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REVIEW

Scientific rationale for using a single inhaler for asthma control

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ABSTRACT: Clinical trials have recently demonstrated that using a budesonide/formoterol combination inhaler as regular maintenance treatment twice daily but also as a rescue therapy for breakthrough symptoms can provide more effective control of asthma, particularly in reducing exacerbations, than using a short-acting β_2-agonist or formoterol as rescue therapy. This suggests that the corticosteroid component of the combination therapy plays an important role in rescue therapy.

Formoterol as a rescue therapy is effective in relieving symptoms by relaxing airway smooth muscle but is also likely to have important inhibitory effects on mast cells, plasma exudation and neutrophilic inflammation.

Inhaled corticosteroids have much more rapid suppressing effects on airway inflammation than previously recognised and the increased dose used as rescue therapy may prevent the increase in airway inflammation that occurs during the evolution of an exacerbation, thus preventing its development.

It is likely that the molecular interactions between β_2-agonists and corticosteroids also enhance the effect of the combination therapy as rescue therapy. There is now a strong scientific rationale for single inhaler therapy in asthma, but more research is now needed to better understand the mechanisms involved.

KEYWORDS: Asthma exacerbation, combination therapy, corticosteroid, inflammation, long-acting β_2-agonist, mast cell

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Inhaled corticosteroids are the mainstay of asthma therapy, but there is now compelling evidence that addition of a long-acting inhaled β_2-agonist (LABA; salmeterol or formoterol) gives better control in terms of reduced symptoms, improved lung function and reduced exacerbations in patients with mild, moderate and severe persistent asthma than increasing the dose of corticosteroids in patients not fully controlled on low doses [1–5]. This has led to the development of fixed combination inhalers, fluticasone/salmeterol (Seretide™/Advair™, GlaxoSmithKline), and budesonide/formoterol (Symbicort®, AstraZeneca), which are now increasingly used in asthma management [6, 7]. Combination inhalers are more convenient to use, control asthma at lower doses of corticosteroids, ensure that the corticosteroid is not discontinued when the LABA is added and are consistently cost-effective. Combination inhalers may also improve adherence to long-term therapy, which is notoriously poor in patients with inhaled corticosteroids used alone, accounting at least in part to the high proportion of asthmatic patients who remain symptomatic despite the availability of effective therapies [8]. There is a convincing scientific rationale for giving a corticosteroid and a LABA together, as they have complementary actions on the complex pathophysiology of asthma and may act synergistically at a molecular level [9].

A SINGLE INHALER FOR MAINTENANCE AND RELIEF: CLINICAL EVIDENCE

It is normal clinical practice to administer combination inhalers twice (sometimes once) daily at a dose that is related to the severity of asthma and to use a short-acting β_2-agonist (SABA), such as salbutamol, as required to relieve any breakthrough symptoms. Frequent use of the SABA indicates either poor compliance with inhaled corticosteroids or the need for a higher maintenance dose of the combination inhaler. A recent large global study involving

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3,000 patients attempted to achieve better, and if possible total, control of asthma, by progressively increasing the dose of the controller inhaler [10]. Control was more easily and rapidly achieved with the salmeterol/fluticasone combination inhaler than fluticasone alone and at a lower total dose of inhaled corticosteroid. However, some patients required rather high doses of the combination inhaler to achieve satisfactory control of their asthma and a proportion of patients had continuing symptoms despite maximum therapy.

In a departure from the conventional dosing regime for combination inhalers as a fixed maintenance dose, a new approach is the use of the budesonide/formoterol combination for symptom relief, rather than the conventional use of a SABA, such as salbutamol or terbutaline. Previous studies have shown that formoterol is an effective reliever medication in asthma, as it has a rapid onset of action with a long bronchodilator effect, yet systemic side effects are of a similar duration to a SABA so that cumulative dosing is possible [11–13]. Repeated dosing with formoterol/budesonide in acute severe asthma has similar efficacy to salbutamol [14], but with a more favourable safety profile [15]. A budesonide/formoterol inhaler has similar efficacy to formoterol alone as a reliever therapy in acute severe asthma [16]. By contrast, salmeterol has an equivalent bronchodilator effect but a slower onset of action and systemic side effects more prolonged than those of formoterol [17–19]. Furthermore, formoterol has a steeper bronchodilator and bronchoprotective dose-response curve than salmeterol, with a greater improvement at higher doses, which probably reflects the fact that formoterol is a full agonist, whereas salmeterol is a partial agonist [20, 21].

