Effects of dual therapy with corticosteroids plus long acting $\beta_2$-agonists in asthma☆

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Summary Asthma is a common condition characterised by inflammation, airway hyperresponsiveness and reversible airflow obstruction. Effective pharmacotherapy must therefore be aimed at attenuating these underlying hallmark features. Despite the use of regular low-to-moderate doses of inhaled corticosteroids, many patients remain symptomatic and require further 2nd line controller therapy. The addition of a concomitant long acting $\beta_2$-agonist provides an effective means in which to alleviate symptoms and reduce exacerbation frequency. Moreover, both agents can be combined in a single inhaler, and provide patients with a more convenient and effective way in which to deliver treatment to the endobronchial tree. This evidenced-based review article discusses the effects of such combination inhalers upon a variety of outcome parameters and their effects upon asthmatics across a range of severities.

Keywords Asthma; Long acting $\beta_2$-agonist; Salmeterol; Eformoterol; Budesonide; Fluticasone; Seretide; Symbicort; Leukotriene receptor antagonist; Montelukast; Zafirlukast; Theophylline; Inflammation; Bronchial hyperresponsiveness; Randomised controlled trial

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Introduction

Asthma is a common chronic heterogeneous condition which displays a complex and varied phenotypic picture. It can present in early childhood as well as adulthood, and varies markedly in severity, clinical course, subsequent disability and response to treatment. Pathologically it is characterised by inflammation, physiologically by airway hyperresponsiveness (AHR) and consequent airflow obstruction, and clinically by wheeze, chest tightness, breathlessness and cough. Symptoms are the final manifestation of an inhaled corticosteroid plus LABA, reversible airflow obstruction with the combination of an inhaled corticosteroid plus LABA, respectively.

Inhaled corticosteroids

Inhaled corticosteroids are a vital component in the successful treatment of persistent asthma of all severities. Once bound to cytoplasmic receptors concentrated in airway epithelial and endothelial cells, they increase and decrease the gene transcription of anti-inflammatory and pro-inflammatory mediators, respectively. Corticosteroids also exert a direct inhibitory effect upon a number of cells (eosinophils, T lymphocytes and epithelial cells) implicated in the asthmatic inflammatory process. As a consequence, they attenuate AHR over several weeks although the maximal effect may not be achieved until after several months of regular use. Moreover, inhaled beclomethasone and fluticasone can prevent changes associated with long-term unchecked inflammation (airway remodelling).

Dose–response studies using inhaled corticosteroids have generally been unable to demonstrate any significant difference between individual doses. For example, a meta-analysis by Holt et al. evaluated 8 studies (2324 asthmatics) where the effects of at least 2 doses of fluticasone were measured. Most therapeutic gain (in terms of airway calibre, symptoms and effects upon exacerbations) was achieved at daily doses of fluticasone between 100 and 250 μg. However, the authors do acknowledge that the study was limited by paucity of data with higher fluticasone doses. It is also important to note that clinical outcome measures such as lung function, rescue medication use and symptoms fail to provide information regarding the intrinsic disease process itself and tend to be downstream markers relatively remote from AHR and underlying inflammation. Indeed, using AHR as the primary outcome measure, a meta-analysis of 25 studies (963 patients) demonstrated that high doses (≥1000 μg of beclomethasone or equivalent) of inhaled corticosteroid did confer greater improvements in terms of attenuating AHR than low doses (<1000 μg). It is pertinent to be aware that this is at the expense of adverse local and systemic sequelae. However, patients with severe persistent asthma appear to be protected from high doses of inhaled corticosteroids due to decreased lung bioavailability as a consequence of reduced airway diameter.

