



## Editorial

## Inhaled Corticosteroids Withdrawal in Severe Patients With Chronic Obstructive Pulmonary Disease: A Wisdom Decision?<sup>☆,☆☆</sup>



### Retirada de corticoesteroides inhalados en pacientes graves con enfermedad pulmonar obstructiva crónica: ¿es una propuesta razonable?

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According to *Global Initiative for Obstructive Lung Disease (GOLD) 2014 Update*, pharmacologic therapy for stable chronic obstructive pulmonary disease (COPD) is used to reduce symptoms, improve health status and exercise tolerance, and decrease the frequency and severity of exacerbations.<sup>1</sup> In this context, long-acting (LA) bronchodilators are central to symptom management in COPD. The dose-response curve and long-term safety of inhaled corticosteroids (ICs) in COPD are not known, and their effects on pulmonary and systemic inflammation are controversial. Likewise, the *National Institute of Clinical Excellence (NICE)* states that none of the ICs currently available are licensed for use alone in the treatment of COPD.<sup>2</sup> GOLD underlines that regular treatment with ICs improves symptoms, lung function and quality of life, and reduces the frequency of exacerbations in stable COPD patients with an FEV<sub>1</sub> <60% predicted (Evidence A).<sup>1</sup> Similar recommendations have been made by the *American Thoracic Society (ATS)* and the *European Respiratory Society (ERS)*,<sup>3</sup> NICE and the Spanish guidelines for the treatment of COPD (*Guía Española de la EPOC –[GesEPOC]* from the *Sociedad de Neumología y Cirugía Torácica [SEPAR]*).<sup>4</sup> An IC combined with a LA beta<sub>2</sub>-agonist (LABA) is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with moderate (Evidence B) to very severe COPD (Evidence A). The *GOLD 2014 Update*<sup>1</sup> underlined that the addition of a LABA + IC combination to LA anticholinergic or antimuscarinic agents (LAMA) improves lung function and quality of life and may further reduce exacerbations (Evidence B) but more triple therapy studies are needed. In patients with COPD, however,

regular IC use is associated with higher prevalence of oral thrush, hoarse voice, bruising and increased risk of pneumonia.

In the WISDOM (*Withdrawal of Inhaled Steroids during Optimised bronchodilator Management*) trial, it was hypothesized that with a controlled stepwise withdrawal of ICs, the risk of exacerbation would be similar to the continued use of ICs in patients with severe or very severe COPD (GOLD 3–4) and a history of exacerbations who were receiving LABA (salmeterol) + LAMA (tiotropium).<sup>5</sup> More than 4000 patients enrolled in a 12-month, double-blind, parallel-group, active-controlled trial received triple therapy (LAMA tiotropium 18 µg once daily, LABA salmeterol 50 µg twice daily and IC fluticasone 500 µg twice daily) in a run-in period of 6 weeks and were then randomized to continued triple therapy or IC withdrawal in three steps over 12 weeks. Exacerbations (primary end-point), spirometric findings, dyspnea and health status were assessed. Ultimately, ICs were withdrawn in 1242 patients and continued in 1243 patients. Compared with continued IC use, IC withdrawal met the pre-specified non-inferiority margin of 1.20 for the upper limit of the 95% confidence interval with respect to the first moderate or severe on-treatment COPD exacerbation. Analysis of data from several previous randomized controlled trials using tiotropium indicated that the outcome for tiotropium compared to placebo was higher than 1.20 (time to exacerbation, patients with ≥ 1 exacerbation, number of exacerbations per patient per year; all expressed as a treatment ratio). Accordingly, since the increased risk of exacerbations did not reach the hazard ratio of 1.20, i.e. a 20% increase in the odds of having an exacerbation, it was concluded that withdrawal of ICs was not inferior to continuation. Likewise, withdrawal of ICs resulted in no change in dyspnea and only a minor variation in quality of life at week 52 ( $P=0.06$ ). Notwithstanding, after withdrawal of ICs at week 18, the adjusted mean decrease from baseline in trough FEV<sub>1</sub> was 38 mL greater in the glucocorticoid-withdrawal group than in the glucocorticoid-continuation group ( $P<0.001$ ), and 43 mL greater at the end of the trial (week 52) ( $P=0.001$ ). Patients performed regular spirometry at home from weeks 0–52 and the analysis of the slope confirmed that the between-group FEV<sub>1</sub> differences remained similar during this follow-up period

