Inhaled corticosteroids for cystic fibrosis

NICE has developed the Cochrane Quality and Productivity topics to help the NHS identify practices that could be significantly reduced or stopped completely, releasing cash and/or resources without negatively affecting the quality of NHS care. Each topic has been derived from a Cochrane systematic review that has concluded that the evidence shows that the practice is harmful or ineffective and should not be used, or that there is insufficient evidence to support widespread use of the practice.

Unless otherwise stated, the information is taken with permission from the Cochrane systematic review.

NICE summary of Cochrane review conclusions

Evidence does not support the routine use of inhaled corticosteroids (ICS) as anti-inflammatory agents in children and adults with cystic fibrosis (CF). There is no evidence of objective improvements in lung function or subjective improvements in exercise tolerance or quality of life. ICS should only be used for the symptomatic relief of recurrent wheezing that is not responsive to bronchodilators alone. Outside of this indication they are likely to result in more harm than benefits.

The 'Implications for practice' section of the Cochrane review stated:

'This review has found little evidence from existing trials to support the practice of routinely prescribing inhaled steroids in CF. Specifically, we cannot conclude that inhaled steroids are beneficial but there is some evidence that at a high dose, they adversely effect growth. There is also some evidence that withdrawal of ICS in the majority of those already being treated with them is safe. We recommend that the use of ICS should be restricted to those with symptomatic wheezing and in whom benefit has been proven. Individuals should be regularly reassessed to see whether ICS are having an effect and consideration should always be given to reducing the dose or stopping the drugs altogether.'

Details of Cochrane review

Cochrane review title

Inhaled corticosteroids for cystic fibrosis

Citation

Balfour-Lynn IM, Welch K. Inhaled corticosteroids for cystic fibrosis. Cochrane Database of Systematic Reviews 2016, Issue 8. Art. No.: CD001915. DOI: 10.1002/14651858.CD001915.pub5.

When the review content was assessed as up to date

15 August 2016

Quality and productivity category

Long-term conditions; medicines use and procurement

Relevant codes	OPCS	ICD10	HRG
	N/A	E84.0	P02, D17

Programme budget:

Long-term conditions; medicines use and procurement; productive care

Evidence

Relevance to the NHS

Repeated chest infections in people with cystic fibrosis cause inflammation and damage to the lungs which, in the long term, is the most common reason for death in people with cystic fibrosis. Inhaled corticosteroids are often used to treat inflammation, but may cause some side effects. Some of these side effects are less serious, for example oral thrush, but others are more serious, such as reduced growth rate in childhood. It is important to establish the current level of evidence for the risks and benefits of ICS.

Thirteen trials were eligible for inclusion, reporting the use of inhaled corticosteroids in 506 people with cystic fibrosis aged between 6 and 55 years. Three trials were in children only, 4 in adults only and 4 were mixed ages; 2 trials did not describe the ages of the volunteers. The lung function and severity of disease of the volunteers varied across trials and only 2 trials gave information about their genetic mutations. All trials took place in Europe. In 10 of the trials, all volunteers were in the same group up to the end of the trial (either a treatment group or a group receiving no treatment or a placebo), but in 3 trials they swapped groups halfway through the trial. In most of the trials volunteers started taking steroids or a placebo at the start of the trial. One study was a withdrawal trial however, where all volunteers were already taking steroids and half of them carried on and the rest took a placebo, in effect stopping the treatment. The trials lasted between 3 weeks and 2 years.

Methodological quality and risk of bias were difficult to assess from published information. Only 2 trials specified how participants were randomised and less than half detailed how allocation was concealed. Trials were generally judged to have a low risk of bias from blinding, except for 2 which were open label or did not use a placebo. Inclusion criteria varied between trials, as did type and duration of treatment and timing of outcome assessments. Objective measures of airway function were reported in most trials but were often incomplete. Significant benefit has not been conclusively demonstrated. Four trials systematically documented adverse effects and growth was significantly affected in 1 study using high doses.

Four trials reported data for absolute forced expiratory volume in one second (FEV_1). No significant difference was seen between people receiving budesonide and those receiving placebo for 6 weeks, 3 months or 6 months of treatment. No statistically significant difference was seen between people receiving fluticasone or placebo for 6 weeks, 6 months or 24 months. Changes in per cent predicted FEV_1 pre- and post-salbutamol did not vary in people receiving fluticasone for 6 months or 12 months compared with those receiving placebo, or in people receiving beclometasone for 30 days.

Five trials measured absolute forced vital capacity (FVC). No significant differences were seen between beclometasone and placebo, or budesonide and placebo. Three trials reported change data for FVC, but no statistically significant differences were seen between beclometasone and placebo.

Secondary outcomes examined included number of days in hospital for respiratory exacerbations, number of days of intravenous antibiotics for respiratory exacerbations, improvements in exercise tolerance, quality of life and adverse effects. No significant differences were seen in any of these outcomes with the use of ICS.

