Review Article

The role of new asthma treatments

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ABSTRACT

Inhaled corticosteroid therapy remains the basis for the treatment of chronic asthma. Recent understanding of its use includes the benefits of early introduction, and of its plateaued dose-benefit effects. Additional beneficial effects on asthma control and prevention of asthma exacerbations can be obtained by combining middle- to high-dose inhaled corticosteroid with long-acting β-agonists and slow-release theophylline. Leukotriene inhibitors, particularly leukotriene receptor antagonists, are novel treatments that may also be combined with inhaled steroid therapy. Although current asthma treatments are very effective, a subgroup of asthma patients (difficult or therapy-resistant asthma) do not respond adequately to these treatments and need maintained oral corticosteroid therapy. New asthma treatments are particularly needed for this group. New treatments for asthma include more potent topical corticosteroids which have less potential for side-effects, inhibition of eosinophil chemotaxis and activation such as anti-IL-5, anti-eotaxin, eotaxin receptor antagonist, anti-VL-A_4, anti-IgE therapy, restoring Th-1/Th-2 balance either by increasing Th-1 or reducing Th-2 T-cell activity, anti-inflammatory cytokines such as IL-10, and specific inhibitors of PDE_4. These treatments may be considered as either controllers, remitters (inducing remission of disease), or preventors according to their modes of action and their clinical effects. Currently, there does not appear to be any prospect of a cure for asthma.

Key words: asthma, β-adrenergic agonists, corticosteroids, eosinophils, treatments.

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INTRODUCTION

In order to understand the role of new treatments for asthma, it is necessary to first review the recent changes that have taken place and to survey the currently unmet clinical needs for asthma so that particular areas of need can be specifically targeted.

Over the last eight or so years since the introduction in many countries of national asthma guidelines, there have been several advances in the treatment of asthma.[1–3] These advances relate to improved understanding of existing drugs such as the pharmacology and molecular mechanisms of corticosteroid actions, the positioning of the new class of long-acting β-agonists on the basis of new studies, and the introduction of a new class of drugs for asthma, the leukotriene inhibitors. The recognition that chronic inflammatory processes are even present in the airways of patients with mild asthma and that such processes may contribute to bronchial hyperresponsiveness and airway narrowing as well as to remodeling of the airways has led increasingly to the use of anti-inflammatory agents as first-line treatment of asthma, leaving the use of short-acting β-agonists for relief of breakthrough symptoms. The initial recommendation has been to use either non-steroidal 'anti-inflammatory' agents such as sodium cromoglycate or nedocromil sodium, particularly in pediatric asthma or low-dose inhaled corticosteroid therapy. However, experience with these agents indicates that low-dose inhaled steroid therapy is more predictably effective and that the anti-inflammatory agent of choice is inhaled corticosteroids even at low doses.[4,5] There are also doubts as to whether nedocromil sodium has anti-inflammatory effects such as reducing eosinophil infiltration in the airways submucosa.[6]

By contrast, more recent studies confirm the effect of topical corticosteroid treatment in reducing the number of inflammatory cells in the airways submucosa, such as

eosinophils, activated T cells and mast cells, together with the restoration of epithelial integrity.[7–9] Other important observations have also been made over the past decade, namely the benefits of early introduction of inhaled corticosteroid therapy, the introduction of more potent topical steroids and the dose-response to inhaled corticosteroids.

EARLY INTRODUCTION OF INHALED STEROID THERAPY

Inhaled corticosteroid therapy started as early as diagnosis is made in mild asthma has led to a greater improvement in lung function compared with its introduction after a delay of two years from diagnosis.[10,11] Early intervention is associated with the greatest response to steroids in terms of lung function, symptom control and daily need for short-acting β-agonists. Established remodeling of the airways, which would not be easily reversed by topical steroids, has been implicated as being the cause of the lack of reversal of lung function following early institution of corticosteroid therapy. Inhaled corticosteroids that are more potent than beclomethasone dipropionate, such as fluticasone propionate and budesonide, have been introduced. With fluticasone, patients with severe persistent asthma needing oral corticosteroid treatment in addition to inhaled corticosteroids were able to discontinue oral corticosteroid therapy with improved asthma control and FEV_1.[12] The effectiveness of single versus divided daily doses of inhaled corticosteroids has been examined, with one advantage of single daily dosing related to improved compliance. Two trials comparing one versus two doses per day, or four versus two doses per day showed that more frequent dosing yielded more effective asthma control, although the differences in results between the two dosing regimens were not striking.[13,14]

Dose–response for efficacy (measured as FEV_1) achieved a plateau at and above 1000 µg/day of budesonide.[15] Poor dose–response relationship with inhaled steroid therapy regarding symptom control or oral steroid-sparing effect has been reported in other studies.[16,17] Dahl *et al.* have reported a dose-dependent effect of graded doses of inhaled fluticasone (100–800 µg/day) in patients with asthma but the mean increases in morning peak expiratory flow rates (PEFR) observed were small, possibly because of the chronicity of the asthma, with patients whose mean baseline FEV_1 was approximately 70% of the predicted value.[18] In this study, there was a plateau response observed regarding the reduction in the number of exacerbations achieved at the dose of 400 µg/day. No clear dose–response was observed with inhaled beclomethasone and budesonide when changes in peak expiratory flow rate were used as the outcome measure.[19,20] Clearly, if the beneficial effects of inhaled corticosteroids plateau at a 'middle' dose and if the potential systemic effects of steroids increase with increasing inhaled dose, the smallest effective dose within the effective dose-range should be used as maintenance therapy.

