Combination therapy for asthma — what are the current options?

Introduction

The BTS/SIGN guidance states that patients should expect to have no symptoms and no exacerbations, and that the goal of asthma management is to minimise future adverse outcomes such as exacerbations and accelerated decline in lung function.[1] BTS/SIGN advise that this is best achieved using a strategy that controls airway inflammation or hyper-responsiveness (ie by using inhaled corticosteroids) than one which controls immediate symptoms (ie with short-term beta$_2$ agonists).[1] Using the recommended stepwise approach to reduce airway inflammation and abolish symptoms many patients with asthma are managed with regular once or twice-daily inhaled steroids — with beclometasone (delivered by pressurised metered dose inhaler [pMDI]) being the most widely prescribed with a favourable risk-efficacy profile.[2]

Managing loss of control: good practice points

Despite adhering to evidence-based inhaled corticosteroid (ICS) inhaler therapy, a proportion of patients will experience symptom exacerbation — wheeze, breathlessness, chest tightness or cough (particularly if worse at night or early in the morning[1]) — at some time in their lives. It will then be necessary to consider the most appropriate management strategy for these patients. A consultation, either by a GP or a specialist respiratory nurse or pharmacist, provides an opportunity to review, reinforce and extend self-management skills with the patient in addition to reviewing their medication and spirometry. Having ensured the patient has good compliance and correct inhaler technique, and avoids known trigger factors, BTS/SIGN and NICE advise that uncontrolled patients should be stepped up to include a long-acting beta$_2$ agonist (LABA) in addition to their inhaled steroid.[1] Indeed, the evidence suggests that many patients will benefit more from add-on therapy than from increasing inhaled steroids above doses as low as 200 mcg/day and an absolute dose threshold cannot be defined.[1] The first choice of add-on therapy is inhaled LABA, because it improves lung function and asthma symptoms, and decreases exacerbations.[1] Although concerns have been raised for the safety of LABA use[3] the Medicines and Healthcare products Regulatory Agency (MHRA) review concluded that these can continue to be used in the management of asthma *provided they are used with inhaled corticosteroids*.[4]

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On the basis that there is no difference in efficacy in giving inhaled steroids and

Table 1. Combination inhalers available

Product	Corticosteroid and inhaled dose	LABA and inhaled dose	Recommended adult daily dosage range	Inhaler device
Fostair®[5]	Beclometasone dipropionate 100mcg/ actuation [equivalent to a delivered dose (ex-actuator) of 86.4mcg of BDP].	Formoterol fumarate dihydrate 6mcg/ actuation [equivalent to a delivered dose (ex-actuator) of 5mcg of FF].	1-2 actuations twice daily to a maximum of 4 inhalations daily	Pressurised metered-dose inhaler
Seretide®[6]	Fluticasone propionate 100, 200 or 500mcg/inhalation	Salmeterol 50mcg/ inhalation	1 actuation of appropriate strength twice daily	Dry powder inhaler (Accuhaler®)
Seretide®[7]	50, 125 or 250mcg of fluticasone propionate delivered from the valve (equivalent to 44, 110 or 220mcg FP delivered from the actuator).	25mcg salmeterol xinafoate (equivalent to 21mcg of SALM delivered from the actuator).	Up to 2 inhalations twice daily	Pressurised inhalation, suspension (Evohaler®)
Symbicort®[8]	Budesonide 100, 200 or 400mcg per inhalation (equivalent to 80, 160 or 320mcg respectively of BUD per inhalation).	Formoterol fumarate dihydrate 6* or 12mcg (equivalent to 4.5 or 9mcg respectively of FF per inhalation). *6mcg is combined with 100 or 200mcg budesonide	1-2 inhalations twice daily to a maximum of: 8 inhalations of 100/6mcg and 200/6mcg doses and 4 inhalations of 400/12mcg dosage regimen daily	Dry powder inhaler (Turbohaler®)

LABA in combination or in separate inhalers the consensus view from BTS/SIGN,[1] MHRA[4] and NICE[9] is that consideration should be given to prescribing combination inhalers rather than separate inhalers for the management of chronic asthma in patients for whom inhaled corticosteroids have failed to achieve control. This would guarantee that patients do not take a LABA without their inhaled steroid and would be more likely to promote compliance, simplify the administration regimen, and because combination inhalers are usually cheaper than separate inhalers, they would also result in reduced cost.

