

Opinion

The role of long acting bronchodilators and inhaled corticosteroids, alone and in combination, in COPD

Introduction

The GOLD Guidelines¹ define chronic obstructive pulmonary disease (COPD) as airflow limitation that is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases. Thus, COPD – like asthma – is a chronic inflammatory disease. Therefore, it might be anticipated that agents such as inhaled corticosteroids (ICS) would be of considerable benefit, just as they are in asthma. However, the cellular and chemical pattern of inflammation in COPD is different from asthma, and bronchial biopsy studies have shown little change after months of treatment with an ICS. The reason for the poor steroid response is unclear.

The role of ICS and long-acting bronchodilators

The role of ICS in COPD relates to their well-documented ability to reduce the frequency of acute exacerbations – usually by about 25%.² This effect is seen predominantly in patients who have more severe disease² and has led the UK NICE Guidelines³ to recommend that ICS therapy should be given to those COPD patients with an FEV₁ below 50% predicted and who have had at least two exacerbations in the past 12 months. ICS also slightly improve lung function and slow the rate of decline of Quality of Life measures. They have no significant effect on altering the rate of decline in FEV₁ with time.

Bronchodilators are the keystone to symptomatic improvement in COPD. Short-acting agents are usually the initial form of therapy for symptomatic relief. If improvement is inadequate, the next step is to add a

long-acting bronchodilator which usually gives better and more prolonged reduction in breathlessness and improvement in exercise ability. Long-acting bronchodilators have the additional benefits of reducing exacerbation frequency, improving health status, and increasing measures of lung function.⁴ Both long-acting beta-agonists (LABAs) such as salmeterol and formoterol, and Long acting antimuscarinics or anticholinergics (LAMAs) such as tiotropium, exhibit these benefits.

While long-acting bronchodilators cause bronchodilatation, they also, and perhaps more importantly reduce lung hyperinflation, thus reducing the work of breathing. Both reduce breathlessness. There appear to be other actions on the inflammatory response but these are not well understood.

Combining long-acting bronchodilators and ICS adds significant improvements in clinical outcomes over and above the benefits when either group of drug is used on its own. There have been several studies with combinations of both salmeterol/fluticasone and formoterol/budesonide which show similar improvements.^{5,6} Adding tiotropium to one of these combinations may confer greater improvement in lung func-

tion, but more major studies comparing all three agents are awaited.

Practical implications

Most guidelines^{1,3} recommend a stepped approach to therapy which should be based on symptoms such as breathlessness and disability rather than on FEV₁ alone. Indices of breathlessness such as the MRC Dyspnoea scale (see Box 1) measures of every day living, and exacerbation frequency, should all influence the type of therapy chosen for an individual patient - see Figure 1.

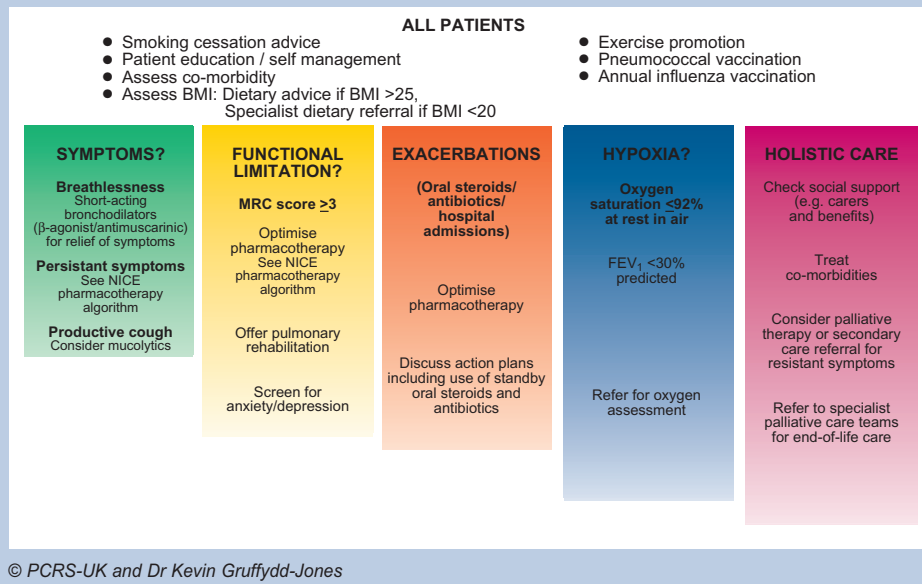
Long-acting bronchodilators should normally be added at a fairly early stage once persistent symptoms have appeared. As with all therapies, a trial of about a month needs to be given and the patient reviewed to see if any symptomatic improvements have occurred. These should not be based on change in FEV₁ as this will not measure any reduction in hyperinflation. Rather, ask the patient if they feel less breathless, are able to walk further, or can do more activity than before. If the response is positive, continue the drug. If not, try a different long-acting bronchodilator – e.g. tiotropium instead of salmeterol. It is always important to check inhaler technique and adherence to therapy.