'ADD-ON' THERAPY TO INHALED CORTICO-STEROIDS WITH LONG-ACTING β-AGONIST AND SLOW-RELEASE THEOPHYLLINE

Long-acting β-agonists were introduced in several countries at the time when there was concern regarding the possible contribution of short-acting β-agonists to increasing asthma deaths and to loss of asthma control.[21,22] The use of long-acting β-agonists in the management of asthma has been clarified in the initial pioneering clinical trials of salmeterol, in which salmeterol was added to inhaled steroid therapy in patients whose asthma was not adequately controlled at a given dose of inhaled steroids (400 µg/day or 800 µg/day). Addition of salmeterol provided better control of asthma in terms of peak flow measurements and day-to-day control of asthma compared to the option of increasing the dose of inhaled steroids in these short-term studies of 3 months' duration.[23,24] These studies also indicated that the dose–response benefits from inhaled steroids do plateau at the doses studied. More recently, the additive effects of another long-acting β-agonist, eformoterol, to inhaled steroid therapy (budesonide inhaled via turbohaler®, 200 and 800 µg/day) has also been demonstrated to be persistent for up to one year of therapy; more importantly, the addition of eformoterol to inhaled corticosteroids at either dose provides additive protection against mild to severe attacks of asthma.[25] Long-acting β-agonists do not appear to possess anti-inflammatory effects on their own, but the effects observed in combination with corticosteroids may reflect more than a bronchodilator effect, perhaps other anti-inflammatory effects such as anti-edema effects.[26] It would be unwise to initiate long-acting β-agonist therapy without corticosteroid therapy. A study in children showed that salmeterol treatment alone for one year caused a trend toward a decrease in lung function and a worsening of bronchial hyperresponsiveness.[27] Whether there are any potentially significant differences between the two long-acting β-agonists, salmeterol, a partial agonist, and

eformoterol, a full agonist, is not known, but perhaps unlikely.

Because both inhaled steroids and long-acting β-agonists are usually administered twice daily, it would make sense to combine both in the same inhaler. This may improve patient compliance. These combinations should allow 2–3 different doses of inhaled steroids with a fixed dose of long-acting beta agonist. Such combinations will be available soon.

Addition of slow-release theophylline to inhaled corticosteroid therapy also provided better control of asthma than increasing the dose of inhaled corticosteroid therapy.[28] The mechanism of action of theophylline in this response is not clear but theophylline, particularly at the doses used which do not achieve the so-called 'therapeutic' levels, has anti-inflammatory and immunomodulatory properties.[29,30] While the addition of slow-release theophylline to inhaled steroid therapy may provide additive effects, in milder asthma children inhaled corticosteroids (200 and 400 μg of beclomethasone) were significantly more effective than continuous theophylline treatment in optimal doses and inhaled bronchodilators.[31,32]

A NEW CLASS OF ANTI-ASTHMA DRUGS: LEUKOTRIENE INHIBITORS

A new class of drugs has been introduced over the last couple of years in many countries around the world, including Japan. Inhibitors of cysteinyl leukotriene synthesis or leukotriene receptor antagonists such as zileuton, zafirlukast, pranlukast and montelukast are available for prescription, although their exact place in asthma management has not been determined in many countries.[33] Regarding the development of mediator antagonists in asthma, it is of interest to note that other mediator antagonists apart from leukotriene antagonists have not been shown to be clinically effective in asthma: for instance, platelet-activating factor, thromboxane and bradykinin receptor antagonists. Cysteinyl-leukotrienes are important mediators of asthma, participating in bronchoconstriction, airway microvascular leakage and probably in eosinophil recruitment in asthma. Leukotriene receptor antagonists are also effective in preventing exercise-induced asthma and allergen-induced early- and late-phase responses.[34,35] When leukotriene inhibitors are administered to patients with moderately severe asthma there is a bronchodilator response as measured either by peak flow or FEV_1 measurements, together with an improvement in symptoms and a reduction in the amount of daily β-agonist therapy needed for controlling asthma symptoms.[36–38] This

effect is observed even in patients already on inhaled corticosteroid therapy.[39,40] Such additive effects of leukotriene receptor antagonists can also be observed in patients with severe asthma needing oral corticosteroid therapy.[41] Indeed, corticosteroid therapy does not appear to modulate leukotriene metabolism. Leukotriene receptor antagonists can be used to reduce the amount of inhaled steroids needed to control asthma.[42] Patients with aspirin-induced asthma respond particularly well to this therapy, as this condition is associated with increased leukotriene production through an upregulation of the leukotriene C4 synthase enzyme.[43] These compounds can be used as an addition to both oral or inhaled steroid therapy to provide additional control of asthma in moderately severe to severe asthmatics. They have been recommended by the US National Heart Lung and Blood Institution Expert Panel Report as a first-line anti-inflammatory agent for asthma and as an alternative to using inhaled steroid therapy, although they are less potent than low-dose inhaled steroids in controlling asthma. Long-term studies are needed in this area, but the leukotriene blockers have the advantage of being an oral therapy, which attracts greater patient compliance.