Combination inhaler option

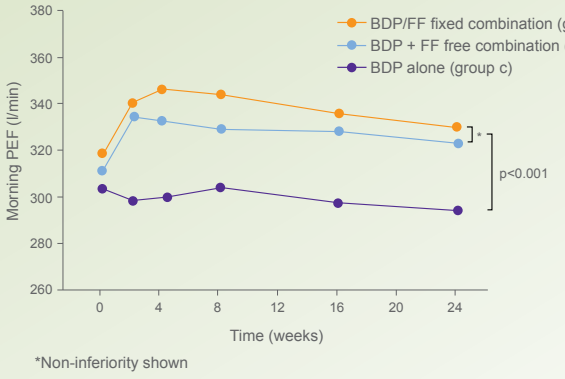
Currently there are three combination inhaler options delivering a corticosteroid and LABA in fixed dose combinations. These are Seretide®,[6,7] Symbicort®[8] and Fostair®[5] (Table 1). Fostair® is the newest combination inhaler to the market and the only one to deliver beclometasone dipropionate (BDP) with formoterol (Table 1). Comparing inhaled corticosteroids BTS/SIGN concluded that BDP and budesonide are approximately equivalent in clinical practice although there may be variations with different delivery devices.[1] Fluticasone, however, provides equal clinical activity to BDP and budesonide at half the dosage.[1] Fostair® contains BDP, which has been formulated with an extra-fine particle size distribution and is delivered by pMDI using hydrofluoroalkane-134a (HFA) as the propellant. Each actuation delivers extra-fine particles of BDP 100mcg and formoterol 6mcg, which has been found to achieve 31% lung deposition throughout the large and small airways.[10] This results in a more potent effect than formulations of BDP with a non extra-fine particle size distribution; a 100mcg dose of extra-fine BDP in Fostair® is equivalent to 250mcg of non extra-fine BDP.[5] But how effective is Fostair® compared with BDP alone and with the other combination inhalers? Some of the studies aimed at answering these questions are briefly reviewed below.

Efficacy of BDP compared

A randomised, double-blind, double-dummy, non-inferiority 6-month study of 645 patients (aged 18–70 years) with moderate-to-severe persistent asthma uncontrolled by regular treatment was undertaken to compare the efficacy of BDP and formoterol delivered in separate inhalers with their co-delivery using a combination inhaler.[11] Patients were randomised to receive either (a) a fixed combination of extra-fine BDP 200mcg plus formoterol 12 mcg via pMDI (Fostair®), twice daily, (b) BDP 500mcg via chlorofluorocarbon (CFC) pMDI and formoterol 12mcg via dry-powder inhaler (DPI), twice daily or (c) BDP 500mcg, via CFC pMDI twice daily.[11] The authors found a significant improvement in morning peak expiratory flow (PEF) — the primary outcome measurement — in those patients given the Fostair® inhaler (group a) and those given BDP and formoterol as separate inhalers (group b), which was superior to that achieved with BDP alone (group c)[11] (Figure 1). Similarly, the percentage of days and/or nights without clinical symptoms and days with asthma control — one of the secondary efficacy endpoints — was significantly greater in patients taking Fostair® (group a) compared with those patients taking separate BDP plus formoterol (group b) or BDP alone by the end of the study (Figure 2).[11] This was associated with a significant decline in salbutamol use in both the Fostair® (a) and the BDP plus formoterol (b) groups.[11]

An earlier study by Rigamonti and colleagues showed clinical equivalence of extra-fine BDP-HFA pMDI at a daily dose of 400mcg and BDP-CFC pMDI at a daily dose of 1000mcg.[12] These data are in accord with the findings of Huchon and colleagues of an improvement in lung function with

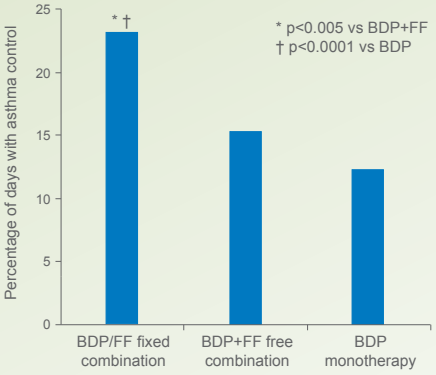
Figure 1. Morning peak expiratory flow rate (l/min) in ITT population.[12]



*Non-inferiority shown

BDP: beclometasone dipropionate
FF: formoterol fumarate
PEF: peak expiratory flow
ITT: intention to treat.

