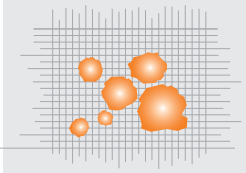
COPD – targeting the use of inhaled corticosteroids



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There is controversy about the role of inhaled corticosteroids in people with Chronic Obstructive Pulmonary Disease (COPD). It appears the more we learn, the less we know. Studies of inhaled corticosteroids (ICS) in COPD have provided average treatment effects across patient populations in different settings and with different inclusion and exclusion criteria, resulting in mixed and conflicting recommendations.

Early studies indicated that we should use inhaled corticosteroids (ICS) for severe COPD (people with FEV_1 less than 50% and more than two acute COPD exacerbations in 12 months). Recently this has been extended to include COPD symptoms (CAT score): ICS use is now recommended in people with GOLD Grade C and D (severe and very severe) COPD.[1] This may involve 20–30% of people with COPD, but up to 70% of people with COPD are estimated to be on an ICS.[2]

There is also increasing recognition of ICS adverse effects such as increased risk of pneumonia, skin thinning, easy bruising, oral candida infection, dysphonia,[3,4] and periodontal disease.[5]

It has become clear that a more sophisticated way to identify people with COPD most likely to benefit from ICS is needed. Perhaps ICS should be started before people are classified as having severe COPD, but also stop initiating ICS in people unlikely to benefit, even if COPD is severe: it is not always simple to discontinue the ICS once it is started. This requires a person-centred approach to COPD pharmacotherapy, rather than a lung function or severity-based approach. Lung function is a relatively poor predictor of exacerbation frequency as people with severe airflow limitation may still have few exacerbations.[6,7]

COPD is a heterogeneous diagnosis characterised by a large phenotype variability[8] or different clinical expressions of COPD. These phenotypes are still being refined but generally are classified as: Asthma-COPD Overlap Syndrome (ACOS), frequent exacerbators (more than twice a year) who are more likely to have eosinophilic inflammation, and less frequent exacerbators who have more neutrophilic inflammation.[3,8,9] An emphysemic phenotype is also suggested.[9]

A New Zealand cross-sectional study found five different phenotypes – moderate-severe childhood onset atopic asthma; ACOS; obese-comorbid; mild childhood onset atopic asthma and mild intermittent.[10]

The clinical categorization of these phenotypes is difficult, particularly for ACOS as diagnosis of asthma in childhood may have been a wheeze rather than asthma *per se*.[11] For the other phenotypes, there is growing evidence that the blood eosinophils provide a good indication of frequent and non-frequent exacerbators.

COPD and eosinophils

Eosinophilic airway inflammation is present in 20–30% of people with COPD during stable periods and acute exacerbations[6,12] and there is some evidence of increased mortality in people with COPD and eosinophilia.[13] In the Copenhagen General Population study, with a median follow up of 3.3 years, people with spirometry-confirmed COPD and blood eosinophil concentrations > 0.34×9^9 cells/L had a 76% increased risk of severe COPD exacerbations.

NUGGETS of KNOWLEDGE provides succinct summaries of pharmaceutical evidence about treatment of common conditions presenting in primary care and possible adverse drug reactions.

KEY POINTS

- Use of inhaled corticosteroids in COPD is best for people with eosinophilic inflammation (eosinophil blood count > 0.3)
- In people with COPD with neutrophilic inflammation the risks of inhaled corticosteroids generally outweighs any benefits. Use a long-acting β_2 agonist plus long-acting muscarinic antagonist in these people
- Tests for eosinophils before starting an inhaled corticosteroid
- Consider withdrawing inhaled corticosteroids in people with COPD without eosinophilia and who have less than two COPD exacerbations a year.