Safety of LABA

Recently, concerns have been raised about the safety of LABA in the management of asthma and this is clearly particularly relevant to the use of a LABA in treating exacerbations. A controlled trial of salmeterol *versus* placebo in >26,000 patients with asthma showed a small but significant excess of asthma mortality and life-threatening events in the LABA-treated patients, raising concerns that this treatment may be causally related to the increased deaths [22]. Subgroup analysis showed that the great majority of these deaths occurred in inner city African-Americans and it is very likely that this can be explained by failure to use concomitant inhaled corticosteroids, as recommended in clinical practice. It is also possible that this could be explained by genetic differences in β_2-receptors in this group. A meta-analysis that included this study with other smaller studies, including those with formoterol treatment, concluded that LABA may increase severe exacerbations and mortality but did not analyse whether this effect was not seen if patients were treated with concomitant inhaled corticosteroids [23]. The likely cause of increased mortality associated with increased use β_2-agonists is over-reliance on a bronchodilator that does not treat the underlying inflammatory disease, which requires inhaled corticosteroid therapy, and the fact that there is confounding by severity, so patients with more severe asthma and exacerbations take higher doses of inhaled β_2-agonists [24]. The problem of safety should be resolved by using concomitant corticosteroids in the form of a fixed combination inhaler. There are extensive data on the safety of combination inhalers, often in high doses, over periods of up to 12 months in asthmatic patients of varying severity. These studies have shown a further reduction in severe exacerbations compared to corticosteroids alone and there are no safety concerns in terms of adverse effects [1, 3, 10].

Clinical trials of SMART

A double-blind controlled parallel group study (involving over 2,500 patients) showed that when budesonide/formoterol was used as maintenance therapy twice daily and additional puffs of the combination inhaler were used as needed for symptom relief, there was a greater improvement in lung function and symptoms compared with using the same dose of budesonide/formoterol or with four times the dose of budesonide alone, both with terbutaline as reliever [25]. The conventional regimes essentially confirm previous studies using separate formoterol and budesonide inhalers [1, 3]. This suggests that a single inhaler can be used for maintenance and relief and has been described as the single inhaler for maintenance and relief therapy (SMART) approach. The most striking difference between these treatment regimes was the marked reduction in severe and mild exacerbations in the single inhaler group, accompanied by a reduced need for courses of oral corticosteroids. Importantly, asthma was controlled more effectively using the single inhaler approach than with budesonide plus a SABA and at a lower total dose of corticosteroids [26]. An unexpected finding was that the treatment with a SMART approach markedly reduced the number of severe exacerbations (the primary outcome measure) over the 1-yr treatment period compared with the other treatments, but also reduced the need for oral corticosteroids, and improved symptom control and lung function compared with the other treatment regimes [25]. A concern about this approach is that some patients might end up using the combination inhaler frequently and receive an unacceptably high dose of inhaled corticosteroid. However, this was not the case, as the mean number of additional doses of combination inhaler was only one dose per day and very few patients required high doses.

Combination inhalers have generally been less effective in children with asthma [27], as LABA do not appear to have such a large add-on effect. In the study by O'Byrne *et al*. [25], children aged 4–11 yrs (12% of study population) were also included, and showed an even more striking reduction in the number of exacerbations that required oral steroids (~80% reduction) with budesonide/formoterol inhaler as a rescue therapy compared with using terbutaline as a reliever. The reasons why children should respond so well to this approach is uncertain but may be due to the fact that their asthma tends to be more labile than in adults.

An important question is how can these unexpectedly good results of the SMART approach be explained mechanistically? The difference between the single combination inhaler and SABA as relievers is the simultaneous administration of a corticosteroid in the combination, suggesting that the relief corticosteroid may play a key role in reducing exacerbations. A recent open study showed that single inhaler therapy with the combination inhaler as rescue therapy was similar to using the same fixed-dose combination therapy with formoterol alone as rescue therapy in terms of the number of additional puffs needed to control symptoms [28]. In a recent large

double-blind study which compared formoterol to budesonide/formoterol as reliever therapy [29], the combination inhaler was significantly better than using formoterol alone as reliever in reducing exacerbations, providing strong support for the idea that the ''as required'' additional use of corticosteroid plays a critical role in reducing asthma exacerbations and improving asthma control.

