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REVIEW

Scientific rationale for inhaled combination therapy with long-acting β_2-agonists and corticosteroids

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Scientific rationale for inhaled combination therapy with long-acting β_2-agonists and corticosteroids. P.J. Barnes. ©ERS Journals Ltd 2002.

ABSTRACT: The addition of an inhaled long-acting β_2-agonist (LABA) to an inhaled corticosteroid (ICS) gives optimal control of asthma in most patients and two fixed combination inhalers (salmeterol/fluticasone and formoterol/budesonide) are increasingly used as a convenient controller in patients with persistent asthma. There is a strong scientific rationale for the combination of these two drug classes.

ICS suppress the chronic inflammation of asthma and reduce airway hyperresponsiveness and this is achieved at low doses in most patients. LABA act on different aspects of the pathophysiology of asthma. In addition to their bronchodilator action, LABA also inhibit mast cell mediator release, plasma exudation and may reduce sensory nerve activation. Thus these two classes of drug address complementary aspects of the pathophysiology of asthma that neither drug class is able to achieve alone.

There are several positive interactions between LABA and ICS. Corticosteroids increase the expression of β_2-receptors by increasing gene transcription. Experimentally this protects against the loss of β_2-receptors in response to long-term exposure to β_2-agonists. While this is unlikely to be important in bronchodilator responses to β_2-agonists, in view of the large β-receptor reserve, it is probably important in preventing loss of β-agonist effects on the nonbronchodilator actions of LABA discussed earlier. β_2-Agonists may potentiate the molecular mechanism of corticosteroid actions, with increased nuclear localization of glucocorticoid receptors and additive or sometimes synergistic suppression of inflammatory mediator release. Thus LABA and ICS may optimize each others beneficial actions in the airways, but the low systemic effects of these drugs do not result in any increase in adverse effects.

Long-acting β_2-agonists corticosteroid inhaler therapy is therefore a logical advance and results in effective control of asthma in the majority of patients without significant adverse effects. This simplified approach to long-term asthma therapy has a strong scientific rationale.

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Inhaled β_2-agonists are the most effective bronchodilators, and inhaled corticosteroids (ICS) the most effective controllers currently available for asthma management. Most patients with persistent asthma in European countries now receive both classes of treatment, in accordance with international guidelines for asthma management [1]. The inhaled long-acting β_2-agonists (LABA) salmeterol and formoterol have a bronchodilator action of 12 h and have been an important new addition to the therapy for asthma. LABA, the new symptom controllers of asthma, are playing an increasingly important role in the management of persistent asthma, particularly when it is moderate and severe [2]. Many studies have now demonstrated the clinical benefit of adding a LABA to ICS in patients with mild, moderate and severe persistent asthma. Indeed, the combination of LABA and ICS is now the most effective means of controlling asthma in the majority of patients. This has led to the logical development of fixed combination inhalers that contain a LABA and corticosteroid in the same inhaler device (LABACS) [3–5]. This review discusses the scientific rationale for combining an inhaled LABA with a corticosteroid.

Clinical studies

Long-acting β_2-agonists as add-on therapy

A landmark study in 1994 showed that asthmatic patients not controlled on a low dose of ICS (beclomethasone dipropionate 400 μg daily) had little improvement in asthma control if the dose was increased (1000 μg daily), but much greater improvement in symptoms and lung function if salmeterol was added [6]. This was surprising at the time, as it was believed that asthma was a consequence of airway inflammation and that control could be achieved by increasing the dose of corticosteroids to suppress the residual inflammation. Furthermore, it was already clear that LABA do not have anti-inflammatory