Figure 2. Percentage of days with asthma control in beclometasone dipropionate/formoterol fixed combination, beclometasone dipropionate plus formoterol free combination and beclometasone dipropionate monotherapy groups (ITT population; post-hoc analysis).[12]



BDP: beclometasone dipropionate
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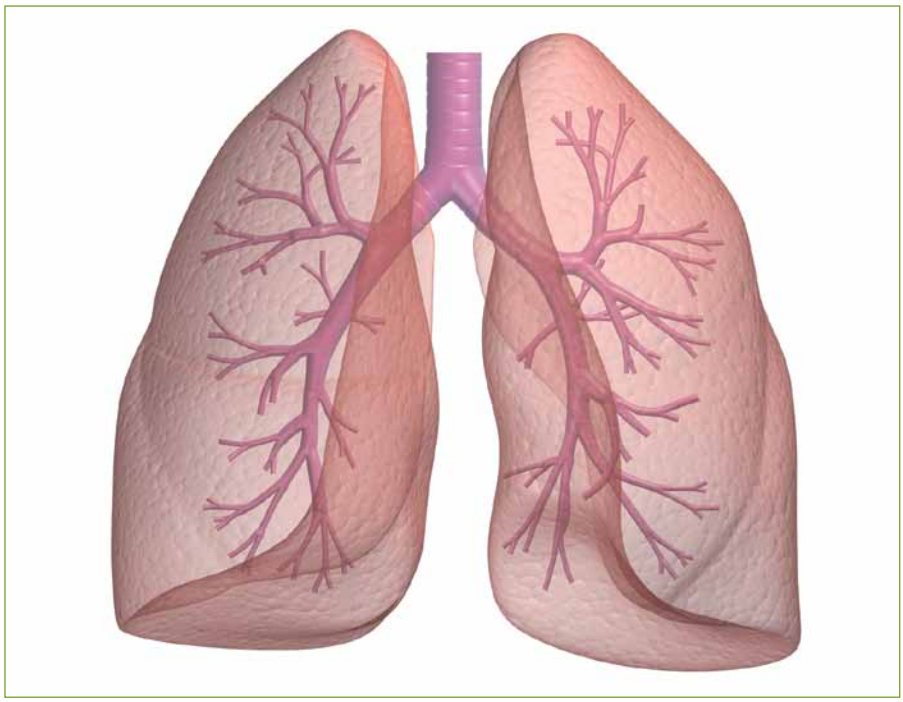
Fostair® over CFC-BDP 500mcg twice daily[11] and support the rationale of using a stepwise approach to asthma management.[1] Huchon and colleagues suggested that their finding of a greater improvement in lung function in patients receiving Fostair® over those receiving separate BDP plus formoterol inhalers could be related to the distribution profile of extra-fine BDP and extra-fine formoterol in both central and small airways.[11]

These combined data suggest that Fostair® is more effective than equivalent BDP doses and could be an appropriate clinical option for patients with chronic asthma for whom existing inhaled corticosteroid medication has failed to achieve control.

Comparisons of Fostair® with Symbicort® and Seretide®

Comparative data are limited but a 12-week, non-inferiority phase III, multi-centre, double-blind, double-dummy, randomised, study of 219 patients with moderate-to-severe asthma compared extra-fine BDP-HFA 200mcg/formoterol 12mcg bd via pMDI with budesonide 400mcg/formoterol 12mcg bd (Symbicort® Turbuhaler DPI).[13] The researchers found a significant improvement from baseline in lung function, symptoms and rescue medication use in both groups at all time-points during the study. There were no differences in the rate of asthma exacerbations or frequency of adverse events between the treatments, showing clinical non-inferiority between the two combination inhalers.[13]

This research team also compared the efficacy of two inhalations, twice daily of either extra-fine BDP/formoterol 100/6 mcg pMDI or fluticasone/salmeterol 125/25mcg pMDI (Seretide®) in a 12-week, non-inferiority, phase III, multi-centre, double-blind, randomised controlled study of 228 patients with moderate-to-severe asthma.[14] In both groups a significant improvement in lung function, symptom scores and rescue medication use was found at all time points, with no significant differences between the treatments in terms of morning PEF, recorded during the last 2 weeks of treatment.[14]



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Speed of onset of activity

The LABA — formoterol — has been assessed in a number of studies in terms of speed of onset. In a double-blind, double-dummy, randomised, placebo-controlled, cross-over study of 36 patients (aged 18–64 years) with mild-to-moderate asthma the efficacy of formoterol (4.5 or 9mcg via Turbuhaler) was measured and compared with that of the short-acting beta-blocker salbutamol (100 or 200mcg via pMDI) for up to 30 minutes after inhalation.[15] No significant difference was found in the efficacy or time to response between formoterol and salbutamol, both giving a higher bronchodilation than placebo, measured by forced expiratory volume in one second (FEV_1), at 3 minutes after dosing — the efficacy correlating with patients' subjective experiences.[16] Formoterol is therefore a fast-onset long-acting bronchodilator that patients can feel working quickly.[16] Papi and colleagues noted that beclometasone plus formoterol showed a significantly faster onset of bronchodilation compared with fluticasone plus salmeterol for up to 1 hour after dosing.[14]