The use of inhaled budesonide did result in a significant reduction in bronchial hyperreactivity as shown by a 1.13% increase in histamine dose steps in a histamine PC20 test (95% confidence intervals [CI] 0.01–2.26%, $p < 0.05$). However, measurement of bronchial hyperreactivity with metacholine challenge did not demonstrate the same effect. In addition, a small but significant ($p < 0.05$) improvement was seen in cough or dyspnoea after 6 weeks of treatment in adults randomised to budesonide.

One of the main outcomes measured in the Belgian trial (De Boeck et al 2007) of pre-pubertal children was the effect on long-term growth and height. During the first 12 months of treatment there was a significant difference in growth rate between fluticasone and placebo groups (mean difference −1.53 cm, 95% CI −2.37 cm to −0.69 cm). Twelve months after fluticasone discontinuation there was no catch-up growth and there was a final difference of 2.4 cm between the two groups. A separate trial found no significant height difference during the first 8 months of fluticasone treatment, but in this trial the average participant age was 14 years, meaning that many of the participants would have already gone through their most significant growth phases. Other side effects reported included more episodes of hoarseness, oral thrush, haemoptysis, pharyngitis and chest pain in the budesonide group. In 1 trial more participants were colonised for the first time with *Pseudomonas aeruginosa* in the treatment group and 1 participant tested positive for *Burkholderia cepacia* for the first time.

There is insufficient evidence from these trials to be able to recommend the routine use of ICS for CF. One study demonstrated that withdrawal in those already taking ICS does not affect the number of acute chest exacerbations, decline in lung function, antibiotic prescribing or rescue bronchodilator use. This, along with evidence that they may cause harm in terms of reduced childhood growth, suggests that their use for anti-inflammatory purposes in CF should be reduced. It has not been established whether long-term use is beneficial in reducing lung inflammation, which should improve survival, but it is unlikely this will be proven conclusively in a randomised controlled trial because of the constraints in the number of potential participants.

ICS should be used for symptomatic relief of recurrent wheezing that is not responsive to bronchodilators alone. Prescribing practice for people with CF should become more like that for people with asthma; there should be a reason for starting ICS, the effectiveness of ICS (particularly on any cough or wheeze) should be reassessed, and consideration should always be given to reducing or stopping ICS altogether. It is likely that most CF patients currently taking ICS can reduce or stop using them: considering the high number of patients prescribed ICS on the NHS, this will result in both a cost saving and a reduction in the number of adverse events seen.

Relevant NICE guidance and products

No NICE guidance was available at the time of publication (November 2016) that specifically addresses ICS for CF; however several technology appraisals around the management of CF using other medicines are available:

TA266 Mannitol dry powder for inhalation for treating cystic fibrosis (2012)

TA276 Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis (2013)

TA398 Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation (2016)

Other accredited guidance and products

BTS Guideline on Pulmonary Rehabilitation in Adults (2013)

Potential productivity savings

Estimate of current NHS use

The number of patients with CF registered in the UK CF Registry (UK Cystic Fibrosis Registry, 2016) is 10,800. Of these, about 60% (6500) are aged over 16 years.

Based on the Cochrane review, about 52% of children (2200) and 56% of adults (3600) receive ICS.

The monthly cost per patient for each of the inhaled steroids is: beclometasone £35, budesonide £43 and fluticasone £28 (NHS electronic drug tariff 2016). Treatment is ongoing.

Level of productivity savings anticipated

For each patient not prescribed ICS who would previously have received them, there will be a saving of between £28 and £43 per month.

Type of saving

Real cash savings should be achieved through reduced expenditure on drug budgets and fewer adverse events.

Any costs needed to achieve the savings

No additional resources required.

Other information

This saving is likely to benefit community prescribing budgets.

Potential impact on quality of NHS care

Impact on clinical quality

Better outcomes anticipated for patients by avoiding the side effects of ICS, particularly in children where ICS might impair growth.

Impact on patient safety

Improved by avoiding the side effects of ICS. There is some evidence that withdrawal of ICS in the majority of CF patients would be safe.

Impact on patient and carer experience

Improved because patients could avoid or reduce the use of ICS.

Likely ease of implementation

Time taken to implement

Can be achieved quickly (0–3 months)

Healthcare sectors affected

Affects one department or team

Stakeholder support

Likely to achieve good buy-in from key influencers

References

British Thoracic Society (2013) Guideline on Pulmonary Rehabilitation in Adults

De Boeck K, De Baets F, Malfroot A, Desager K, Mouchet F, Proesmans M (2007) Do inhaled corticosteroids impair longterm growth in prepubertal cystic fibrosis patients? European Journal of Pediatrics; 166(1):23–8.

National Institute for Health and Care Excellence (2012) TA266 Mannitol dry powder for inhalation for treating cystic fibrosis

National Institute for Health and Care Excellence (2013) TA276 Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis

National Institute for Health and Care Excellence (2016) TA398 Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation

NHS electronic drug tariff (2016)

UK Cystic Fibrosis Registry (2016)