effects like corticosteroids [7, 8]. The superiority of salmeterol compared to increasing the dose of ICS was confirmed in more severe asthmatic patients [9] and subsequently in a meta-analysis of nine studies, all indicating that addition of salmeterol was superior to doubling (or more) the dose of ICS [10]. Similarly, addition of formoterol to ICS is more effective than a four-fold increase in the dose of inhaled budesonide in patients with moderate and severe asthma, and this add-on benefit persisted for the 12 months of the study, demonstrating that tolerance does not develop with prolonged therapy [11]. Although addition of a LABA improved lung function and symptoms there was concern that the lack of anti-inflammatory effect would mask the underlying chronic inflammation and that this may lead to increased numbers of exacerbations. In this study formoterol reduced the number of mild and severe exacerbations when added to a low and even high dose of inhaled budesonide. Furthermore, the pattern of exacerbations was unchanged, with no evidence that they were more rapid in onset, more severe or more prolonged [12]. This makes it unlikely that addition of formoterol is masking underlying inflammation. This has been specifically addressed in a follow-on study that looked at the effect of the high dose of budesonide compared to the low dose with added formoterol on eosinophils in induced sputum, following the same experimental design. In both treatment groups sputum eosinophilia was suppressed with no difference between the treatments [13]. These results have recently been mirrored in a similar trial design in patients with mild persistent asthma in whom even lower doses of budesonide were used [14].

Other add-on therapies

Other classes of drug are also effective as add-on therapies in persistent asthma. Low-dose theophylline is a useful add-on therapy in patients on low to high doses of inhaled corticosteroids [15–17]. It may be particularly useful in patients with severe disease as it appears to have some anti-asthma effect that is not provided by ICS. However a recent systematic review concluded that it is somewhat less effective as an add-on therapy than salmeterol but with an increased risk of adverse effects [18]. However, there may be some patients in whom it is more effective.

Antileukotrienes are also used as an add-on therapy, but there are relatively few studies documenting their benefit. Montelukast appears to have some benefit when added to low doses of ICS [19], but is less effective as an add-on therapy than salmeterol [20, 21] and is ineffective in patients with severe asthma [22]. However, it is possible that some patients may do well with antileukotrienes and may be identified by molecular genetic profiling in the future.

Dose-response to corticosteroids

Although ICS have been used in the treatment of asthma for >30 yrs it is only recently that the dose-response to their effects has been studied in detail. This is partly because it is not possible to carry out a cumulative dose/response in individual patients because of the slow and variable onset of the beneficial effects. So for each dose, a large number of patients are needed in view of the variability of the response between patients. Dose/response studies have demonstrated that in patients with moderate asthma there is a relatively flat dose/response curve, with most of the benefit obtained at the lowest doses [23–26]. This presumably means that the inflammation is suppressed by a relatively low dose of corticosteroids in most patients and that higher doses achieve no greater clinical benefit but only increase the risk of systemic side-effects. Some evidence for this was found using measurements of exhaled nitric oxide (NO) as a non-invasive maker of airway inflammation in asthma. In this study the dose/response to inhaled steroid was also relatively flat [27]. The flatness of the dose/response to ICS means that most of the benefit of ICS is obtained at relatively low doses in most patients, but that other classes of drug given as add-on therapy can provide some benefit not provided by corticosteroids. LABA are the most effective add-on therapy and this suggests that β_2-agonists must be exerting some additional action on the airways that is complementary to the effect of corticosteroids.

Nonbronchodilator effects of β_2-agonists

Although relaxation of airway smooth muscle is the major bronchodilator mechanism of β_2-agonists, β_2-adrenergic receptors are widely distributed in the airways and β_2-agonists may affect other cellular functions, particularly inflammatory cells, that may be relevant in asthma control [28]. Three of the mechanisms that may be relevant to the effects of LABA in asthma will be discussed.

Mast cells

β-Agonists inhibit the release of histamine from both chopped human lung and dispersed human lung mast cells *via* β_2-receptors, but this effect if often variable between preparations [29]. Both short-acting and long-acting β_2-agonists are effective in inhibiting the release of histamine and cysteinyl-leukotrienes *in vitro* [30, 31]. The inhibitory effect of β_2-agonists is mediated *via* a sustained increase in cyclic adenosine 5′-monophosphate (AMP) [32]. In some human mast-cell preparations salbutamol acts as a partial agonist, having less effect than the full agonist isoprenaline, and in these preparations there is evidence for receptor reserve, whereas in other preparations there appears to be no receptor reserve [29]. The reasons for these differences are not yet understood, but it may indicate that there are different effects between patients.