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COPD and inhaled corticosteroids

Evidence of ICS benefits in COPD is inconsistent, possibly because of heterogeneous phenotypes included in studies. A 2012 Cochrane review found that ICS in stable COPD did not consistently reduce declines in FEV_1 or mortality, although the mean rate of exacerbations reduced 0.19 – 0.26 per person per year. Mean improvement in the St George Respiratory Questionnaire was not clinically significant.[4]

With increasing studies of a Long Acting β_2 Agonists (LABA) plus ICS versus LABA plus Long Acting Muscarinic Antagonists (LAMA) a meta-analysis has found that the LABA/LAMA combination resulted in greater improvement in trough FEV_1 of 71 ml, less exacerbations (OR 0.77) and less pneumonia (OR 0.28).[14]

Pneumonia is an adverse event with inhaled corticosteroids: 18 more hospitalisations with pneumonia per 1000 people treated with fluticasone over *18 months*; and 6 more people hospitalised per 1000 people treated with budesonide over *9 months*.[15] Pneumonia risk may be dose and/or potency related. ICS also increases the risk of oral candidiasis by 265% and of hoarseness.[4]

Table 1. People for whom ICS are more likely to be beneficial

- With Asthma-COPD Overlap Syndrome (a clear history of asthma and some reversibility)
- People who have frequent exacerbations (more than two a year)
- People with eosinophils ≥ 2% or absolute blood count greater than 0.3

Table 2. If considering withdrawing a ICS

- Does the person have a clear history of asthma or reversibility?
  - If yes, possible asthma-COPD Overlap Syndrome. Do not withdraw ICS
- Does the person have more than two exacerbations a year?
  - Do not withdraw the ICS for a frequent exacerbator
- Do a blood eosinophil test
  - Do not introduce ICS or withdraw if blood eosinophils > 3
- Optimise with LABA and LAMA use
- Halve the ICS dose every six to 12 weeks

ICS withdrawal studies

The changing view of ICS use in COPD has led to studies of ICS withdrawal. A 2011 meta-analysis found no evidence of important deterioration when ICS were withdrawn from people with COPD.[16] The more recent WISDOM study found a 37% decrease in the risk of pneumonia when LABA plus LAMA therapy was optimised and ICS withdrawn over three to six months. FEV_1 was reduced by 43 ml at the end of 18 months, although this was not statistically significant and is not considered clinically relevant. The reduction was mostly within the first 18 weeks and then it stablised.[17] A database study with 4.9 years follow up found similar reductions in pneumonia, primarily with fluticasone discontinuation.[18]

COPD, eosinophils and ICS

This small clinical benefit of ICS, plus increased risk of adverse events, makes their targeted use important. Blood eosinophilia may be a helpful indicator of ICS benefit.

The studies exploring relationships between blood eosinophils and ICS benefit have so far been post-hoc analyses, but the results have been consistent and indicate that for people with a blood eosinophil count of ≥ 2%, there are significantly fewer exacerbations if ICS are used, but for people people with a blood eosinophil count < 2%, ICS provide no significant benefit.[19–21]

More research is needed to define the expected proportion of people with COPD who have eosinophilia: post-hoc analyses found approximately two thirds of people had an eosinophil count of ≥ 2%, compared to the expected one third.

The Northern Region Healthpoint Severe COPD (FEV_1 < 40%) pathway suggests that eosinophilic inflammation is indicated by a blood eosinophil count > 0.3, and that these are the people with COPD who are suitable for a trial of ICS in severe COPD. Caution is required as higher doses of ICS increase susceptibility to pneumonia.[22]

Practice point: Unlike with use in asthma, a LABA does no routinely require an ICS to be prescribed in combination

Current status

There are different phenotypes of COPD with some subgroups obtaining more benefit from ICS and others having no benefit. Targeting people most likely to benefit from ICS is important as it can cause serious adverse effects. ICS use should be individualized.

Although there is still some uncertainty about the use of absolute eosinophil counts versus percentage, and the threshold, an eosinophil count can assist with decisions about introducing (Table 1), or considering discontinuing an ICS (Table 2).

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