WISDOM STUDY

Despite the widespread use of inhaled corticosteroids (ICS) in the treatment of patients with COPD, the extent of their contribution to efficacy and long-term safety in COPD maintenance therapy is still being investigated. Because of the potential side effects of ICS, including an increased risk of developing pneumonia, cataracts, glaucoma, osteoporosis and a potential contribution to the risk of developing type II diabetes, it is important to understand more about their efficacy to better evaluate their risk-benefit profile.[1-3]

The large, 52-week WISDOM (Withdrawal of Inhaled Steroids During Optimised bronchodilator Management) study evaluated the effects of stepwise withdrawal of ICS in patients with severe to very severe COPD and an exacerbation history, while receiving tiotropium (Spiriva®)† and a LABA*. For these patients, the GOLD (Global initiative for chronic Obstructive Lung Disease) guidelines support the addition of ICS to long-acting bronchodilator therapy.[4]

WISDOM is larger than all the previous ICS-withdrawal studies combined[5-10] and the first study to examine stepwise withdrawal of ICS in COPD on top of maintenance therapy with Spiriva® and a LABA. WISDOM adds to the growing clinical evidence-base on the impact of ICS withdrawal against the background of long-acting bronchodilators, including the recently-published OPTIMO study. The OPTIMO study showed that withdrawal of ICS in patients with moderate COPD at low risk of exacerbation could be safe provided that patients are left on maintenance treatment with long-acting bronchodilators.[5]

The WISDOM study results were presented for the first time at the European Respiratory Society International Congress 2014, Munich, Germany, with simultaneous publication in the New England Journal of Medicine.

What were the key findings?

Based on the primary end point (time to first moderate or severe on-treatment COPD exacerbation during the 12-month randomised period), WISDOM has shown that in severe to very severe COPD patients with a history of exacerbation, the risk of moderate/severe exacerbations was comparable between those patients that continued on ICS, and those where ICS therapy was withdrawn in a stepwise fashion while patients received a baseline maintenance treatment of Spiriva® and a LABA.[11]

There was a transient numerical increase in severe exacerbations soon after ICS treatment was finally stopped, but this was not sustained over the study period.[11]

Additional findings

Following the final step of ICS withdrawal (from 100 µg twice daily to no ICS at week 18), a 38ml greater reduction in trough forced expiratory volume in 1 second (FEV_1) was observed in the ICS withdrawal group than with maintained ICS use ($P<0.001$). A similar difference was seen at week 52.[11] This change was similar to that observed in previous ICS withdrawal trials,[6,7,9,10] and it does not seem to be predictive of exacerbations.

No change in dyspnoea and minor changes in health status occurred in the ICS withdrawal group. The change from baseline in the total St. George's Respiratory Questionnaire (SGRQ) score was -0.42 and +0.55 in the ICS continued and ICS withdrawal treatment groups respectively at week 27 ($p=0.08$) and -0.07 and +1.15 at week 52 ($p=0.05$).[11] The frequently used minimum clinically important difference is 4 points.[12]

† Tiotropium 18µg administered via HandiHaler®
* Long-acting beta-2 agonist

What are the implications of these findings?

The WISDOM study results imply that in respect of moderate to severe exacerbations:

- Many patients with severe to very severe COPD and a history of exacerbation may not benefit from the addition of an ICS on top of Spiriva® and a LABA
- Even with the use of ICS in line with the GOLD guidelines and at doses recommended on the EU label, the results of WISDOM have indicated that not all patients with severe to very severe COPD seem to benefit from including an ICS in their treatment regimen

WISDOM study methodology and endpoints

The WISDOM study was designed to evaluate the effects of stepwise ICS withdrawal in COPD patients with severe to very severe lung function impairment (GOLD spirometric grade 3-4 with a history of at least one exacerbation during the 12 month period prior to screening) who were receiving maintenance therapy of tiotropium and salmeterol (LABA).[11,13]

In contrast to previous ICS withdrawal studies, stepwise withdrawal was implemented to minimise the potential risk of rebound steroid effects.

The primary endpoint in WISDOM was time to first moderate or severe on-treatment COPD exacerbation during the 12 month randomised period.

Secondary end points included time to first severe COPD exacerbation, number of moderate or severe on-treatment COPD exacerbations, difference from baseline in on-treatment lung function, health status (SGRQ), and dyspnoea (modified Medical Research Council [mMRC]).