Functional evidence suggests that inhaled β-agonists may have an effect on mast cells *in vivo* since a nebulized β-agonist has a significantly greater effect on AMP-induced bronchoconstriction than on histamine- or methacholine-induced bronchoconstriction [33, 34]. This increased protective effect is also

seen after the normal therapeutic dose of β-agonist from a metered-dose inhaler [34]. The increased protection against AMP challenge compared with the directly-acting constrictors may reflect an additional effect on airway mast cells, since AMP-induced bronchoconstriction in asthmatics is reduced by an antihistamine [35], and adenosine-induced constriction of asthmatic bronchi *in vitro* is inhibited by histamine and leukotriene antagonists [36]. Formoterol has a greater protective effect against AMP than against histamine challenge, whereas these differences are less marked with salbutamol and salmeterol [37, 38]. This difference between salmeterol and formoterol may be due to the differences between a nearly full agonist and a partial agonist, if occupation of all β_2-receptors is needed for the mast cell stabilizing effect.

The protection provided by β_2-agonists against mast cell mediator release may be very important in protecting against acute exacerbations of asthma, which are, in part, mediated *via* mast-cell activation. This action may contribute to the reduction in severe and mild exacerbations seen with formoterol treatment over 1 yr [39].

Plasma exudation

Exudation of plasma from postcapillary venules is an important component of acute inflammation. β_2-receptors are present on postcapillary venular endothelial cells and β_2-agonists inhibit plasma exudation by preventing separation of endothelial cells in postcapillary venules [40]. This effect is seen with both salmeterol and formoterol [41–43]. In this way β_2-agonists may exert anti-inflammatory and anti-oedema effects in the airways. In addition, LABA reduce the adhesion of neutrophils and eosinophils to venular endothelial cells and thus inhibit the trafficking of granulocytes into the airway wall [42–44]. While intravenously administered β-agonists are ineffective in inhibiting plasma exudation in guinea pigs [45], they are effective in inhibiting the leakage induced by inhaled mediators when given *via* the aerosol route, indicating that high local concentrations may be useful in inhibiting exudation of plasma [46, 47]. Whether these effects of inhaled β-agonists are relevant to their anti-asthma actions is not yet certain as plasma exudation in the lower airways is difficult to quantify in human airways. Terbutaline applied topically to the nose significantly reduces albumin concentrations in nasal lavage fluid after allergen challenge, suggesting an inhibitory effect on plasma exudation, although this could also be explained by an inhibitory effect on mast cell mediator release [48]. Topical salmeterol also reduces the increase in albumin in nasal secretions following allergen challenge in subjects with allergic rhinitis, suggesting an inhibitory effect on plasma exudation [49]. Inhaled formoterol reduces the increase in plasma proteins induced by inhaled histamine in the sputum of normal subjects, indicating that therapeutic doses of inhaled LABA can inhibit plasma exudation [50].

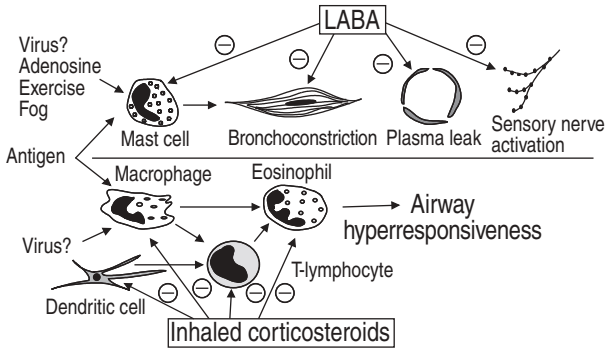

Fig. 1. – Complementary actions of long-acting β_2-agonists (LABA) and corticosteroids on the pathophysiology of asthma. β_2-Agonists relax airway smooth muscle, but also inhibit mediator release from mast cells, prevent plasma exudation and inhibit activation of sensory nerves, whereas corticosteroid have inhibitory effects on the cells of chronic inflammation, including T-lymphocytes, eosinophils, macrophages and dendritic cells, resulting in reduced airway hyperresponsiveness.