Analysis of >400 severe exacerbations that were documented in the Formoterol and Corticosteroid Establishing Therapy (FACET) study, which compared the addition of formoterol to budesonide with increased doses of budesonide [1], showed that exacerbations (defined by the need for oral corticosteroids or hospitalisation) are not explosive events, as previously believed, but evolve slowly over several days until the clinical worsening prompts the introduction of oral corticosteroids [30]. The pattern of exacerbations was not changed by either high doses of budesonide or the addition of formoterol. The most sensitive index of worsening asthma was the increased need for rescue β_2-agonists, followed by a fall in peak flow and an increase in night-time symptoms.

FORMOTEROL FOR ACUTE EXACERBATIONS

Airway smooth muscle relaxation

Formoterol has a rapid onset of bronchodilator action and this is mediated mainly by a relaxing effect on contracted airway smooth muscle. Formoterol as a reliever gives rapid and sustained relief of symptoms during an exacerbation [31]. As expected, budesonide/formoterol also gives rapid bronchodilatation, which mirrors the action of formoterol on methacholine-induced bronchoconstriction [18] and equivalent bronchodilator effects to a high dose of salbutamol in treating acute severe asthma [15]. The bronchodilator response to formoterol shows a small reduction during initiation of treatment due to the rapid development of tolerance but this does not progress [32]. Tolerance to the bronchodilator effects of β_2-agonists is not clinically important and this may reflect the large β_2-receptor reserve (''spare receptors'') in airway smooth muscle cells, so that loss of receptors has no effect on the functional response to β_2-agonists. Concomitant treatment with an inhaled corticosteroid may further reduce the development of tolerance.

In addition to its direct bronchodilator effect, formoterol may also have important nonbronchodilator effects that may contribute to its efficacy in relieving an exacerbation.

Reduced plasma exudation

Airway oedema is present during an exacerbation and may contribute to airway narrowing. Formoterol is effective in inhibiting plasma leakage in the airways through an action on β_2-receptors on the endothelial cells of post-capillary venules, the major site of plasma leakage [33, 34]. This relaxes the cells and closes the gaps to prevent further oedema formation. Unfortunately, it is not possible to quantify oedema in asthma exacerbations directly with currently available techniques. However, measurement of sputum α_2-macroglobulin, a plasma marker, is significantly reduced by formoterol after histamine-induced increase in leakage in normal subjects [35], indicating that therapeutic doses of formoterol are able to inhibit plasma exudation. The anti-leakage effect of β_2-agonists shows the development of tolerance when high doses are used, but it is not certain if this is prevented by corticosteroids [36].

Mast cell stabilisation

Mast cells play a key role in exacerbations of asthma through the release of bronchoconstrictor mediators, such as cysteinyl-leukotrienes, prostaglandins and histamine. Human lung mast cells express β_2-adrenoceptors, although in rather low density, and β_2-agonists inhibit the release of bronchoconstrictor mediators, including cysteinyl-leukotrienes and histamine [37]. This can be demonstrated in asthmatic patients *in vivo* by the greater protective effect of β_2-agonists against adenosine-induced bronchoconstriction, which is mast cell dependent, compared to direct bronchoconstrictors, such as histamine or methacholine [38, 39]. The protective effect of formoterol against adenosine monophosphate (AMP)-induced bronchoconstriction can be seen 2 h after administration, indicating a rapid mast cell stabilisation effect [40].

The mast cell response to β_2-agonists becomes rapidly tolerant *in vitro*, reflecting the low receptor density of β_2-receptors on these cells [41, 42]. In asthmatic patients, there is tolerance to the mast cell protective effect of β_2-agonists (against adenosine and allergen), but not to the protective effect against direct bronchoconstrictors [43, 44]. A corticosteroid can reverse the tolerance to β-agonists in mast cells *in vitro* [45]. This suggests that regular treatment with inhaled corticosteroids should prevent the tolerance to the mast cell stabilising effects of β_2-agonists and this may be an important mechanisms in reducing asthma exacerbations, as in the FACET study, and with combination inhalers.