Taken together these albeit limited data indicate that Fostair®, which contains extra-fine BDP and formoterol is not clinically inferior to either Seretide® or Symbicort®, but it has a clinically significant faster improvement in bronchial dilation than Seretide® which is maintained for up to 1 hour after a dosing.[13,14]

Adverse effects and systemic steroid exposure

Studies in which tolerability and adverse events were recorded found no significant difference in tolerability or frequency of adverse events between patients taking extra-fine BDP/formoterol and Seretide®[14] or between extra-fine BDP/formoterol and Symbicort®.[13] Pharmacokinetic studies found that Fostair® (400mcg BDP/24mcg formoterol) administration resulted in 35% lower steroid exposure than non extra-fine BDP (1000mcg) administered with formoterol (24mcg) as separate components.[17] The authors attribute this to a reduced swallowed amount of steroid concomitant with a greater lung delivery.[17] This reduced systemic exposure is of relevance to findings of Huchon and co-workers[11] who compared morning cortisol levels in patients taking Fostair®

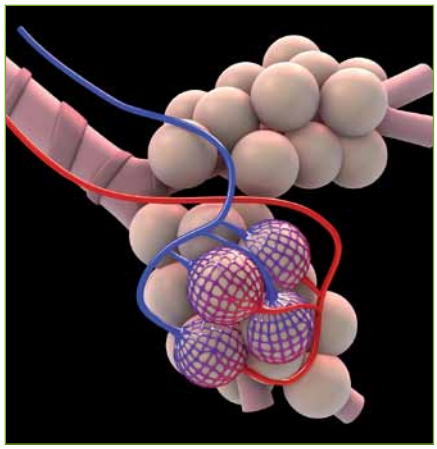
(group a), BDP plus formoterol (group b) and BDP alone (group c). At the end of the study morning cortisol levels increased significantly compared with baseline levels in the Fostair® group but remained substantially unchanged in the other groups.[11] Huchon suggested that the lack of cortisol suppression with Fostair® confirmed its favourable safety profile compared with non extra-fine formulations,[11] and is likely to reflect the lower systemic steroid exposure in the Fostair® group. For those patients to whom systemic steroid exposure is a concern, therefore, Fostair® may be a suitable therapeutic option.

Stepping up must be followed by stepping down

Combination inhalers can offer the advantage of ensuring delivery of a steroid with a LABA and are associated with improved lung function and reduced use of rescue medication compared with BDP alone. However, 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] The daily steroid/LABA doses that can be delivered from all currently available combination inhalers can be stepped up and down to allow adherence with current recommended guidelines in accordance with patients' needs.

Summary

All available guidance, based on an established body of evidence, recommends that if a patient is poorly controlled when using an inhaled corticosteroid (ICS) alone, adding a LABA is more effective than increasing the dose of ICS.[1] Cost comparisons made between taking a combination device and taking the same components separately show that combination products are almost always cheaper than the separate devices.[1] NICE therefore recommended that appropriate patients at step 3 should be offered the option of having a combination device within its marketing authorisation, and if this is chosen then the least costly product suitable for an individual is recommended.[1] However, healthcare professionals must



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decide on a patient-by-patient basis and in discussion with each patient whether to prescribe a combination inhaler or separate ICS and LABA inhalers, based on the likelihood for adherence and therapeutic need.

There are now three combination inhalers — Seretide® (fluticasone/salmeterol DPI or pressurised suspension inhalation), Symbicort® (budesonide/formoterol DPI) and Fostair® (extra-fine BDP/ formoterol pMDI). Limited comparative studies indicate that Fostair® is non-inferior to Seretide® and Symbicort® in terms of improving lung function. However, Fostair® has been found to have a faster onset of action than Seretide® and to offer a reduced systemic steroid exposure compared with non extra-fine BDP (and consequent reduced adrenal suppression). The three ICS plus LABA combination inhalers now available, with similar efficacies and adverse-effect profiles, increase therapeutic choice for poorly controlled patients with asthma. The addition of Fostair® to the armamentarium provides prescribers with another inhaler option for patients.

Christine Knott, editor

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