Focus on inhaled corticosteroids in the treatment of chronica asthma in adults

In the first article of this special section on asthma management, practice pharmacist Catherine Lowe and GP Mary Goudge provide an overview of asthma prevalence, important clinical signs and symptoms, and recommended management strategies. In the second article, medical writer Christine Knott focuses on the available corticosteroid plus long-acting beta$_2$ agonist combination inhalers — Symbicort®, Seretide® and Fostair®▼. Fostair® is the newest addition to the combination therapy armoury and has not hitherto been considered in NICE assessments. This article, therefore, looks at the place of Fostair® in asthma management alongside its counterparts.

Introduction

In March 2008 NICE published guidance on the use of inhaled corticosteroids (ICS) in the treatment of chronic asthma.[1] The guidance aimed to consider which inhaled corticosteroid was most effective in asthma and which approach was most effective at introducing a long acting beta$_2$ agonist (LABA) into the treatment regimen. One of the conclusions drawn was that there was no significant difference in effectiveness between combination devices as opposed to separate devices. This view was subsequently supported by the BTS/SIGN guidelines published in May 2008.[2] Furthermore, they added that once a patient is taking stable therapy combination inhalers have the advantage of ensuring that the LABA is taken with the steroid.

Until January 2008 there were two combination inhalers available — Symbicort® (budesonide/formoterol) and Seretide® (Fluticasone/salmeterol). However, in January 2008 a third combination inhaler was introduced — Fostair® (beclomethasone/formeterol). It is therefore timely to review the strengths and weaknesses of the available combination inhalers, to clarify the prescribing information about the three products and to identify the patient groups who are most likely to benefit from each of these.

Overview of asthma

In the UK it is estimated that there are 5.2 million people with asthma.[1] These figures consist of 2.9 million women and girls and 2.3 million men and boys.[1] Furthermore, 0.7 million people with asthma are aged more than 65 years and 0.6 million are teenagers.[1] In 2005 the NHS confirmed 1318 deaths from asthma in the UK. A diagnosis of asthma is clinical and there is no gold standard definition. It is a chronic disorder of the airways caused primarily by inflammatory processes and constriction of airway smooth muscle. In adults there is a variable pattern of signs and symptoms. The main clinical signs are the presence of wheeze, breathlessness, chest tightness and cough. In addition, descriptions of airway hyper-responsiveness and inflammation are included. Table 1 is taken from the BTS/SIGN guidelines.[2]

Management of asthma

The aim of asthma management is to

Table 1. Clinical features in adults that influence the probability that episodic respiratory symptoms are caused by asthma[2]

Features that *increase* the probability of asthma:

- ☐ More than one of the following symptoms: wheeze, breathlessness, chest tightness and cough, particularly if:
  - ☐ symptoms are worse at night and in the early morning
  - ☐ symptoms occur in response to exercise, allergen exposure and cold air
  - ☐ symptoms are seen after taking aspirin or beta blockers
- ☐ History of atopic disorder
- ☐ Family history of asthma and/or atopic disorder
- ☐ Widespread wheeze heard on auscultation of the chest
- ☐ Otherwise unexplained low FEV_1 or PEF (historical or serial readings)
- ☐ Otherwise unexplained peripheral blood eosinophilia

Features that *lower* the probability of asthma:

- ☐ Prominent dizziness, light-headedness, peripheral tingling
- ☐ Chronic productive cough in the absence of wheeze or breathlessness
- ☐ Repeatedly normal physical examination of chest when symptomatic
- ☐ Voice disturbance
- ☐ Symptoms with colds only
- ☐ Significant smoking history (ie > 20 pack years)
- ☐ Cardiac disease
- ☐ Normal PEF or spirometry when symptomatic

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achieve disease control which is defined in the BTS/SIGN guidance as:[2]