Reduced neutrophils

β_2-Receptors are expressed on human neutrophils and β_2-agonists inhibit the release of reactive oxygen species [46, 47]. This response is rapidly tachyphylactic, reflecting the low density of β_2-receptors on these cells. In animal models of neutrophilic inflammation, such as lipopolysaccharide-induced lung inflammation in mice, β-agonists have an inhibitory effect on neutrophil recruitment to the lung [48], which may be mediated by an inhibitory effect on the adhesion molecule CD11b on the cell surface [49]. Clinical studies have shown that in patients with mild asthma there is a decrease in neutrophils in bronchial biopsies and bronchoalveolar lavage after treatment with salmeterol, as well as a reduction in myeloperoxidase and human neutrophil lipocalin, indicating an inhibitory effect of neutrophil degranulation [50]. A recent study in patients with mild asthma showed that formoterol significantly reduced the number of neutrophils in induced sputum as well as the concentration of interleukin (IL)-8, whereas an inhaled corticosteroid was without effect [51]. The corticosteroid, but not the LABA, reduced sputum eosinophil counts as expected. There is debate about the functional role of neutrophils in asthma, but it is likely that activation of neutrophil products released during exacerbations, including reactive oxygen species, have detrimental effects.

INHALED CORTICOSTEROIDS FOR ACUTE EXACERBATIONS

Traditionally, it was believed that inhaled corticosteroids have a slow onset of action in asthma with some effects, such as reducing airway hyperresponsiveness, taking several months

to achieve a maximal response. However, other clinical responses occur more rapidly and reduction of symptoms is usually apparent after several days of therapy. More recently, there has been increasing evidence that corticosteroids have a relatively rapid suppressive effect on inflammation.

Molecular mechanisms of action

Inhaled corticosteroids cross the cell membrane of target cells in the airways, of which epithelial cells appear to be the most important. There have been important advances in understanding the molecular mechanisms for the anti-inflammatory effects of corticosteroids [52, 53]. Corticosteroids bind to glucocorticoid receptors (GR) in the cytoplasm, which then rapidly translocate to the nucleus of the cell. Some genes have a recognition site(s) in their promoter region for the activated GR dimer known as a glucocorticoid response element (GRE) and are activated by the interaction with the GR. A good example of gene activation by corticosteroids is the β_2-receptor; a significant increase in β_2-receptors in human lung *in vitro* can be detected as early as 2 h after exposure to a corticosteroid [54]. An important anti-inflammatory enzyme that is activated by corticosteroids is mitogen-activated protein kinase phosphatase (MKP)-1, which is the endogenous inhibitor of mitogen-activated protein (MAP) kinase pathways that are proinflammatory. Corticosteroids induce a rapid 10-fold increase in MKP-1 mRNA within 2 h of exposure and an increase in MKP-1 protein within 4 h, with concomitant inhibition of MAP kinase cell signalling [55]. However, the major anti-inflammatory effects of corticosteroids are mediated through suppression of inflammatory genes that have been activated by pro-inflammatory transcription factors, such as nuclear factor (NF)-κB, which activate transcription through acetylation of core histones around which DNA is wound. The activated GR recruits a nuclear enzyme, histone deacetylase (HDAC)-2 to the activated inflammatory gene complex, resulting in deacetylation of core histones and suppression of inflammatory genes [56]. A key action of HDAC2 is to deacetylate the acetylated form of GR so that it can inhibit NF-κB [57]. Time-course studies show that these actions of corticosteroids occur within minutes. Once the inflammatory gene is switched off the encoded inflammatory proteins, such as a cytokines, decay at a rate determined by the stability of their mRNA. For many inflammatory genes, such as granulocyte-macrophage colony stimulating factor and chemokines, this decay is relatively rapid and thus there is significant reduction in the secretion of the cytokine or chemokine within 6–12 h. This demonstrates that corticosteroids have relatively rapid anti-inflammatory actions *in vitro*.