Adverse effects of inhaled corticosteroids tend to occur in a dose-dependent way. Clinicians should therefore aim to have patients controlled on the lowest dose of inhaled corticosteroid which optimises airway benefit and minimises the risk of systemic adverse effects, thus improving the overall therapeutic ratio. Indeed, it is generally accepted that at daily doses greater than 800 μg of beclomethasone or equivalent in adults, the
It is important to be aware that LABAs do not exhibit in vivo anti-inflammatory activity. For example, Lazarus et al. evaluated well controlled asthmatics using triamcinolone 800 μg/day and randomly switched them to receive salmeterol as monotherapy or continue with triamcinolone. Patients assigned the former group experienced more exacerbations and demonstrated an increase in sputum and blood inflammatory markers. In another trial, Lemanske et al. randomised patients after a 6-week run-in not controlled on triamcinolone 800 μg/day, to receive either salmeterol or placebo. During the next 4 months, inhaled corticosteroids were discontinued in the entire placebo group and in one-half of the salmeterol group. The mean overall treatment failures with either salmeterol or placebo were similar in both groups. In other words, add on salmeterol had no effects on disease control following discontinuation of triamcinolone. As a consequence, guidelines do not advocate the use of LABAs as monotherapy in asthmatics of any severity.

Polymorphisms of the β2-adrenoceptor have been identified, of which substitution of glycine for arginine at codon 16 (occurring in about 40% of the UK population), enhances the susceptibility to down regulation by β2-agonists. Due to prolonged receptor occupancy, the β2-adrenoceptor becomes internalised and degraded. As a result, an attenuated bronchoprotective response can be observed with different types of inhaled stimuli. Furthermore, in the clinical setting of an acute asthma attack, it may be relevant that a blunted response to inhaled salbutamol occurs with chronic treatment with LABAs. However, there is little compelling evidence to suggest that tolerance develops to the bronchodilator effects of LABAs.
and inhaler devices required, while the fairly immediate bronchodilation especially with eformoterol,24 provides patients with an instant boost. Furthermore, the fact that the two moieties are inseparable, implies that compliance with anti-inflammatory therapy might be enhanced as the LABA (which the patient perceives as beneficial shortly after dosing) cannot be used at the expense of inhaled corticosteroid.

Possible drawbacks

Despite the advantages of a single inhaler, on a practical level altering the inhaled corticosteroid dose, without altering the LABA dose, becomes less straightforward. This has the potential consequence that patients may remain on unnecessary or insufficient doses of anti-inflammatory treatment for a prolonged period of time. Indeed, due to the variable nature of asthma, patients are advised to adjust their inhaled corticosteroid dose according to symptoms and personal best peak expiratory flow (PEF).6 An evidenced-based review by Gibson and Powell highlighted the benefit of written action plans—involving at least doubling the inhaled corticosteroid dose—when incorporated into the routine care of asthmatic patients.34 During periods of deteriorating asthma control, patients using a Seretide Accuhaler would therefore require a separate inhaler in order to titrate upwards the dose of fluticasone. Similarly, when asthma is well controlled and "step-down" considered appropriate, patients would have to consult their primary care physician to be provided with a further inhaler containing less corticosteroid. In order to overcome this difficulty, Symbicort—largely due to the less steep dose–response curve of eformoterol compared to salmeterol24—can be used in a more flexible manner. This allows different corticosteroid doses to be delivered to the lung along with a variable dose of eformoterol. Indeed, in a study by Aalbers et al.,35 an adjustable maintenance dose of twice daily budesonide 160 μg plus eformoterol (in a single inhaler) was shown to provide effective asthma control when individuals were instructed to titrate treatment according to symptoms. Moreover, when compared to a fixed fluticasone plus salmeterol dosing regime, there were 40% (P = 0.018) fewer exacerbations.