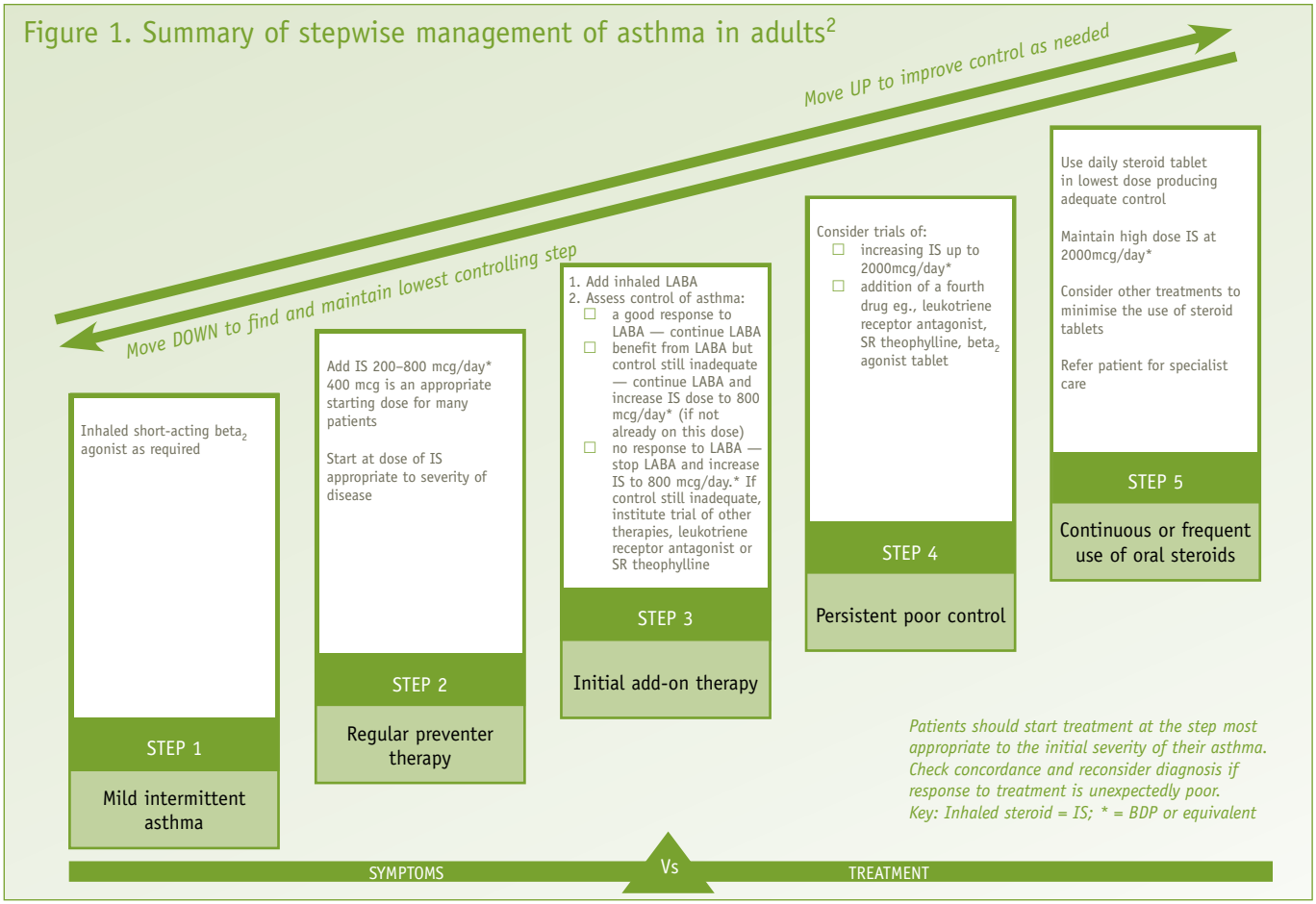
- ☐ no daytime symptoms
- ☐ no night-time awakening because of asthma
- ☐ no need for rescue medication
- ☐ no exacerbations
- ☐ no limitations on activity including exercise
- ☐ normal lung function.

The therapeutic management of asthma is outlined, using a stepwise approach, in Figure 1.[2] The aim is to abolish symptoms as soon as possible by starting at the step most appropriate to the severity of the asthma. The patient either progresses up the steps to improve symptom control or down when the symptoms have resolved. The aim is to use the minimum treatment that is able to control the symptoms. The variable nature of asthma will mean that patients have to monitor their condition and progress up or down the steps appropriately. This makes it imperative that patients make appropriate judgments and take their treatment accordingly. A key part of the patient consultation therefore is to check knowledge, compliance and inhaler technique. At step 2, where regular preventer treatment is needed, patients should be titrated to the lowest dose at which effective control of asthma is maintained.