Sensory nerves

β-Agonists may also have effects on activation of airway sensory nerves. β-Agonists inhibit excitatory non-adrenergic non-cholinergic (NANC) bronchoconstrictor responses in guinea-pig bronchi *in vitro* at concentrations which do not block equivalent tachykinin-induced responses [51]. This modulatory effect is mediated *via* β_2-receptors on capsaicin-sensitive sensory nerves in the airways. Whether β-receptors modulate sensory nerves in human airways is less certain. Some evidence which suggests that β_2-receptors may be modulatory is provided by the inhibitory action of salbutamol on cough responses [52].

Complementary effects

β_2-Agonists affect different aspects of the pathophysiology of asthma than corticosteroids (fig. 1) and for most patients both treatments are needed to fully control symptoms (fig. 2) [53]. This provides a strong rationale for combining a LABA and corticosteroid in a fixed combination inhaler in order to provide optimal control.

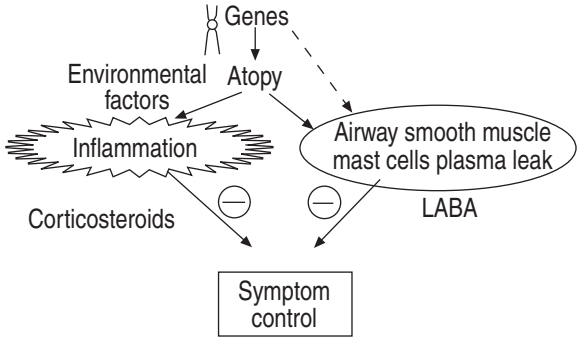

Fig. 2. – Inhaled corticosteroids suppress airway inflammation at relatively low doses, whereas long-acting inhaled β_2-agonists (LABA) affect some other aspects of pathophysiology, including airway smooth muscle, mast cells and plasma exudation. Both treatments may be necessary in order to achieve optimal asthma control.

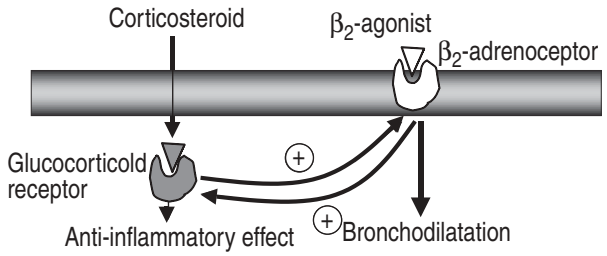

Fig. 3. – Interaction of corticosteroids and β_2-agonists. Corticosteroids increase the expression of β_2-receptors and protect them against down-regulation in response to long-term β_2-agonist exposure, whereas β_2-agonists may enhance the anti-inflammatory actions of corticosteroids. Thus each class of drug enhances the others beneficial actions.

Interaction of β_2-agonists and corticosteroids

Many patients with asthma are taking regular inhaled corticosteroids together with β_2-agonists and therefore the interaction between these drugs is an important clinical issue [54] (fig. 3).

Effect of corticosteroids on β_2-receptors

The human β_2-receptor gene has several glucocorticoid response elements in its promoter sequence, predicting that corticosteroids should increase transcription [55, 56] (fig. 4). Corticosteroids increase the transcription of the β_2-receptor gene in human lung *in vitro* and rat lung *in vivo*, doubling the rate of transcription [57, 58]. Similarly, in normal human subjects β_2-receptor density in the nasal mucosa is doubled after 3 days of treatment with a topical corticosteroid [59], indicating that therapeutic doses of topical corticosteroids are effective.