Considerable concern has been focused on the use of LABAs and the masking of underlying airway inflammation. Theoretically, patients may use such drugs for relatively instant bronchodilation and adhere less stringently to inhaled corticosteroid therapy (when used as separate inhalers). This in turn could result in persistent chronic mucosal inflammation of which the patient is unaware, in turn paving the way towards an exacerbation. Indeed, in a study by McIvor et al., the use of salmeterol controlled symptoms and maintained bronchodilation but resulted in an increase of sputum eosinophils when inhaled corticosteroids were tapered in 13 asthmatics.36 This small study of patients using daily doses of inhaled corticosteroid X 1500 μg may not be applicable to "real-life", as doses were reduced until either criteria for an exacerbation was reached or until no corticosteroids were being used at all. In another study, after a run-in using budesonide 1600 μg/day, 60 moderately severe asthmatics were randomised to receive budesonide 800 μg/day (mean FEV1 82% predicted) or budesonide 200 μg/day plus eformoterol (mean FEV1 84% predicted).37 After 1 year of randomised treatments, there were no differences in either surrogate markers of inflammation and perhaps surprisingly of lung function. Thus, this

| Table 1 | Symbicort and Seretide constituents, doses, devices and adult dosing regimes. |
|---------------------------|---------------------------------|-----------------|-----------------|-------------------|
| Inhaled corticosteroid dose | Long acting β2-agonist dose | Device | Dosing regime |
| Symbicort 100/6 | Budesonide 80 μg | Eformoterol 6 μg | Turbohaler | 1-2 inhalations once or twice daily |
| Symbicort 200/6 | Budesonide 160 μg | Eformoterol 6 μg | Turbohaler | 1-2 inhalations once or twice daily |
| Seretide 50 | Fluticasone 50 μg | Salmeterol 23 μg | Evohaler | 2 inhalations once or twice daily |
| Seretide 125 | Fluticasone 125 μg | Salmeterol 23 μg | Evohaler | 2 inhalations twice daily |
| Seretide 250 | Fluticasone 250 μg | Salmeterol 25 μg | Evohaler | 2 inhalations twice daily |
| Seretide 100 | Fluticasone 100 μg | Salmeterol 50 μg | Accuhaler | 1 inhalation twice daily |
| Seretide 250 | Fluticasone 250 μg | Salmeterol 50 μg | Accuhaler | 1 inhalation twice daily |
| Seretide 500 | Fluticasone 500 μg | Salmeterol 50 μg | Accuhaler | 1 inhalation twice daily |
study demonstrated no deleterious consequences in terms of underlying inflammation in patients using a four-fold smaller corticosteroid dose in conjunction with a LABA.

Effects of long acting $\beta_2$-agonists as add-on therapy to inhaled corticosteroids

Mild asthmatics

Inhaled corticosteroids are advocated to be used as 1st line controller therapy in persistent asthmatics over and above intermittent short acting $\beta_2$-agonists. Moreover, regular use of short acting $\beta_2$-agonists demonstrates no benefit in long term asthma control. However, the question of whether mild persistent asthmatics now should be treated with inhaled corticosteroids in combination with LABAs arises, mainly in recognition of their demonstrated beneficial effects in patients with more severe disease over anti-inflammatory therapy as monotherapy.

A study by O’Byrne et al. evaluated the effects of placebo, budesonide 200 $\mu$g/day as monotherapy or combined with eformoterol in 698 corticosteroid naïve asthmatics. Symptomatic patients had a mean FEV$_1$ of approximately 90% predicted in all three randomised groups. After 1 year of treatment, those receiving budesonide alone had a 60% and 48% reduction in risk of first severe asthma exacerbation and rate of poorly controlled asthma days, respectively, compared to placebo. Budesonide treated patients also benefited from a reduction in symptoms and increase in FEV$_1$. Compared to inhaled corticosteroid alone, concomitant treatment with eformoterol conferred no other improvement other than significant (although unlikely to be clinically so) small improvements in FEV$_1$ (1.8% predicted, $P = 0.023$) and PEF (15 L/min, $P = 0.0001$). In the same study, 1272 mild asthmatics using $\leq$400 $\mu$g/day of inhaled corticosteroid were randomised to receive budesonide 200 $\mu$g/day, budesonide 200 $\mu$g/day plus eformoterol, budesonide 400 $\mu$g/day or budesonide 400 $\mu$g/day plus eformoterol. In these symptomatic patients (mean FEV$_1$ of approximately 86% predicted), the addition of eformoterol to either budesonide dose reduced the risk of first asthma exacerbation by 43% and poorly controlled asthma days by 30%, respectively. Adding eformoterol to budesonide 200 $\mu$g/day was more effective than doubling the dose of the latter in terms of asthma control.