Compliance with treatment

Effective treatments are available for the management of asthma — but they are only effective when they are taken by patients. Extensive international research has found that non-compliance with asthma therapy is widespread and is a significant risk factor for asthma morbidity and mortality.[3] Non-compliance can take a number of different forms. The most common form of non-compliance is erratic medicine taking caused by forgetfulness, changing schedules or busy lifestyles. Also, patients may be inadvertently non-compliant because they have failed to fully understand how to use their therapy. The overuse of beta agonists when symptoms deteriorate would be a good example of this. Equally, patients may make decisions not to use or even not to start ICS. This reasoned decision by the patient is often based on the fear of perceived short- or long-term side-effects of the steroids. The INSPIRE study[4] found that asthma control was suboptimal in more than half the patients receiving regular maintenance therapy. Often patients

Figure 1. Summary of stepwise management of asthma in adults[2]



underestimated their asthma symptoms or tolerated suboptimal control. Typically they increased their intake of short-acting beta$_2$ agonist and only increased their inhaled steroid dose when symptoms were at the peak of asthma worsening.

It is also important to consider non-pharmacological factors associated with asthma. Good evidence exists to support the benefits of stopping smoking and reducing weight. Many patients and their carers also have a perception that modification of environmental factors, dietary and other triggers will improve asthma. There is a range of alternative therapies that patients believe will improve asthma control. However, there is either no or limited evidence to support dietary manipulation, probiotics, acupuncture, air ionisers, Buteyko breathing technique, herbal/Chinese medicine, homeopathy, hypnosis/relaxation techniques, spinal manipulation, massage or physical exercise training.[2] It is important to be aware of patients' concerns and beliefs because if these are ignored by health care professionals then patients' compliance with recommended treatment may be compromised.

Comparison of inhaled steroids

The NICE guidance aimed to answer a number of questions about the place of ICS in asthma. These are summarised in Table 2.[1]

Five corticosteroids are available as inhaled formulations in the treatment of asthma: beclometasone diproprionate (BDP), budesonide, fluticasone propionate, mometasone furoate and ciclesonide. These ICS are available in two main types of devices — metered dose inhalers (MDIs) or dry powder inhalers (DPIs). In its systematic review the NICE assessment group compared ICS using the same inhaler device. All ICS were compared with fluticasone propionate and budesonide and there were no pairwise comparisons between BDP, mometasone furoate and ciclesonide. From its review of the studies the assessment group found that there were few statistical differences between the ICS, whether at low or high doses. They concluded that it was reasonable to assume that there were no differences in clinical effectiveness between them.[1]

Beclometasone and budesonide are approximately equal in dosage in clinical practice.[2] Fluticasone and mometasone provide equal clinical activity to these steroids at half the dose.[2]

Combination therapies for uncontrolled asthma

The NICE assessment group compared combination devices containing a ICS and LABA. The two devices compared were Symbicort®(budesonide/formoterolfumarate) and Seretide® (fluticasone propionate/salmeterol) combinations. They concluded that the addition of a LABA was significantly superior to increasing the dose of ICS when looking at a range of outcomes related to lung function, symptoms, rescue medication and asthma exacerbations.[1] There were few differences between combination inhalers across a range of efficacy outcomes when they were compared with their component drugs. However, the study design often used was double-blind and double-dummy. Thus, the full benefits of adherence with a combination device were not fully captured. The assessment group also concluded that when Symbicort® and Seretide® were directly compared they showed mixed results with each device being statistically superior for different outcomes. Thus they did not make a recommendation favouring a particular device.[1]

Recent publications have evaluated Symbicort® for use as both regular maintenance therapy and 'as needed' reliever therapy, whereby the patients took additional inhalations as required to provide rapid symptom relief. This evidence, published subsequent to the NICE guidelines, suggests that when Symbicort® was used

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in this way there were fewer severe asthma exacerbations compared with using either formoterol or terbutaline as the reliever.[5,6]

In January 2008 Fostair® (beclometasone/formoterol), became available. Fostair® is the first combination inhaler containing 100mcg BDP and 6mcg formoterol per actuation in a MDI. The product uses a new technology called Modulite® which has been developed to obtain an extra-fine particle size of the component drugs. This has the advantage of improving drug delivery to peripheral airways resulting in a 2.5-fold lower BDP dose requirement when compared to chlorofluorocarbon-BDP for the same efficacy and anti-inflammatory effect.