The 2010 update of the NICE

Box 1. Medical Research Council (MRC) Dyspnoea Scale Grade

Grade	Degree of Breathlessness related to activities.
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying or waking up a slight hill
3	Walks slower than contemporaries on level ground because of breathlessness or has to stop for breath when walking at own place.
4	Stops for breath after walking about 100m or after a few minutes on level ground.
5	Too breathless to leave the house or breathless when dressing or undressing

Figure 1. Patient-Centred Approach to COPD Management



Guideline recommends the earlier use of both LABA and LAMAs if the patient remains breathless on regular short acting inhalers. The guideline suggests that combinations of ICS and long acting drugs can be given if the FEV₁ >50% in those with breathlessness and exacerbations. Triple therapy with ICS, LABA and LAMA may also be used if dual therapy is inadequate.

The ICS should be in fairly high dosage – since all the trial evidence was conducted on higher doses and there is no evidence that low doses work.

Short and long term benefits

Short term and longer term these agents improve symptoms and exercise ability. Other forms of therapy such as pulmonary rehabilitation should always be considered. The main longer term benefit is reduction of exacerbation frequency.

The recent large TORCH study⁷ set out to examine whether long-acting bronchodilators, ICS or the combined drug had any effect over three years on mortality reduction in patients with an FEV₁ less than 60% predicted. Although there was a trend for the combined drug to reduce deaths this did not quite reach statistical significance (P = 0.052). However, the trial did confirm the greater benefits of the combined drug in terms of exacerbation frequency, quality of life (QOL),

and lung function. However, the changes in QOL (as measured on the St George's Respiratory Questionnaire, SGRQ), even though statistically significant, did not reach clinical significance (i.e. a change in 4 points on the SGRQ).

Cost benefits of COPD therapies have also been reported recently, mainly in the context of exacerbations. The Canadian HTA⁸ found that ICS were more effective than LABAs alone at all COPD severity stages. Adding ICS was deemed cost effective in more severe patients.

Exacerbations

COPD exacerbations cause worsening of symptoms and reduction in quality of life, and may take up to three months to resolve. They also cause a huge burden on secondary care, accounting for 13% of all acute medical admissions. A combination ICS/LABA inhaler, with or without tiotropium. This will have the greatest effect on reducing exacerbations, by 25 to 38%, which is greater than any of the drugs on their own. Halpin⁹ has calculated the number needed to treat (NNT) to avoid one exacerbation requiring medical intervention in one year for formoterol/budesonide as 2.4.

Side effects

These are usually mild and are well

known. The TORCH study⁷ looked carefully for side effects and found no adverse effect on bone density or cataracts on ICS-based therapy. There was an unexplained increased incidence of reported pneumonia in both arms containing ICS. A recent review by Mapel¹⁰ comments that this was not found in 3 studies with budesonide/formoterol and had not been noted in earlier studies. There appears to be a small but real risk of pneumonia which needs further study.

References

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. 2006 GOLD 2006. www.goldcopd.com
2. Burge PS, Calverley PM, Jones PW, *et al*. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease; the ISOLDE trial. *BMJ* 2000;**320**:1297-303.
3. National Institute for Clinical Excellence (NICE). Chronic Obstructive Pulmonary Disease; National Clinical Guidelines on management of chronic obstructive pulmonary disease in adults in primary and secondary care. *Thorax* 2003;**59** (supplement 1).
4. Burasco V, Hodder R, Miravittlies M, *et al*. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. *Thorax* 2003;**58**:399-404.
5. Calverley P, Pauwels R, Vestbo J *et al*. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003;**361**:449-56.
6. Szfranski W, Cukier A, Ramirez A, *et al*. Efficacy and safety of budesonide /formoterol in the management of chronic obstructive pulmonary disease. *Eur Respir J* 2003;**21**:74- 81.
7. Calverley PM, Anderson JA, Celli B *et al*. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *New Engl J Med* 2007;**356**:775-89.
8. Brady B, Siebert U, Sroczynski G, *et al*. Long acting beta2-agonists (LABA) plus corticosteroids versus LABA alone for chronic obstructive pulmonary disease. 2007 www.crd.york.ac.uk
9. Halpin DMG . Evaluating the effectiveness of combination therapy to prevent COPD exacerbations: the value of NNT analysis. *Int J Clin Pract* 2005;**59**:1187-94.
10. Mapel DW, Hurley JS, Dalal AA, Blanchette M. The role of combination inhaled corticosteroid / long acting beta-agonist therapy in COPD management. *Prim Care Resp J* 2010;**19**(2):93-103.

Date of Preparation: May 2008, Revised June 2010 Author: David Bellamy, Bournemouth, UK Conflict of interest: None
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