

The role of inhaled corticosteroids and long-acting β_2 -agonists, alone and in combination, in the management of asthma

Introduction

Asthma is a chronic inflammatory disease of the airways that can affect people of all ages. The typical symptoms of asthma – episodic shortness of breath, wheeze, chest tightness, and/or cough – occur as a consequence of airway narrowing caused by smooth muscle contraction.¹ National,² international¹ and primary care-based³ guidelines have been published. Many of these guidelines have similar approaches to the pharmacological management of chronic asthma, incorporating a stepwise approach to treatment depending on the severity and persistence of symptoms.¹⁻³ There are now numerous asthma treatments available, including short- and long-acting β_2 -agonists (SABAs and LABAs, respectively), inhaled corticosteroids (ICS), inhaled anti-cholinergics, leukotriene receptor antagonists (LTRAs), oral corticosteroids for emergency use (and occasionally for regular use in patients with very severe disease), and, most recently, the humanised monoclonal antibody omalizumab. Each of these drugs has a different role depending on its mode of action and clinical effect.

The role of inhaled corticosteroids

ICS are the mainstay of asthma treatment. This is because their clinical effects are essential in order to achieve guideline-defined control of asthma.⁴ These attributes have been demonstrated in numerous well-conducted clinical trials. There is also evidence that ICS reduce hospitalisations⁵ and asthma deaths.⁶ Consequently, all national and international guidelines recommend ICS treatment for all asthma patients except those with very mild disease – in which case, as-needed SABA treatment can be used as long as the frequency of use is less than several times a week.

There are five inhaled steroids currently available in the UK – beclometasone dipropionate (BDP), budesonide, fluticasone dipropionate (FP), mometasone furoate and ciclesonide. The similarities and differences between these have been reviewed recently.⁴ The relative potency of different ICS has been debated, but, in summary, BDP (with one form of chlorofluorocarbon (CFC) propellant) and budesonide are about equipotent, whereas

FP is equally active at half the microgram dose. Mometasone is thought to be approximately equipotent to FP, and the potency of ciclesonide is somewhere between BDP and FP. There are now two different forms of BDP available with CFC-free propellant, and care needs to be taken when comparing the two. In addition, different types of device will have different drug-delivery properties.

Side effects of ICS

The main local side effects of ICS are oral candidiasis, cough, hoarse voice and dysphonia. Cough can usually be managed by switching to a different device and/or by addition of a spacer device. Oral candidiasis is dose-related; it can be treated with antifungals and prevented by mouth rinsing and gargling after inhaler use. Hoarse voice and dysphonia – caused by the ICS being deposited on the vocal cord and causing a myopathy of the arytenoid muscles – is more difficult to treat.⁴ The problem is dose-related, however, and is usually not too problematic at low ICS doses. There is some evidence that ciclesonide has lower potential for local side effects than other ICS.⁴

The systemic side effects of ICS are caused by their absorption into the systemic circulation. Potential side effects include adrenocortical suppression, increase risk of osteoporosis and bone fractures, skin thinning and purpura, weight gain, cataracts, glaucoma, diabetes, increased pulmonary infections, and growth retardation in children. The main site for systemic absorption of ICS is the alveoli, and absorption is higher in normal subjects than in patients with airway inflammation and obstruction. This is a strong argument for reducing the dose of ICS once asthma control has been obtained, and to keep the ICS dose at the lowest dose possible to control the disease. The potential for systemic ICS side effects is rare at doses of 400mcg/day BDP equivalent or less.

The role of long-acting β_2 -agonists

Salmeterol was the first LABA introduced into clinical practice in the late 1980s amidst great interest but also considerable concern that prolonged bronchodilatation could mask the signs of an impending

asthma exacerbation. These concerns were partially relieved by the Greening *et al* study published in 1994,⁷ which showed that adding salmeterol was superior to increasing the dose of ICS in patients with poorly-controlled asthma. Further evidence came with the FACET study,⁸ where addition of formoterol to either low- or high-dose budesonide reduced asthma exacerbation rates, improved symptoms, and improved lung function, as compared to ICS alone.

By the late 1990s, addition of a LABA to ICS was a therapeutic option at Step 3 of the BTS guidelines, but the dose of ICS at which the LABA should be added has been a source of considerable debate. Most guidelines now recommend that a LABA should be added if the patient is symptomatic at a low ICS dose of 400mcg/day BDP equivalent.¹⁻³

LABAs can cause mild tachycardia and tremor, but these side effects are usually mild at standard doses. Salmeterol, used at its licensed dose of 50mcg twice daily, is at the top of its dose-response curve, and so there is no benefit in increasing the dose. Formoterol, however, has a dose-response curve between 6mcg and 72mcg, so its dose can be varied; in addition, its onset of action is as fast as salbutamol.⁹

LABAs must be used in conjunction with ICS for the treatment of asthma.