How does Fostair® compare with Seretide® and Symbicort®? Although clinical data for Fostair® is limited there is widespread clinical use and evidence for both BDP and formoterol as monotherapies. Two head-to-head, randomised, double-blind studies were carried out[7,8] in adults with moderate to severe asthma. These studies took place over 12 weeks and morning peak expiratory flow in the last 2 weeks was the primary outcome measure. They showed that Fostair® has comparable efficacy with

Table 2. Questions addressed by NICE in their guidance for inhaled corticosteroids for the treatment of chronic asthma[1]

- ☐ Which ICS is the most clinically effective at low doses?
- ☐ Which ICS is the most clinically effective at high doses?
- ☐ Which is the more clinically effective approach to introducing a LABA into a treatment regimen?
- ☐ Which is the more clinically effective treatment of:
  - ☐ Fluticasone/salmeterol in a combination device or separately
  - ☐ Budesonide/formoterol in a combination device or separately
- ☐ Which is the more clinically effective treatment — Fluticasone/salmeterol in a combination device or budesonide/formoterol in a combination device?

the Seretide® and Symbicort® inhalers at equivalent doses.

Summary: choice of combination inhaler

There are three products available that combine an ICS with a LABA — Seretide®, Symbicort® and Fostair®. On the basis of NICE guidance[1] there would not be a strong basis for selecting one product over the other. They are available in different delivery devices and have different costs as summarised in Table 3. Patient preference is particularly important in inhaler choice because this impacts upon compliance. Fostair® for example, could be a consideration for patients already established on BDP and who are able to manage or who prefer a MDI, or those who voice particular anxiety about systemic exposure to ICS and who want high lung delivery per dose. When transferring to Fostair® it is important to remember that the extra-fine particle size means that 100mcg of BDP in Fostair® is equivalent to 250mcg non extra-fine BDP or Clenil® CFC-free. Patients changing from Qvar® will need a smaller dose adjustment (125mcg Qvar® to 100mcg Fostair®). Similarly, patients already using fluticasone may prefer to use Seretide® and those who prefer turbohalers might wish to use Symbicort® which is the product with the greatest dose range (Table 3) and is suitable for those patients at step 4 who require high levels of ICS.

The recent study suggesting superiority of budesonide plus formoterol over salmeterol as a reliever treatment[6] appears to be a promising approach to managing asthma acute exacerbations, and potentially might be applicable to a BDP plus formoterol combination inhaler. However, authors have emphasised that this approach is unsuitable for non-responders to formoterol or for patients needing more than 10 'as needed' inhalations and that the opposite findings have been documented from studies conducted by other research groups.[9] This suggests that further independent evidence is required to address such concerns. Combination inhalers are nevertheless likely to make a positive impact upon patient compliance ensuring delivery of an ICS with a LABA.[1,2] Current recommendations stress that all patients should be maintained at the lowest possible dose of inhaled steroids and should be slowly stepped down when they have been stable for a minimum of three months.[1,2] The daily ICS/LABA doses that can be delivered from all currently available combination inhalers can be stepped up and down to allow adherence to national guidelines in accordance with patients' needs. The three combination inhalers increase therapeutic choice for poorly controlled patients with asthma but health care professionals must decide on a patient-by-patient basis in discussion with each patient whether to prescribe a combination inhaler or separate ICS and LABA inhalers, based on the patient's likelihood for adherence and the therapeutic need.[2] ✤

Declarations of interest

The authors have no interests to declare.

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(Websites accessed Feb 2009).

Table 3. Summary of products available

Product	Contents	Device characteristics	Cost (£)	Usual dosage range
Fostair®	Beclometasone dipropionate/ Formoterol fumerate	Metered dose inhaler using Modulite® technology to obtain extra-fine particles; 100/6	29.32	1-2 puffs twice daily; max 4 puffs daily
Symbicort®	Budesonide Formoterol fumerate	Turbohaler: 100/6	33.00	1-2 puffs twice daily with 1 puff as needed; max 8 puffs daily
		200/6	38.00	1-2 puffs twice daily with 1 puff as needed; max 12 puffs daily
		400/12	38.00	1 puff twice daily increased to max 2 puffs twice daily
Seretide®	Fluticasone propionate Salmeterol	Accuhaler: 100 accuhaler	31.19	1 blister twice daily of accuhaler 100 up to 1 blister twice daily of accuhaler 500
		250 accuhaler	35.00	
		500 accuhaler	40.92	
		Evohaler: 50 evohaler	18.00	2 puffs twice daily of evohaler 50 up to 2 puffs twice daily of evohaler 250
		125 evohaler	35.00	
		250 evohaler	59.48	

Information source: http://www.ppa.org.uk/edt/April_2009/mindex.htm