

## January 2015 Tucson Pulmonary Journal Club: Withdrawal of Inhaled Glucocorticoids in COPD

**Magnussen H, Disse B, Rodriguez-Roisin R, et al. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. N Engl J Med. 2014;371(14):1285-94. [\[CrossRef\]](#) [\[PubMed\]](#)**

GOLD guidelines recommend various combinations of inhaled corticosteroids (ICS), long-acting beta-agonists (LABA), and long-acting muscarinic agonists (LAMA) to treat patients with chronic obstructive pulmonary disease (COPD) who are at high risk of exacerbation. A substantial portion of patients are ultimately prescribed triple-therapy at some point. The WISDOM trial examined the risk of exacerbation among patients taking triple therapy who were subsequently weaned from their ICS treatment.

The present WISDOM trial was a randomized, double-blind, non-inferiority trial sponsored by Boehringer Ingelheim Pharma. Over 4 years, approximately 2500 participants in 23 non-US countries with severe or very severe COPD were randomized. Participants were eligible if they were >40 years of age, were current or former smokers with  $\geq 10$  pack-year history, and had at least one exacerbation within the year prior to screening. Numerous exclusion criteria included significant comorbidity, prior lung resection, asthma or bronchiectasis, chronic oxygen use, oral steroid requirement, recent exacerbation, respiratory tract infection, or pulmonary rehabilitation. The study had 90% power to evaluate a pre-specified non-inferiority margin of 1.20 for the upper limit of the 95% confidence interval for the hazard ratio.

All participants received an initial 6 week treatment with fluticasone 500 mcg BID, salmeterol 50 mcg BID, and tiotropium 18 mcg daily. Based on random assignment, participants either continued triple therapy or had their fluticasone withdrawn in a step-wise fashion. The primary outcome was the time to first moderate or severe COPD exacerbation during the 52 week study period. Eighty-three percent of participants were men, the overall mean age was 64 years, and the mean FEV<sub>1</sub> was 0.93 liters (33% of predicted). Approximately 40% were receiving triple therapy prior to enrollment. Approximately 20% of participants did not complete the study.

The non-inferiority margin was confirmed with a hazard ratio of 1.06 (CI<sub>95%</sub> 0.94 - 1.19). The mean reduction in FEV<sub>1</sub> for the ICS withdrawal group was 38 mL greater than the reduction for the control group at week 18, and this difference increased to 43 mL by the end of the study ( $p < 0.001$ ). The difference in the St. George's Respiratory Questionnaire (SGRQ) score were statistically significant at week 52, an increase of 1.15 in the withdrawal group vs. decrease of 0.07 in the continuation group ( $p = 0.047$ ). Adverse events did not differ among the two groups.

The results suggest that gradual withdrawal of ICS from a triple therapy regimen is not associated with a meaningfully increased risk of exacerbation among patients with moderate-to-severe COPD. However, there were statistically significant, but perhaps not clinically meaningful, deterioration in FEV<sub>1</sub> and SGRQ scores. Strengths of this study included a large participant population, a year-long follow-up, and use of clinically relevant and patient-centered outcomes. While the study was conducted in many countries, most participants were white and male. The homogeneity of this group makes

it difficult to generalize to other patient groups. Patients who had no exacerbations in the prior year (arguably the group most appropriate to step-down therapy) were not included. It also does not provide information on the safety of abrupt withdrawal of ICS. The long-term consequences of the small reductions in FEV<sub>1</sub> and health status are uncertain. For patients intolerant to or reluctant to consider ICS treatment, dual LABA and LAMA treatment appears to yield clinically similar outcomes.

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