Several years ago, concerns were expressed regarding the safety of LABAs following prospective and anecdotal studies which showed an increase in asthma exacerbations and deaths in asthmatic patients using LABAs.¹⁰ However, all of these studies assessed outcomes after asthma patients had been treated with a LABA alone and in the absence of ICS treatment. This issue has been reviewed recently.¹¹ In summary, there is no evidence of any increased risk when a LABA is used with ICS for the management of asthma – i.e. ICS must be used first in order to treat the underlying inflammation, and then a LABA can be added if full symptom control is not obtained at appropriate doses of ICS.

ICS/LABA combination inhalers

Since LABAs must always be used in

conjunction with ICS for the treatment of asthma, the logical step is to combine the two drugs into one inhaler. The current GINA guideline recommends use of a combination ICS/LABA inhaler rather than separate ICS and LABA inhalers for patients who require both drugs.¹ There are now three different combination ICS/LABA inhalers available in the UK: budesonide/formoterol (Symbicort); FP/salmeterol (Seretide); and, most recently, BDP/formoterol (Fostair). Most study data relate to the first two products which have been in use for at least five years.

The difference between budesonide/formoterol and FP/salmeterol combination inhalers

Both of these ICS/LABA combination inhalers have been shown to be highly effective in numerous well-conducted clinical trials. However, the FP/salmeterol combination inhaler can only be used at a fixed dose because the salmeterol is at the top of its dose-response curve. Therefore, the ways of altering the FP dose on a daily basis are to prescribe different strength FP/salmeterol inhalers (with different FP strengths per actuation), or to prescribe an FP inhaler to be used in addition to the combination, when needed, for control.

In contrast, because of formoterol's dose-response curve (between 6mcg and 72mcg), the budesonide/formoterol combination inhaler can be used at higher doses than its normal maintenance dose of one or two inhalations twice-daily, providing an increased dose of both ICS and LABA to the airways depending on the number of inhalations used.

Use of ICS/LABA combination inhalers for patient self management

1. Adjustable maintenance dosing

The GOAL study aimed to achieve 'total control' of asthma in patients who were sub-optimally controlled; using different strength combination FP/salmeterol inhalers (different strengths of FP ranging from 50mcg to 250mcg) according to symptoms and lung function readings, significantly more patients obtained guideline-defined control more rapidly, and at a lower total dose of ICS, compared to using FP alone.^{12,13}

Studies comparing fixed dose FP/salmeterol and fixed dose budesonide/formoterol at equipotent doses have shown that both inhalers are equally effective. Studies with budesonide/formoterol using an 'adjustable

maintenance dosing' regime showed that patient-directed change in the twice-daily maintenance dose of budesonide/formoterol, depending on symptoms or SABA use, led to improved treatment benefit, improved quality of life, and increased sense of 'enablement', at a lower dose of maintenance treatment overall.¹⁴

2. Single inhaler Maintenance And Reliever Therapy (SMART) with budesonide/formoterol

Since formoterol is a quick-acting LABA, with a speed of onset comparable to salbutamol,⁹ it can be used for symptom relief. Use of the budesonide/formoterol (Symbicort) inhaler for both maintenance and reliever treatment is now licensed in the EU for adults aged 18 yrs and older (up to a maximum of 12 inhalations of the 200/6 inhaler in a 24-hour period), and this has been given national² and international¹ guideline approval. Of course, a patient requiring 12 inhalations/day of a combination budesonide/formoterol inhaler has poorly controlled asthma, and patients – as part of their written asthma management plan – need to be advised to seek prompt medical advice in these circumstances. The SMART regime is an option for patients with moderate persistent asthma who have persisting symptoms despite low-dose ICS – i.e. patients at Step 3 of the BTS/SIGN guideline for whom use of an ICS/LABA combination inhaler is appropriate.

Studies have shown that the SMART regime with budesonide/formoterol reduces asthma exacerbation rates, increases the time to first exacerbation, and significantly improves symptoms, night-time awakenings and lung function, compared to other options such as fixed dose budesonide/formoterol with terbutaline as a reliever^{15,16} and FP/salmeterol with SABA as a reliever.¹⁷ Two cost-effectiveness studies have shown that SMART reduces the incidence of severe exacerbations at a similar or lower cost than high-dose fixed budesonide/formoterol and FP/salmeterol.^{18,19}

Conclusions

ICS are the mainstay of treatment for asthma. Guidelines recommend the addition of a LABA if asthma is not controlled on low-dose ICS (beclometasone 400mcg/day or equivalent). LABAs must not be used for the treatment of asthma except in conjunction with ICS. Combination ICS/LABA inhalers prevent the possibility of taking LABA treatment without ICS. The FP/salmeterol and budesonide/formoterol combination

inhalers are equally effective when used at equivalent doses for fixed-dose maintenance treatment. The properties of formoterol allow the budesonide/formoterol combination inhaler to be used for both maintenance and reliever therapy. The SMART regime reduces exacerbation rates and improves symptom control compared to other regimes, and this has been shown to be cost-effective.

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Address for Correspondence: PCRS-UK, Smithy House, Waterbeck, Lockerbie, DG11 3EY, UK

Telephone: +44 (0)1461 600639 Facsimile: +44 (0)1361 331811 Email: info@pcrs-uk.org Websites: <http://www.pcrs-uk.org>, <http://www.thepcrj.org>