Another study evaluated the effects of add-on eformoterol in mild patients receiving <400 $\mu$g/day of beclomethasone or equivalent. In this multi-centre study, 663 symptomatic mild asthmatics (mean PEF 74% predicted) were randomised to receive budesonide 800 $\mu$g/day plus either eformoterol or placebo. After 4 weeks, patients whose asthma was well controlled ($n = 505$) were randomised again to receive budesonide 400 $\mu$g/day plus eformoterol or placebo for further 6 months. It was discovered that the addition of eformoterol to either dose of budesonide resulted in more effective control of asthma. However, it is relevant to point out that comparison of additional effects of the LABA were only being made to placebo (and not for example a higher inhaled corticosteroid dose or alternative 2nd line controller). In another study, the combination of fluticasone 200 $\mu$g/day plus salmeterol was compared to fluticasone 200 $\mu$g/day alone in patients (mean PEF of around 80% predicted) only using short acting $\beta_2$-agonists for as required use. Compared to fluticasone alone, combination therapy conferred significant improvements in terms of daytime symptom scores and diurnal PEF over a 24 week period. No differences were observed in nighttime symptoms or frequency of short acting $\beta_2$-agonist use. Moreover, it is relevant to point out that no assessment of underlying inflammation or AHR was made, while a third randomised limb evaluating the comparative effects of double the dose of fluticasone (400 $\mu$g/day) would have been of potential interest.

In mild asthmatics there is generally a paucity of data concerning the use of LABAs in conjunction with inhaled corticosteroids with the consequence that definite conclusions are difficult to make. However, it is reasonable to believe that such patients with essentially normal lung function, should continue to be treated with an inhaled corticosteroid alone; those with persistent symptoms (and especially with impaired lung function) could proceed to have a therapeutic trial of LABA. However, further trials are required to compare the effects of initiating asthma treatment with an inhaled corticosteroid alone versus add-on LABA especially in mild asthmatics with both completely normal and also mildly impaired lung calibre. Ideally these should evaluate effects upon a variety of endpoints such as symptoms, lung function, biomarkers of airway inflammation, AHR and airway remodelling.

Moderate to severe asthmatics

An important early study into the use of LABAs evaluated 429 asthmatics uncontrolled on beclomethasone 400 $\mu$g/day. Individuals were rando-
mised to receive more than double their pre-existing inhaled corticosteroid dose (1000 μg/day) or add-on treatment with salmeterol for 6 months. Patients using concomitant LABA demonstrated greater lung function and fewer symptoms than those using inhaled corticosteroid alone, although no difference in exacerbation rates were observed between the two groups. It is also important to note that effects upon surrogate biomarkers of inflammation or AHR were not measured. In another study, Woolcock et al. randomised 738 asthmatics not controlled on beclomethasone 1000 μg/day to receive either double their inhaled corticosteroid dose, or addition of twice daily salmeterol 50 μg or 100 μg. No differences were observed upon exacerbation rates or AHR in all three groups, but patients who were treated with either dose of LABA benefited from fewer symptoms and a greater PEF. In the multicentre study by Pauwels et al., optimising the inhaled corticosteroid dose to 800 μg/day of budesonide and then adding eformoterol, resulted in a significantly reduced number of severe exacerbations compared to adding eformoterol to 200 μg/day of budesonide (a 49% versus 26% reduction, respectively). In other words, budesonide reduced exacerbations by its anti-inflammatory effect, while eformoterol produced a further reduction by stabilising airway smooth muscle in patients using the higher budesonide dose. In the same study, there was also a disconnect between lung function and exacerbations; in other words, despite a reduction in exacerbations, FEV1 and PEF were unchanged when increasing the dose of inhaled corticosteroid, or addition of twice daily salmeterol 50 μg or 100 μg. No differences were observed upon exacerbation rates or AHR in all three groups, but patients who were treated with either dose of LABA benefited from fewer symptoms and a greater PEF. In the multicentre study by Pauwels et al., optimising the inhaled corticosteroid dose to 800 μg/day of budesonide and then adding eformoterol, resulted in a significantly reduced number of severe exacerbations compared to adding eformoterol to 200 μg/day of budesonide (a 49% versus 26% reduction, respectively). In other words, budesonide reduced exacerbations by its anti-inflammatory effect, while eformoterol produced a further reduction by stabilising airway smooth muscle in patients using the higher budesonide dose. In the same study, there was also a disconnect between lung function and exacerbations; in other words, despite a reduction in exacerbations, FEV1 and PEF were unchanged when comparing budesonide 200 μg/day versus budesonide 800 μg/day. This indicates that when optimising the dose of inhaled corticosteroid, lung function is relatively distant from the underlying inflammatory process and despite no change in value, further beneficial clinical effects may actually be apparent. Thus, while endpoints such as lung function are of undoubted value, clinicians must not lose sight of the basic pathophysiological hallmarks of the asthma syndrome (i.e. AHR and inflammation) along with the impact of asthma pharmacotherapy upon exacerbations.