Chronic treatment of animals with β-agonists, results in down-regulation of pulmonary β_2-receptors, which is due to reduced transcription secondary to a reduction in activity of the transcription factor CREB (cyclic AMP response element binding protein) [60, 61].

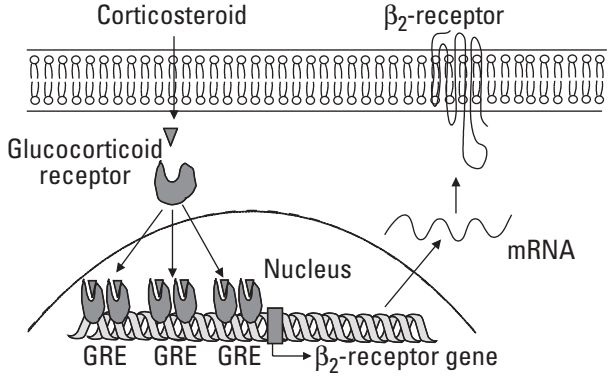

Fig. 4. – The effect of corticosteroids on expression of β_2-receptors. Corticosteroids enter the cell to bind to glucocorticoid receptors in the cytoplasm that then translocate to the nucleus, where they bind to glucocorticoid response elements (GRE) in the promoter region on the β_2-receptor gene, resulting in increased transcription and thus increased synthesis of β_2-receptors. mRNA: messenger ribonucleic acid.

The increased transcription of β_2-receptors compensates for the reduced transcription of β_2-receptors induced by chronic exposure to β_2-agonists, so that co-administration of a β-agonist and a corticosteroid results in no overall change in β_2-receptor expression in animal lungs [58]. Using autoradiographical mapping it was shown that this interaction occurred in epithelial cells and airway smooth muscle cells. This protective effect of corticosteroids may not be important in airway smooth muscle, as the large receptor reserve of β_2-receptors means that the bronchodilator response to β_2-agonist is not desensitized. However, it may be very important for the nonbronchodilator actions of β_2-agonists, such as its actions on mast cells, plasma exudation and sensory nerves [62]. For example, corticosteroids prevent desensitization of the protective effect of β_2-agonists on human lung mast cells *in vitro* [63].

Clinical studies have demonstrated that ICS do not prevent the loss of protection provided by salmeterol against cholinergic bronchoconstriction [64, 65]. However, this may be because the ICS does not reach β_2-receptors in airway smooth muscle. However, even oral corticosteroids fail to protect against the loss of bronchoprotective effect of formoterol [66]. However, it remains to be determined whether ICS would protect against the loss of protection against mast-cell activating constrictor stimuli, such as AMP or allergen, or against the desensitization of plasma exudation effects.

Reversal of detrimental effects of β_2-agonists

Inflammation may lead to uncoupling of β_2-receptors and therefore reduced responses to β_2-agonists. In rats interleukin-1β reduces responses to β_2-agonists, as a result of uncoupling of β_2-receptors [67]. This involves increased activation of a kinase, G-protein receptor kinase-2 (GRK-2), that phosphorylates occupied β_2-receptors, uncoupling them from interaction with the stimulatory G-protein, G_s [68]. Corticosteroids are able to reverse this by decreasing the expression of GRK-2 and thus prevent desensitization of β-agonists [69] (fig. 5).

β_2-Agonists may have other deleterious effects that can be reversed by corticosteroids. For example, β_2-agonists increase the expression of tachykinin neurokinin type 1 (NK_2)-receptors in airway smooth muscle, that might increase bronchoconstrictor responses, but this is prevented by corticosteroids which have the reverse effect on transcription of the NK_2-receptor gene [70, 71].

There is growing evidence that β_2-agonists alone may increase eosinophil survival, whereas corticosteroids reduce survival though opposing effects on apoptosis [72, 73]. Similarly β_2-agonists may increase the late response to allergen and the number of eosinophils recruited into the airways, whereas corticosteroids have the opposite effect [74]. Thus corticosteroids have the capacity to prevent any potentially adverse inflammatory consequences of chronic β_2-agonist therapy.