During a six week run-in period, a total of 2,485 patients were treated with tiotropium 18 µg once daily, salmeterol 50 µg twice daily and fluticasone propionate 500 µg twice daily. These 2,485 patients were then randomised in a double-blind, parallel-group, active-controlled fashion; one group of patients continued to receive tiotropium, salmeterol and fluticasone propionate (ICS) while, for the second group, stepwise withdrawal of fluticasone propionate was initiated (see figure 1). Following the stepwise withdrawal period, patients in both treatment groups were observed over a stable treatment phase of 40 weeks.

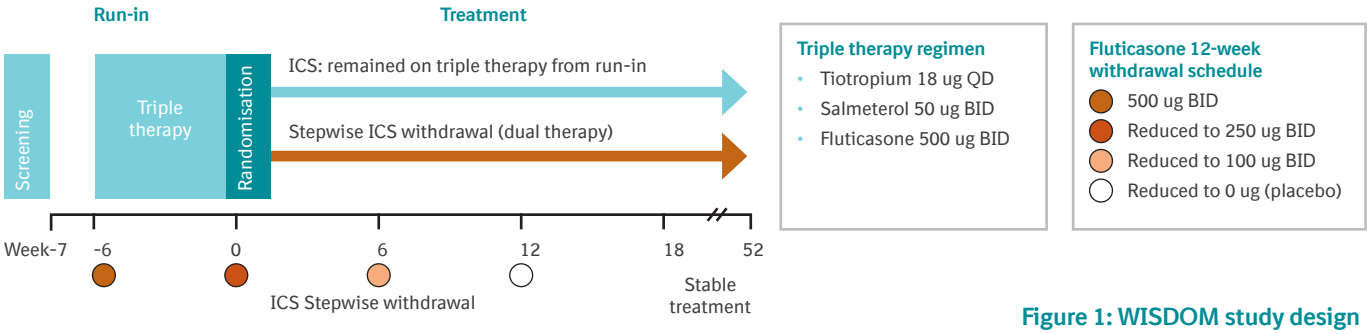

Figure 1: WISDOM study design

1. Cates C. Inhaled corticosteroids in COPD: quantifying risks and benefits. Thorax 2013; 68: 499-500.
2. Price D, Yawn B, Brusselle G, Rossi A. Risk-to-benefit ratio of inhaled corticosteroids in patients with COPD Prim Care Respir J 2013; 22(1): 92-100.
3. Suissa S, Kezouh A, Ernst E. Inhaled corticosteroids and the risks of diabetes onset and progression. The American Journal of Medicine 2010; 123: 1001-1006.
4. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. 2013. http://www.goldcopd.org/guidelines-globalstrategy-for-diagnosis-management.html [last accessed July 2014]
5. Rossi A, Guerriero M, Corrado A, on behalf of the OPTIMO/AIPO study group. Withdrawal of inhaled corticosteroids can be safe in COPD patients at low risk of exacerbation: a real-life study on the appropriateness of treatment in moderate COPD patients (OPTIMO). Respiratory Research 2014, 15:77.
6. Choudhury AB, Dawson CM, Kilvington HE, et al. Withdrawal of inhaled corticosteroids in people with COPD in primary care: a randomised controlled trial. Respir Res 2007; 8: 93.
7. Wouters EFM, Postma DS, Fokkens B, et al. Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial. Thorax 2005; 60: 480-7.
8. Schermer TRJ, Hendriks AJC, Chavannes NH, et al. Probability and determinants of relapse after discontinuation of inhaled corticosteroids in patients with COPD treated in general practice. Prim Care Respir J 2004; 13: 48-55.
9. Van der Valk P, Monninkhof E, van der Palen J, et al. Effect of discontinuation of inhaled corticosteroids in patients with chronic obstructive pulmonary disease. The COPE study. Am J Respir Crit Care Med 2002; 166: 1358-63.
10. Jarad NA, Wedzicha JA, Burge PS, Calverley PMA, for the ISOLDE study group. An observational study of inhaled corticosteroid withdrawal in stable chronic obstructive pulmonary disease. Respir Med 1999; 93:161-6.
11. Magnussen H, Disse B, Rodriguez-Roisin R, et al. Withdrawal of inhaled glucocorticosteroids and exacerbations in COPD. N Engl J Med. DOI: 10.1056/NEJMoa1407154
12. Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. Eur Respir J 2002; 19: 398–404
13. Magnussen H, Watz H, Kirsten A, et al. Stepwise withdrawal of inhaled corticosteroids in COPD patients receiving dual bronchodilation: WISDOM study design and rationale. Respiratory Medicine. 2014; 108, 593-599.