In a meta-analysis (n = 9 trials, 3685 patients), Shrewsbury et al. evaluated the effects of increasing the dose of inhaled corticosteroid versus the addition of salmeterol. Add on therapy with LABA tended to be superior on most lung function endpoints and symptoms. However, despite no trial included in the meta-analysis conferring a significant reduction in exacerbations, there was a small but significant reduction (2.4%) in severe exacerbations on pooling of the results.

**Interactions between inhaled corticosteroids and long acting β2-agonists**

Despite knowledge that co-administered inhaled corticosteroids plus LABAs are superior to doubling the dose of the former in terms of asthma control, it has previously been considered that both agents work independently of one another. In other words, inhaled corticosteroids exert potent anti-inflammatory effects while the LABA moiety relaxes airway smooth muscle. However, recent studies have demonstrated that beneficial synergism may occur on a molecular and histological basis.

Roth et al. evaluated the effects of budesonide and eformoterol (alone and in combination) upon transcription factors and cell proliferation. The combination of inhaled corticosteroid plus LABA provided a synergistic effect upon transcription factors and an inhibitory effect on smooth muscle cell proliferation. In another study, salmeterol enhanced the activation of the glucocorticoid receptor in primary human lung fibroblasts and vascular smooth muscle cells. In a placebo controlled study involving 45 symptomatic asthmatics receiving inhaled corticosteroids, the effects of supplemental salmeterol was examined in by way of changes in bronchial biopsy material. Patients treated with a LABA showed a significant reduction in blood vessel density in lamina propria which the authors suggested could have been as a direct consequence of modifications of angiogenic growth factors.

Conversely, corticosteroids have been shown to influence the effects of β2 adrenergic receptors. For example, they can regulate β2 adrenergic receptor function by increasing its expression through gene transcription. Moreover, they also demonstrate an inhibitory effects upon G–protein coupling and β2 adrenergic receptor downregulation, and in turn desensitisation.

In light of these observations, it can be seen that there is interplay between both moieties on a molecular level, however there is far less convincing evidence that the observed synergy between inhaled corticosteroids and LABA actually translates into "real-life" benefit. For example, in a randomised controlled crossover study in mild-to-moderate asthmatics (mean FEV1 80% predicted), fluticasone 500 μg/day plus salmeterol was compared to double the dose of fluticasone alone. The latter treatment conferred significant superiority in terms of surrogate inflammatory markers comprising of adenosine monophosphate threshold concentration and...
exhaled nitric oxide (Fig. 1). In another study, fluticasone 500 mg/day plus salmeterol in combination was no different from fluticasone 500 mg/day alone on exhaled nitric oxide, adenosine monophosphate threshold concentration and blood eosinophils (Fig. 2).