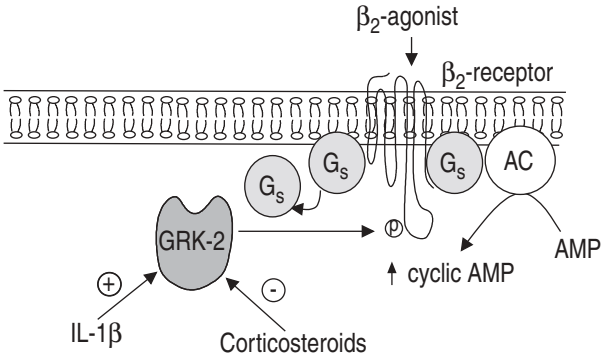

Fig. 5. – Desensitization of β_2-receptors occurs when they are occupied by β_2-agonists and this is achieved by the activity of an enzyme G-protein receptor kinase-2 (GRK-2), which uncouples the receptor from the stimulatory G-protein (G_s) so that adenylate cyclase (AC) is not activated, resulting in a reduction in cyclic adenosine 3′, 5′monophosphate (cyclic AMP) and a loss of β_2-agonist effect. This results in desensitization of the receptor. This is enhanced by inflammatory stimuli, such as interleukin-1β (IL-1β), but is reversed by corticosteroids.

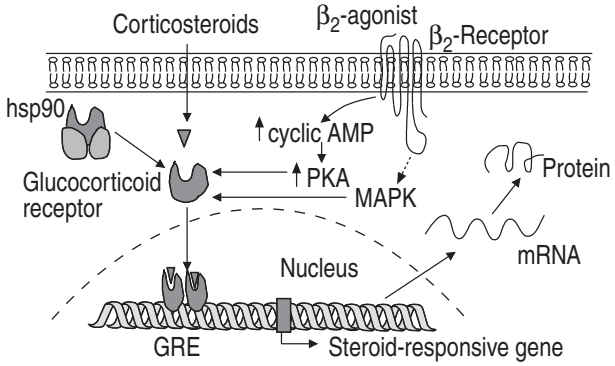

Fig. 6. – Interaction of β_2-agonists with corticosteroid effects. β_2-Agonists increase the intracellular concentration of cyclic adenosine 3′,5′monophosphate (cyclic AMP) which activates protein kinase A (PKA), and this may have a direct effect on the nuclear translocation of glucocorticoid receptors or they may be indirectly affected through the activation of mitogen-activated protein kinases (MAPK). mRNA: messenger ribonucleic acid; GRE: glucocosteroid response element; hsp 90: heat shock protein-90.

Effects of β_2-agonists on corticosteroids

High concentrations of β_2-agonists activate the transcription factor CREB and there are interactions between CREB and other transcription factors, such as activator protein-1 and glucocorticoid receptors [54]. Theoretically, this may mean that high concentrations of β_2-agonists may interfere with the anti-inflammatory actions of corticosteroids. This blocking effect of β_2-agonists on corticosteroid effects has been demonstrated in rat lung with high concentrations of β_2-agonists [75]. However this has not been seen in human monocytes, where the effects of β_2-agonists and corticosteroids are additive in inhibiting cytokine release [76]. The final functional outcome will depend on the net balance between the number of glucocorticoid receptors, the amount of CREB, the density of β_2-receptors and the presence of other pro-inflammatory cytokines and will therefore differ from cell to cell and under different conditions.