Rapid anti-inflammatory effects in clinical studies

A rapid anti-inflammatory effect of inhaled corticosteroids was demonstrated with a single high dose of inhaled budesonide (2,400 μg) with a significant reduction in sputum eosinophils and increased protection against hypertonic saline-induced bronchoconstriction only 6 h after administration of treatment in patients with mild asthma [58]. Protection against the bronchoconstrictor effect of AMP appears to be a very sensitive response to corticosteroids in asthma [59, 60] and is likely to be due to a rapid inhibitory effect of the inhaled corticosteroid on mucosal mast cells. A significant reduction in bronchoconstrictor response to inhaled AMP was seen as early as 2 h after a single inhalation of 100 μg fluticasone with no significantly greater protection seen with 1,000 μg fluticasone [61]. However, there was no protective effect against histamine-induced bronchoconstriction, suggesting that the inhaled corticosteroid was acting on mast cells. The mechanism for this rapid effect of corticosteroids on mast cell activation is not yet understood but may be explained by migration of mast cells away from the mucosal surface or rapid apoptosis of mast cells. Cytokines from T-helper (Th)-2 cells play an important role in orchestrating airway inflammation in asthma through the release of specific cytokines, and particularly on the infiltration of eosinophils, which is mediated by interleukin-5. The present author has shown that nasal grass pollen challenge gives a rapid increase in Th2 cytokines, including IL-5, measured by direct nasal sampling, and that this is completely inhibited by pre-treatment for 30 min with an inhaled corticosteroid [62]. This is likely to be due to an inhibitory effect of corticosteroids on the transcription factor GATA-3 in Th2 cells which regulates the synthesis of Th2 cytokines. This presumably contributes to the rapid inhibitory effect of inhaled corticosteroids on sputum eosinophils [58], although there may be additional effects mediated *via* the suppression of eosinophil chemotactic factors, such as eotaxins from epithelial cells [63]. Increased concentrations of exhaled nitric oxide (NO) reflect airway inflammation in asthmatic patients and are rapidly reduced by inhaled budesonide, with a significant effect 2 days after commencing treatment [64]. In an unpublished study, it has also been demonstrated that nebulised budesonide caused a significant reduction in exhaled NO 6 h after administration (S.A. Kharitonov and P.J. Barnes; unpublished data).

Inhaled corticosteroids cause rapid blanching of the skin when applied topically (McKenzie test), which may be due to vasoconstriction of dermal vessels, but the mechanisms of action of skin blanching are not understood. The equivalent response has been demonstrated in the airways of asthmatic patients with reduced airway blood flow 30 min after administration of an inhaled corticosteroid [65, 66]. This mechanism may reduce airway oedema and therefore contribute to the effect of inhaled corticosteroids on evolving inflammation in the airways.

These studies suggest that inhaled corticosteroids have a relatively rapid anti-inflammatory effect, suppressing inflammation within 6 h and persisting for several hours. In the context of rescue therapy with budesonide/formoterol, this could prevent the evolution of an acute exacerbation by suppressing the increase in inflammation, thus resulting in marked reduction in the number of mild and severe exacerbations. Thus, both budesonide and formoterol have inhibitory effects on the inflammatory process during an exacerbation (fig. 1).

INTERACTIONS BETWEEN β_2-AGONISTS AND CORTICOSTEROIDS

There is increasing evidence that there are positive interactions between β_2-agonists and corticosteroids [9] (fig. 2). These interactions may contribute to the efficacy of combination therapy as a rescue therapy as well as a maintenance treatment.

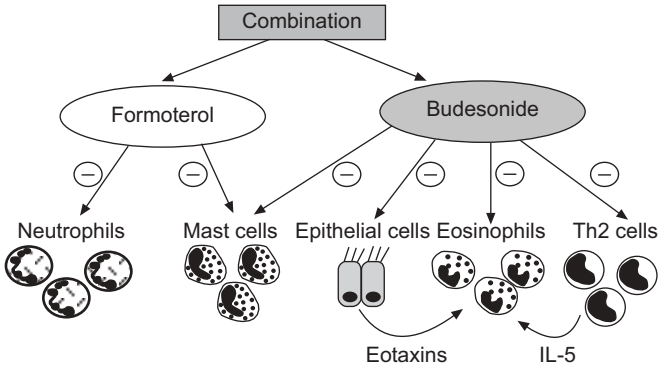

FIGURE 1. Anti-inflammatory effects of a budesonide/formoterol inhaler relevant to asthma exacerbations. Formoterol has inhibitory effects on neutrophils and mast cells, whereas budesonide also inhibits mast cell function and also inhibits T-helper (Th)-2 cells and epithelial cells, resulting in reduced eosinophils. IL: interleukin.