Thus, while data of Roth" and Eickelberg" show interesting in vitro observations to suggest a positive and beneficial interaction between the two moieties, this has not been substantiated by in vivo work. Nonetheless, inhaled corticosteroids and LABAs do provide complementary effects on inflammation and smooth muscle dysfunction, respectively, which frequently results in improved asthma control when taken together.

**Comparison of add on long acting β₂-agonists versus other 2nd line agents**

Prior to escalation of treatment, symptomatic asthmatics should have inhaler technique checked and compliance assessed, along with an effort to look for co-existent conditions such as allergic rhinitis or gastro-oesophageal reflux disease which may be contributing to symptoms. After doing so, current guidelines suggest that in asthmatics not controlled on a low-to-medium dose of inhaled corticosteroid (400–800 μg/day of beclomethasone or equivalent) a therapeutic trial of add-on LABA should be considered (step 3). Only in patients who subsequently remain symptomatic (step 4) or derive no benefit from the addition of a LABA, the addition of a leukotriene receptor antagonist (LTRA) or theophylline should be considered. Table 2 shows the relative properties of possible 2nd line controller therapies.

**Leukotriene receptor antagonists**

Despite transforming asthma management, inhaled corticosteroids do not suppress all aspects of inflammation. For instance, it has become apparent...
that eosinophilic inflammation can persist despite high doses of inhaled corticosteroids, while oral corticosteroids can cause an increase in the number of neutrophils. It is also of potential therapeutic importance that inhaled corticosteroids have a limited impact on the synthesis or release of cysteinyl leukotrienes.

The cysteinyl leukotrienes (C4, D4 and E4) are lipid mediators which are implicated in producing an array of effects such as bronchoconstriction, increased vascular permeability, mucous secretion, inflammatory cell recruitment and airway smooth muscle proliferation. Antagonism of the effects of cysteinyl leukotrienes can be achieved by drugs preventing their synthesis using a 5-lipoxygenase inhibitor, or blocking specific leukotriene receptors using a LTRA. Currently two LTRAs are licensed for clinical use in Europe, namely montelukast and zafirlukast. These drugs demonstrate bronchodilator and anti-inflammatory properties and can attenuate AHR to a variety of bronchoconstrictor stimuli. A further therapeutic benefit is that LTRAs exert their effects following single doses and are orally active. This latter property may enhance compliance especially in children, adolescents and the elderly in whom technical difficulties associated with and dislike of inhaled medication may occur. Furthermore, unlike LABAs, tolerance to their bronchoprotective effects has not been demonstrated.

A number of studies have performed head-to-head comparisons of add-on therapy with a LTRA compared to LABA in uncontrolled asthmatics using inhaled corticosteroids alone. In a double blind, double dummy, parallel group, multicentre trial over 12 weeks, it was demonstrated that the addition of salmeterol was superior to that of add-on montelukast 10 mg/day in uncontrolled asthmatics using inhaled corticosteroids. This was in terms of measures of lung calibre (the primary endpoint), salbutamol use and symptom scores. Similarly, in a multi-centre trial, Nelson et al. demonstrated that adding salmeterol to fluticasone was superior to concomitant treatment with zafirlukast 20 mg twice daily. Indeed, compared with oral zafirlukast, treatment with salmeterol conferred significantly greater improvements in pulmonary function, relief of both daytime and nighttime asthma symptoms and Asthma Quality of Life Questionnaire. It is pertinent to consider that in these studies, the primary endpoint was lung function which in turn can be considered as being "smooth muscle dependant", or in other words, one in which the effects of a LABA would likely be greater than those of a LTRA.