Recently, several studies have demonstrated that β_2-agonists may enhance the actions of corticosteroids and even show a synergistic interaction. β_2-agonists increase the nuclear localization of glucocorticoid receptors (GR) and the deoxyribonucleic acid (DNA) binding of GR in a fibroblast cell line, resulting in increased gene transcription induced by the corticosteroid [77]. At a functional level salmeterol enhances the inhibitory effect of a corticosteroid on allergen-induced activation of cytokines from peripheral blood mononuclear cells [78]. An interaction of β_2-receptors and corticosteroids has also been seen upon induced IL-8 and eotaxin release from human airway smooth muscle cells, with a greater suppressive effect of salmeterol and fluticasone together than with either drug alone [79, 80]. Salmeterol also enhances the suppressive effect of fluticasone on the expression of intercellular adhesion molecule (ICAM)-1 in fibroblasts [81]. Low concentrations of formoterol increase the suppressive effect of budesonide on the release of granulocyte macrophage colony stimulating factor (GM-CSF) from cultured human airway epithelial cells [82]. The molecular basis for these interactions is uncertain, but β_2-agonists, through an increase in cyclic AMP and protein kinase A, may phosphorylate GR or may activate other kinases, such as mitogen-activated protein kinase cascades, that do so (fig. 6). β_2-Agonists may also increase the sensitivity of the molecular pathways that are utilized by corticosteroids to suppress inflammation, including their action on histone acetylation and deacetylation [83, 84], or through effects on the activation of transcription factors, such as nuclear factor-κB [85].

Additive effects or synergy?

It is still uncertain whether adding a LABA to an ICS results in an additive effect, because both classes of drug have effects on a common mechanism, or whether there is true synergy. In some studies it is apparent that while the LABA may have little effect on the inflammatory process alone, there is an enhancement of the corticosteroid effect when both LABA and ICS are administered suggesting that there is true synergy. This type of interaction is likely to be dependent on the cell type, the response measured and the concentrations of each drug. Whether it translates into clinical synergy has not yet been clearly established. However, even an additive interaction is likely to be clinically beneficial if the same control can be achieved with lower doses of each drug.

Clinical implications

Clinical benefit

There is now persuasive evidence that β_2-agonists and corticosteroids target different and complementary aspects of the inflammatory process in asthma and that both classes of treatment are needed for optimal control in most patients with asthma [53].

Furthermore, β_2-agonists and corticosteroids interact in a beneficial way, with corticosteroids preventing the loss of function of β_2-agonists with chronic use, whereas β_2-agonists may potentiate the local anti-inflammatory actions of corticosteroids. There is therefore a powerful scientific rationale for combining β_2-agonists and corticosteroids in a single inhaler (LABACS), as most patients with asthma will need both treatments. LABACS inhalers with salmeterol/fluticasone (Seretide/Advair/Viani) and budesonide/formoterol (Symbicort) are now widely available and have proved to be remarkably effective in clinical trials [4, 5, 86–92]. LABACS inhalers provide better overall control of asthma and are the new "gold standard" of therapy [93]. LABACS inhalers are more convenient for patients and may increase adherence to regular therapy. They may be more cost-effective than giving the two drugs separately, may also reduce overall costs of asthma managements through more effective disease control [94]. Another advantage of LABACS inhalers is the fact that it is not possible to discontinue the ICS while taking the LABA, which is often observed when these inhalers are given separately. LABACS importantly achieve asthma control at lower doses of ICS and this is a particular advantage in the management of childhood asthma.

The clinical studies have demonstrated that LABACS inhalers are better than either corticosteroid or LABA inhalers alone in all parameters of asthma control, but in some studies the fixed combination is even superior to delivery of the two components by separate inhalers. This is not explained by improved compliance, as placebo inhalers were used, but may be due to differences in formulation, or to the fact that both drugs are reaching target cells in the airways simultaneously. This "coincident pharmacology" might increase the probability of drug interaction through the mechanisms described above.

The long-term benefits on LABACS therapy is not yet known, but it is possible that there may be a beneficial effect on the structural changes in the airway that occur in chronic asthma. One of these changes is an increase in airway blood vessels (angiogenesis). A recent biopsy study showed that addition of salmeterol to low a dose of ICS significantly reduced the number of blood vessels in the airway mucosa, compared to treatment with an increased dose of ICS [95]. Further studies are needed to look at long-term effects on lung function in patients with chronic asthma who have an accelerated decline in lung function over time.

