

## Time for reasoning ICS prescription in obstructive airway diseases

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It is time to better target the patients with chronic obstructive airway diseases who really benefit from a chronic treatment with inhaled corticoids

Inhaled corticoids (ICS) are powerful drugs to combat airway inflammation that have revolutionised the management of obstructive airway diseases and particularly that of asthma (1). Given the high prevalence of chronic obstructive airway diseases, ICS have become one of the most prescribed drugs worldwide. Although putting subjects at lower risk of undesirable side effects than systemic corticosteroids, ICS may not be entirely safe when used at high dosage. In this issue of the journal Chung et al. shows that, in a population-based study conducted in Taiwan over more than 30,000 people, the risk of TB is linearly correlated with the dose of inhaled corticoids. Overall ICS use caused a 2.04-fold increased risk of developing TB. Interestingly, it appeared from this study that high doses of ICS place the patient at a risk level (OR 2.32) similar to that found in those receiving disease modifying anti-rheumatic drugs such as anti-TNF $\alpha$  (2). Chung's study actually confirms another recent cohort study conducted in South Korea from a large database of the Health Insurance Review and Assessment Service although the risk was somewhat lower in the latter with an odd ratio for TB diagnosis of 1.2 in those receiving ICS whichever the underlying obstructive disease (3). These findings somehow contrasted with those of another large cohort study from Taiwan that has shown COPD itself as a risk factor for TB but has not confirmed the link between TB and ICS use in COPD patients (4). If most of the studies published so far have come from Asian countries with intermediate-to-high TB incidence, the same relationship was shown in a low TB country. In a population-based study from Canada Brassard et al. found a relative risk for TB of 1.48 among non-users of oral corticoids up to 1.95 for those receiving high dose equivalent to fluticasone 1000  $\mu\text{g}/\text{day}$  (5).

Tuberculosis is not the only respiratory infection that may be favoured by ICS usage. The first alert on the link between ICS and lower respiratory tract infection actually came from the TORCH study (Towards a Revolution in COPD Health), a randomised controlled trial looking the effect of ICS and LABA on COPD mortality (6). In this study, the authors showed that 1000  $\mu\text{g}/24$  h fluticasone was associated with an increased risk of pneumonia compared with placebo or LABA (even if pneumonia was not ascertained by chest X ray in all cases). In keeping with this is the recent warning from a retrospective population-based study conducted in Scandinavia that shows an increased risk of pneumonia and hospitalisation in patients receiving high dose (783  $\mu\text{g}/\text{day}$ ) inhaled fluticasone, compared with those receiving moderate dose of budesonide (568  $\mu\text{g}/\text{day}$ ) (7,8). Furthermore, a recent COPD cohort study from Canada using Quebec Health Insurance Databases has shown an increased risk of 69% to develop serious pneumonia among patients currently using ICS. Even if the authors found it was a class effect, the risk was particularly elevated and dose related with fluticasone (9). It is, of course, not to say that ICS are useless in COPD. Early studies with high dose of fluticasone showed a reduction in exacerbation and the rate of decline in health (10,11). However, no convincing dose ranging studies have been published to support that these effects might not have been achieved by lower dose of ICS. A recent cross-sectional multi-centre study conducted in Belgium/Luxemburg has shown that 75% of COPD followed by chest physicians in clinical practice were receiving regular ICS, often at high dose, although nearly half of them were GOLD stage 2 (12). Clearly, usage of ICS in COPD in clinical practice goes well over the currently recommended GOLD guidelines that limit the prescription to those with severely impaired FEV1 (< 50% predicted) and recurrent exacerbations. On the other hand, the benefit of ICS in COPD is likely to be related to the presence of an eosinophilic airway inflammation, which is present in up to 30-40% of stable COPD (13). Indeed, management strategy that aims to minimise eosinophilic airway inflammation with corticosteroids is associated with a reduction in severe exacerbation (14). It is also important to bear in mind that roughly 20-30% stable COPD are colonised by potentially pathogenic microorganisms (PPM) when assessed by routine culture (15) but this figure can raise to 57% when PCR is performed (16). We also know that exacerbations of COPD are mainly driven by acute airway infection (15). Although it has not been demonstrated yet, it is conceivable that COPD whose airways are

colonised by PPM should receive the lowest possible dose of ICS or even had better to avoid chronic treatment with this class of drug. There is a clear need for prospective studies that better target the patient phenotype and better calibrate the optimal ICS dosage to improve the benefit to risk ratio in these fragile patients (17).

As for asthma, the demonstration that regular ICS were more efficient drugs than regular  $\beta_2$  agonists to control the disease, was a pivotal moment in asthma management (18). From that time, all asthma guidelines have highlighted the importance of ICS as the mainstay treatment which resulted in dramatic reduction in asthma morbidity and mortality in the following decades (1). Soon after, it was demonstrated that combination of ICS and long acting  $\beta_2$  agonist (LABA) was a powerful strategy to further reduce symptoms (19) and exacerbation (20) while maintaining low dose of ICS. The gaining optimal asthma control study (GOAL) showed that 70% of asthmatics could achieve satisfactory control by a step-up strategy that increases the dose of ICS in a combination ICS/LABA until control was obtained (21). This study has generated enthusiasm and disseminated the idea that combination therapy was able to control asthma as long as a sufficient dose of ICS was administered, which, in a way, pushed the clinician to use high doses of ICS. While recommending to step-up treatment in case of lack of control, asthma guidelines also emphasise the necessity to step down ICS when patients have been controlled for several months (22). This strategy has, however, had difficulty in making its way to clinical practice, partly because not being strongly promoted by drug industry, but also because patients do not seek medical attention when disease is under control.

The mirror conclusion of the GOAL study is, however, that 30% of asthmatics failed to respond to increasing the dose of inhaled corticoids thereby proving some corticosteroid resistance. Analysis of airway inflammation in asthma shed light in our understanding of poor response to ICS. The application of induced sputum in clinical practice has allowed to recognise several inflammatory phenotypes in asthma with roughly half of the patients being non eosinophilic (23), a phenotype which shows poor response to ICS over a few weeks treatment period (24). In contrast moderate to severe eosinophilic asthmatics were shown to benefit from high doses of ICS or oral corticoids with a reduction in exacerbation and hospitalisation when the dose of corticosteroids was adjusted to control airway eosinophilic inflammation (25).

The monitoring of airway inflammation may help the clinician in stepping down ICS. Measuring eosinophil count in induced sputum, or fractional exhaled nitric oxide (FENO) as a surrogate marker of sputum eosinophils (26), is advised when proceeding to step down. It appeared that those patients who display a persistent sputum eosinophilia before stepping down (27) or those who show a rise in sputum eosinophil after stepping down (28) are at risk of loss of asthma control in the following weeks. The need to find the right minimal dose of ICS in asthmatics is further supported by their increased susceptibility to develop severe bacterial infection such as invasive pneumococcal disease irrespective of ICS treatment (29).

Given the accumulating evidence of potentially serious side effects of high doses of ICS, it is necessary to better target the patients with chronic obstructive airways disease that really benefit from this class of drug and which dose should be administered. This will force the clinician to phenotype their patients with chronic airway disease by investigating in depth the airway inflammation and microbiology and, when ICS was found to be necessary, to choose the minimal dose that brings sufficient disease control.

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## Disclosure

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