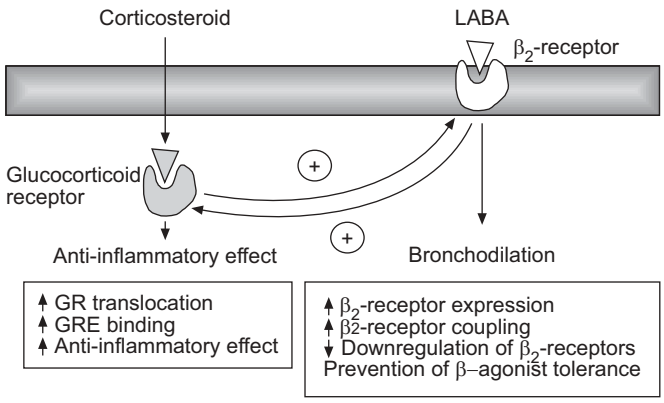

FIGURE 2. Interaction between corticosteroids and long-acting β_2-agonists (LABA). Corticosteroids have anti-inflammatory effects but also increase the numbers of β_2-receptors, whereas β_2-agonists, as well as inducing direct bronchodilatation, act on glucocorticoid receptors (GR) to increase the anti-inflammatory effects of corticosteroids. GRE: glucocorticoid response element.

Effect of corticosteroids on β_2-receptors

Corticosteroids increase the transcription of the β_2-receptor gene, resulting increased expression of β_2-receptors at the cell surface. This can be demonstrated in human lung *in vitro* [54] and in the nasal mucosa *in vivo* after application of a topical nasal corticosteroid [67]. As discussed above, these effects of corticosteroids on increased β_2-expression occur rapidly within a few hours. In experimental animals, corticosteroids prevent the downregulation of pulmonary β_2-receptors and tolerance that occurs after prolonged β_2-agonist administration [68] and reverse the uncoupling of β_2-receptors that occurs after exposure to β_2-agonists [69]. This suggests that treatment with inhaled corticosteroids may prevent the development of tolerance to LABA. This may not be relevant to the bronchodilator response to β_2-agonists due to the large β_2-receptor reserve in airway smooth muscle cells, but may be relevant to the nonbronchodilator effects of β_2-agonists where there is no such receptor reserve. Thus, β_2-agonists may preserve the response to β_2-agonists in mast cells and neutrophils, which would normally rapidly develop tachyphylaxis in response to β_2-agonists. This would be relevant in the use of budesonide/formoterol as rescue therapy as the acute effects of formoterol and mast cells and neutrophils may be preserved by the maintenance treatment with inhaled budesonide.

Effect of β_2-agonists on corticosteroid responses

There is growing evidence to show that β_2-agonists enhance the action of corticosteroids, particularly through enhancing the translocation of GR. This has been demonstrated in cultured airway smooth muscle cells and airway epithelial cells *in vitro* [70, 71]. The molecular basis for this effect of β_2-agonists is not yet understood but is more marked with LABA compared with SABAs, suggesting that a prolonged action for β_2-agonists is necessary. Salmeterol enhances the GR translocation in response to a corticosteroid in epithelial and macrophage cell lines with an increase in GRE binding of GR [72].

Functional studies have demonstrated that a LABA increases the anti-inflammatory effects of corticosteroids in airway smooth muscle cells [73]. The interaction between corticosteroids and β_2-agonists may be very relevant in airway smooth cells. Corticosteroids increase the expression of β_2-receptors in airway smooth muscle cells through increasing gene transcription and may thus enhance the bronchodilator response to β_2-agonists [68]. In turn, LABAs increase the nuclear translocation of GRs in human airway smooth muscle cells and increase the activation of a transcription factor, CCAAT enhancer binding protein-α, which regulates several genes including those involved in smooth muscle proliferation [70]. Airway smooth muscle cells are now recognised to be an important source of inflammatory mediators in the airways of asthmatic patients through the expression of multiple proinflammatory genes, including those that encode chemokines, such as CXCL8, CXCL1, CCL3 and CCL5, which are involved in neutrophil and eosinophil recruitment into the airways [74]. The enhancement of the anti-inflammatory effects of corticosteroids by LABA in chronic obstructive pulmonary disease may therefore enhance the anti-inflammatory effect of corticosteroids in suppressing acute inflammation.