Possible problems

The potential disadvantage of LABACS inhalers is their lack of flexibility when asthma is not well controlled. This has been addressed in the case of salmeterol/fluticasone by using three doses of corticosteroid with a single dose of salmeterol, so that switching to another inhaler is possible, just as the dose of inhaled steroids is currently regulated by changing the strength of inhaler. In the case of formoterol/budesonide it is possible to vary the dose to a greater extent, as it is possible to increase the dose of formoterol considerably without adverse systemic effects, since the systemic side effects do not have a long duration of action, in contrast to its prolonged bronchodilator effect [96].

Another concern is that concurrent treatment with LABA and corticosteroid may obscure the control of the underlying inflammatory process. However, concurrent treatment with formoterol and low-dose budesonide (200 μg daily) gives a similar suppression of sputum eosinophils to high-dose inhaled budesonide (800 μg daily) which gives equivalent clinical control, suggesting that there is no masking of airway inflammation [13]. However, combination treatment with formoterol/budesonide does not give any greater effect on markers of inflammation (exhaled NO, airway responsiveness to AMP) than a similar dose of budesonide alone [97].

LABACS inhalers are also safe; there is no evidence that adverse effects of either drug are potentiated [98]. Thus, there is no evidence that β_2-agonists increase systemic side effects of ICS, and this is likely to be the case because both drugs have only very low systemic concentrations. On the contrary, asthma control can be achieved at lower doses of ICS, thus reducing potential systemic side effects. Thus, in children one study showed that substitution of budesonide for half the dose together with formoterol gave equivalent asthma control, but had less effect on short-term growth (knemometry) [99].

There is little doubt that LABACS inhalers will become the treatment of choice for the majority of patients with persistent asthma, and will be effective in mild, moderate and severe disease. This will simplify asthma management and is likely to improve the control of asthma in the community, where asthma control is still poor, as evidenced by results of a telephone survey in several European countries [100]. The fact that this is a logical approach to the treatment of this complex disease will further reinforce the value of this combined approach to therapy.

Future therapies

Many treatments are now in development for the future treatment of asthma [101–103]. It is unlikely that bronchodilators more effective than β_2-agonists can be discovered, and new classes of bronchodilator have had major problems with vasodilator side effects. Most of the new treatments are more specific inhibitors of the inflammatory process than corticosteroids and are therefore less likely to be as effective, at least in a broad range of asthmatic patients. Anti-leukotrienes have been disappointing in the treatment of most patients with asthma, but it is unrealistic to expect that blocking a single mediator can be nearly as effective as corticosteroids which inhibit the expression and effect of multiple mediators. Anti-IL-5 blocking antibody (mepolizumab) is very effective in reducing peripheral and airway eosinophils, but does not appear to affect the underlying asthmatic process [104, 105]. This may imply that other strategies designed to reduce eosinophils, such as chemokine

CCR3-receptor antagonists and inhibitors of the adhesion molecule very late antigen (VLA)-4, may also be ineffective. Anti-immunoglobulum (IgE) antibody (omalizumab) is in advanced clinical development and has clinical benefit in the management of patients with more severe asthma and reduces exacerbations [106–108], but it is likely to be relatively expensive and may therefore be indicated mainly in patients with severe allergic asthma that is difficult to control with inhaled therapy. Other new approaches to treatment are either specific inhibitors, that are less likely to be effective than ICS, or less selective blockers, such as NF-κB and p38 mitogen-activated protein kinase inhibitors that may be more effective but will carry a risk of adverse effects. Immunological approaches, including vaccines, are only in the early stages of development and the long-term consequences of such therapies will need to be carefully evaluated.

Because it takes approximately 15 years to bring a novel drug to the market, it is unlikely that there will be any major advances in asthma therapy in the near future. This means that LABACS inhalers are likely to remain the most effective treatment for asthma over at least the next 10 years.

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