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<sup>☆☆</sup> RRR and EA were WISDOM study investigators. RRR was a member of the WISDOM Steering Committee

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(unpublished data). Previous attempts at abrupt IC stepping down not associated with regular dual LA bronchodilation resulted in similar lung function impairment, more worsening of symptoms, poorer quality of life and/or recurrence of exacerbations.<sup>6,7</sup>

The mechanisms by which corticosteroids improve lung function in patients with COPD remain poorly understood. Up to 3 different mechanisms have been invoked. First, bronchodilation may be enhanced by up-regulation of beta<sub>2</sub>-adrenergic receptors located in the airway walls and bronchial vessels. It is known that in patients with asthma fluticasone reduces bronchial blood flow within less than 2 h following inhalation.<sup>8</sup> Second, airway wall edema may be reduced by the anti-exudative effects of ICs together with vasoconstriction of the bronchial circulation. Third, ICs may reduce the release of inflammatory mediators and induce vasoconstriction of the pulmonary vasculature.

To conclude, while the risk of moderate or severe exacerbations was similar among those who discontinued ICs and those who continued IC treatment, there was a greater decrease in lung function following the final step of IC withdrawal. For clinicians considering re-evaluating maintenance COPD therapy in their stable COPD patients with GOLD 3–4, the WISDOM findings show that a stepwise withdrawal of ICs is not associated with an increased risk of exacerbations.

Although experts concluded that the trial design was well executed, results were internally consistent and met the pre-specified non-inferiority statistical limit, concerns may be raised about the significance of the findings. In the absence of increased side effects of triple therapy (ICs+LABA+LAMA) compared with dual bronchodilation, the WISDOM observations provide robust information but insufficient clinical direction regarding the choice between double and triple therapy in severe COPD. Several issues need to be addressed. What is the clinical relevance of the between-group FEV<sub>1</sub> differences at the end of the trial? A longer study follow-up would have certainly provided more insights, but this needs to be balanced against the fear caused by the degree of COPD severity in these patients. Was the IC withdrawal timeframe appropriate? It could be probably have been shortened, but this still needs to be proven. Can the current dosage of ICs for COPD patients be reconsidered? The WISDOM trial suggests that a reduction in IC dosage should be seriously considered. As rightly pointed out by the accompanying editorial,<sup>10</sup> can we consider the use of alternative therapies to ICs, such as azithromycin or phosphodiesterase-4 inhibitors,<sup>9</sup> to reinforce the effects of stepping down ICs? This seems likely, but further research is required. Last but not least, are we seeing the beginning of the end of ICs in stable COPD?

If this is not the case, which COPD patients would benefit more from the regular use of combination therapy with ICs? Currently, at least, patients with coexisting asthma and COPD overlap syndrome (ACOS), the real prevalence of which is still far from certain, remain the most appropriate subjects for the regular use of ICs in combination with mono or dual bronchodilation.<sup>1</sup> So, are we facing a paradigm shift in the management and therapy of COPD? Certainly such a breakthrough has not yet been achieved.

### Conflict of Interests

RRR (2011-14) lectured for Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Ferrer, Menarini, Novartis, Pfizer, Takeda and TEVA; consulted with AstraZeneca, Boehringer Ingelheim, Foster, Merck, Sharp & Dome, Mylan, Novartis, Pearl Therapeutics, Pfizer, Takeda, and TEVA, and received grant support from Almirall. He is a member of the GOLD Science Committee. EA (2011-14) has no conflict of interests to declare.

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