In induced sputum cells from asthmatic patients, both formoterol and salmeterol enhanced the nuclear translocation of GRs in response to a corticosteroid *in vitro*, and in parallel enhanced the suppressive effect of the corticosteroid on the release of CXCL8 and CCL5 [75]. In cultured human airway epithelial cells, there is a synergistic suppression of rhinovirus-induced release of chemokines (particularly those involved in lymphocyte recruitment) by a combination of salmeterol and fluticasone [76]. This is very relevant to exacerbations of asthma since rhinovirus infections are the commonest cause of severe asthma exacerbations. There is also evidence that these interactions between β_2-agonists and corticosteroids occur in asthmatic patients *in vivo*. Inhaled fluticasone induces a dose-related increase in translocation of GR in macrophages obtained by induced sputum in patients with mild asthma. Inhaled salmeterol, which does not itself enhance GR nuclear translocation, significantly enhances the translocation in response to low doses of fluticasone so that they reach the same levels of translocation as seen with high doses of the corticosteroid [72]. These studies suggest that there is a

two-way interaction between β_2-agonists and corticosteroids, with each drug enhancing the effect of the other, and this interaction is likely to be relevant in the use of budesonide/formoterol as a rescue therapy.

FUTURE DEVELOPMENTS

The single inhaler approach to therapy is very effective, particularly in reducing asthma exacerbations, is simple for patients to follow and is cost-effective. It is likely that this will become a widely used approach to asthma management in the future and will be useful for children as well as adults. It is likely that adherence may be better for this approach as the rescue therapy is symptom guided, but ensures increased anti-inflammatory effects when they are most needed. The use of formoterol, but not salmeterol, allows flexible dosing, so other combinations of a corticosteroid with formoterol are now in clinical development, including beclomethasone dipropionate, fluticasone and ciclesonide. A fixed combination pressurised metered-dose inhaler with beclomethasone dipropionate/formoterol has now been developed and shows similar efficacy to the other combination inhalers as a maintenance therapy [77]. It is likely that these combinations with formoterol will be suitable for single inhaler therapy, but specific studies need to be done. Ultra-long-acting β_2-agonists, such as indacaterol, carmoterol and GSK-159797, are now also in clinical development [78], but it is not yet known whether they are also suitable for flexible dosing.

Clinical effectiveness studies using the single inhaler approach in the ''real world'' are now needed. The use of combination inhalers as rescue therapy is likely to increase compliance or at least to compensate for the poor compliance with regular maintenance therapy. This also complies with what patients do when their asthma worsens with an increase in the use of rescue medication as they first become aware of worsening asthma, but no increase in their maintenance therapy with either corticosteroid inhalers alone or combination inhalers [79]. This suggests that patients take their rapidly acting reliever to obtain symptom relief, but if this strategy also delivers an increased dose of corticosteroid at a time when inflammation is worsening, this might explain why single therapy is so effective against exacerbations. Although it is logical to take maintenance treatment as well as reliever therapy with a combination inhaler, it may also be possible to control asthma, at least in milder patients, with the combination used as reliever therapy alone since the corticosteroid will be taken at the time of clinical need.

Specific studies on children are needed, in view of the promising results of the single inhaler approach in the young patients included in the recent SMART studies [25]. The results to date look very promising in view of the disappointing effects of adding LABA to inhaled corticosteroids in children and suggest that timing the combination inhaler is appropriate to childhood asthma where there is likely to be a greater liability of the airways and less structural abnormalities.

More research is needed on the mechanisms of action of combination inhalers as rescue therapy with invasive and noninvasive measurements of airway inflammation. At a molecular level, a better understanding of how β_2-agonists interact with corticosteroid signalling pathways is needed. The mechanism whereby β_2-agonists enhance nuclear translocation of the GR is not yet understood but is likely to involve phosphorylation of some other modification of the receptor that allows more effective nuclear import. The recent study on the synergistic interaction between a LABA and a corticosteroid in suppressing the inflammatory response to rhinovirus infection of epithelial cells is of particular relevance as many severe exacerbations are precipitated by rhinovirus infections [76]. The molecular mechanisms for the rapid action of corticosteroids in exacerbations are not completely understood and measurements of inflammatory biomarkers may shed light on this.

There is little doubt that single inhaler therapy will revolutionise asthma therapy, providing more effective control and allowing asthma to be controlled with lower doses of inhaled corticosteroids. Although, as discussed above, there exists some understanding of how this strategy may be working, more studies on cellular and molecular mechanisms are needed, particularly as this approach may become the mainstay of asthma treatment in the future.

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