Two more recent studies have examined the effects of add-on LABA or LTRA in terms of exacerbation frequency. For example, 1490 chronic asthmatics uncontrolled on inhaled fluticasone 200 μg/day, were randomised to receive add-on montelukast 10 mg/day or salmeterol. After a year of treatment, 20.1% of patients in the montelukast group compared with 19.1% in the salmeterol group experienced an exacerbation of asthma, with no significant difference between randomised treatments. However, salmeterol treated patients had a greater FEV1 and morning PEF (P < 0.001), while the combination of fluticasone plus montelukast conferred a greater reduction (P = 0.011) upon blood eosinophils than add-on salmeterol. Moreover, similar to previous in vivo data, no potentiation of the anti-inflammatory effects of inhaled corticosteroids by the LABA moiety was observed in this study. In another multi-centre study using 1473 symptomatic asthmatics, the effects of add-on montelukast 10 mg/day or salmeterol to fluticasone 220 μg/day were evaluated. After 48 weeks, no significant difference in exacerbation frequency was observed between treatments. However, salmeterol improved lung function and symptom scores to a greater extent than montelukast, although the latter provided significantly greater effects upon blood eosinophils.

It can therefore be seen that in trials evaluating the addition of a LABA or LTRA, the choice of

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<th>Table 2</th>
<th>Relative effects of 2nd line add-on therapies to inhaled corticosteroids: ++, + and 0 represent, marked, some and no effects, respectively.</th>
<th>Long acting β2-agonist</th>
<th>Leukotriene receptor antagonist</th>
<th>Theophylline</th>
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<tr>
<td>Orally active</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Anti-Inflammatory properties</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>Effects upon airway hyperresponsiveness</td>
<td>+ (&quot;airway stabilising effect&quot;)</td>
<td>+</td>
<td>+</td>
<td></td>
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<tr>
<td>Bronchodilator properties</td>
<td>++</td>
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primary endpoint is crucial in determining which treatment confers superiority. Moreover, many trials in asthmatics have a prerequisite to entry of reversibility of 15% to short acting bronchodilator, irrespective of extent of underlying inflammation or AHR. While this is one of the classical feature in the diagnosis of asthma, it may not be representative of the asthmatic population at large and is not crucial in making the diagnosis. Indeed, many symptomatic asthmatics demonstrate preserved lung function which in turn suggests that underlying inflammation and AHR are the driving forces behind symptoms and exacerbations. It remains to be seen whether in future updated guidelines the addition of a LTRA to a low-to-moderate inhaled corticosteroid dose sits more comfortably beside add-on LABA.

Theophyllines

Theophyllines are phosphodiesterase inhibitors which have some additional effect in asthmatics when added to inhaled corticosteroids. They are weak bronchodilators and possess some anti-inflammation. Their use is frequently limited due to concerns of cardiac arrhythmias, gastrointestinal upset and the need for monitoring plasma levels due to a narrow therapeutic index. Moreover, there is considerable variation in the half-life of theophyllines and care requires to be taken in for example, smokers, patients with liver disease or heart failure and those taking certain drugs. A meta-analysis \((n = 9 \text{ trials, } 1330 \text{ patients})\) directly compared the effects of theophylline versus salmeterol in asthmatics and concluded that the use of a LABA was significantly superior in terms of lung function and symptoms along with a more favourable adverse effect profile.

Conclusions

The use of an inhaled corticosteroid plus LABA in a single inhaler is likely to continue to increase in popularity in view of its convenience, efficacy and beneficial effects upon exacerbation reduction. Moreover, this provides patients with a convenient and effective treatment which deals concomitantly with suppression of underlying inflammation and relaxation of bronchial smooth muscle. Patients are also likely to prefer this option, as compared to a higher inhaled corticosteroid dose, in view of better symptom control plus reducing the risk of local and systemic adverse sequelae.

