increase, or moderate or severe exacerbation (composite point 2) in patients with GOLD stage B COPD.

• Further studies are warranted to prospectively study this effect.

Limitations

• In contrast to the UPLIFT study analysis, 2 a clinically important event did not have to be confirmed at a second visit and patients have to be followed up for 52 weeks.

• The temporal relationship between clinically significant events is not known, as only the time to first individual event is included in the analysis.

References


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