Initial concerns regarding the problem of masking underlying inflammation with the LABA moiety has not been substantiated to any great degree. However, there are few data comparing their effects versus higher doses of inhaled corticosteroids in terms of airway remodelling. Indeed, in a study by Ward et al., significant reductions in basement membrane thickness did not occur until after 3 months of high dose inhaled corticosteroid treatment \((1500 \mu g/\text{day of fluticasone})\). Moreover, Reddel et al. demonstrated that patients starting with 3200 \(\mu g/\text{day of budesonide} \) had greater normalisation in AHR and fewer exacerbations than even 1600 \(\mu g/\text{day of budesonide} \). It is therefore important to ensure that untoward long-term sequelae do not occur at the expense of short-term superior bronchodilation with the use of LABAs. Further prospective studies incorporating surrogate inflammatory biomarkers and parameters reflecting airway remodelling are therefore required to fully evaluate the effects of combination inhalers versus, for example, double the inhaled corticosteroid dose.

It is also important for prescribing clinicians to be aware of the relative lack of data advocating their use in patients with very mild—although persistent—disease, especially when lung function \((\text{FEV}_{1})\) is not compromised. In other words, in many such patients airway calibre cannot be further improved and it is in fact the underlying airway inflammation and AHR which requires treatment with anti-inflammatory therapy to alleviate symptoms. Moreover, perhaps in these patients who have persistent symptoms despite the use of a low-to-moderate inhaled corticosteroid dose, the addition of a LTRA might be the more sensible pharmacological intervention in view of beneficial effects upon attenuating AHR and inflammation.

In more severe patients, the study by Pauwels succinctly demonstrated the benefits of optimising the inhaled corticosteroid dose to 800 \(\mu g/\text{day of budesonide} \), prior to introduction of a LABA. It is important to be aware however that there is a degree of interindividual variability in terms of response to inhaled corticosteroids. In other words, not all asthmatic patients require the same inhaled corticosteroid dose in which to suppress inflammation to a satisfactory degree and therefore at which point further 2nd line therapy is required for persistent symptoms varies. Indeed, the problem with conventional measures of asthma control remains the fact that they are distant from the pathophysiological hallmarks and merely reflect the clinical consequences of a cascade of complex cellular events. Moreover, “mean patients” are often created from the findings of multi-centre
randomised controlled trials and meta-analysis, the results from which have been derived from many thousands of individuals across a range of socio-economic backgrounds, asthma phenotype, age and racial background.

To overcome these difficulties in an ideal world, clinicians would have access to a reliable surrogate inflammatory biomarker (Table 3). This in turn would provide information as to when exactly corticosteroid responsive inflammation was adequately suppressed and when additional 2nd line controller therapy such as a LABA to maximally dilate the airway should be instituted. For example, in a study by Green et al., an asthma management strategy targeted against a surrogate inflammatory marker (sputum eosinophils) led to significantly fewer severe asthma exacerbations than using standard guidelines alone.20 Moreover, the effects on eosinophils and other inflammatory markers were dissociated from lung function and symptoms. However, the practicality of performing sputum induction in everyday clinical practice, especially in terms of obtaining instant feedback of the result for the patient in the clinic is questionable. Perhaps in the future, clinicians will have ready access to a convenient tool in which to monitor the extent of underlying airway inflammation, help tailor pharmacotherapy to individual patients and in turn reduce the burden of asthma in both primary and secondary care.

**References**

17. Nials AT, Ball DI, Butchers PR, et al. Formoterol on airway smooth muscle and human lung mast cells: a comparison

**Table 3** Characteristic features of the ideal surrogate inflammatory marker in asthma.

<table>
<thead>
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<th>Feature</th>
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<tr>
<td>Raised only in asthma</td>
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<tr>
<td>Raised only when endobronchial inflammation is present</td>
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<tr>
<td>Simple and cheap to measure</td>
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<tr>
<td>Easy to measure in primary and secondary care settings</td>
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<td>Patient acceptability</td>
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<td>Linear reduction on institution of anti-inflammatory therapy with clear cut dose-response effect</td>
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<td>Demonstrated to provide superior clinical control when used along with conventional measures than the latter alone</td>
</tr>
</tbody>
</table>

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