The response to these compounds is variable and at present there are no ways of predicting those who will respond to the treatment. In a recent study of responses to the 5-lipoxygenase inhibitor, zileuton, the bronchodilator response was related to a polymorphism of the 5-lipoxygenase gene promoter that modifies transcription factor and the activity of the enzyme.[44]

UNMET CLINICAL NEEDS IN ASTHMA: TOWARDS WHOM SHOULD NEW THERAPIES BE TARGETED?

It can be argued that the treatment for mild to moderately severe asthma is effective with the use of inhaled steroid therapy and the addition of other therapies such as long-acting β-agonists, slow-release theophylline and leukotriene inhibitors, and that new treatments should be targeted towards patients whose asthma is not well controlled by existing therapies. One approach to determining the role of new treatments in asthma would be to look for current unmet clinical needs and target new treatments towards these needs.

One group of patients who particularly need new effective treatments are those with 'difficult therapy-resistant' asthma who appear to have uncontrolled asthma despite being on inhaled and often on oral corticosteroid therapy.[45,46] While much needed data should be collected

from such patients, difficult asthma may comprise several distinct clinical phenotypes such as brittle asthma with recurrent and sometimes rapid onset of life-threatening asthma exacerbations, fixed asthma with chronic obstructive component and rapid loss of lung function, and those on high-dose oral corticosteroid therapy for control of their asthma (corticosteroid dependent). Research on these patients is difficult given the problem of obtaining a sufficient number of them for a detailed study. However, the development of protocols to define these patients in cooperative multicenters may provide a database for collecting such patients. The question is what are the characteristics of these difficult asthmatics that make them different from the asthmatic whose disease is controlled by low to middle doses of inhaled corticosteroids alone.

A recent study of proximal mucosal airway biopsies and of transbronchial lung biopsies from such difficult asthmatics taking at least 20 mg of prednisolone per day showed that these patients had a predominance of neutrophil influx in their proximal as well as distal airways.[47] However, it is unclear whether this could have resulted from the oral corticosteroid treatment itself. Part of the problem is that we may not have the efficacious interventions to deal with the specific inflammatory responses in these patients.

One particular difference between the difficult and the mild asthmatic is the difference in responsiveness to corticosteroids. What determines this responsiveness remains unclear but restoring corticosteroid responsiveness could be an important therapeutic exercise. Much has been learnt from the rare corticosteroid-resistant asthmatic patients who demonstrate a bronchodilator response to β-agonists but not to two weeks' treatment with 40 mg of prednisolone per day.[48] One proposed mechanism of primary steroid resistance is that there is increased activation of the transcription factor activator protein-1, resulting in binding to glucocorticoid receptors, thus preventing the anti-inflammatory actions of steroids, either through binding to glucocorticoid elements or through the inhibition of another transcription factor, nuclear factor-κB.[49]

Other mechanisms of glucocorticoid down-regulation are also possible. Down-regulation of glucocorticoid receptors has been shown in circulating lymphocytes after oral prednisolone in normal individuals,[50] but it is not known whether this occurs in the airway epithelium exposed to high concentrations of topical steroids. Worsening of asthma symptoms either through allergen exposure or during spontaneous attacks is accompanied by a decreased affinity of the steroid receptors on circulating mononuclear cells,[51,52]

and patients with severe steroid-dependent asthma also demonstrate similar reduction in receptor affinity.[53] This reduction in receptor affinity can be demonstrated by incubation of mononuclear cells *in vitro* with the combination of cytokines IL-2 and IL-4,[54] and recent evidence indicates that this can be prevented by an inhibitor of the intracellular signaling p38 kinase.[55] Whether these measurements are also reflected in airway cells as a result of exposures to these cytokines released in the airways is not known, but prevention or restoration of steroid receptor affinity may provide one way of improving the therapy of asthma.

Current treatments for corticosteroid-dependent asthma include the use of immunosuppressant drugs such as methotrexate, cyclosporin A and gold salts, which have been demonstrated as leading to a reduction in maintenance steroid therapy without worsening control of asthma.[56–59] Whether these agents improve steroid receptor affinity is not known. It is believed that they act on certain T cells to inhibit activation and expression of cytokines such as IL-5. However, no studies have been performed which support this. Indeed, there is very little data on the pathology of difficult asthma.

WHAT SHOULD WE BE STRIVING FOR AS IDEAL ASTHMA TREATMENTS?

Although the term 'anti-inflammatory treatments' has been applied to drugs such as corticosteroids and sodium cromoglycate, another term has been used that is more relevant to the concept behind the use of such drugs, namely 'controllers'. Within this category, other drugs which are not anti-inflammatory drugs are included, such as long acting β-agonists and leukotriene inhibitors. They are controllers because, when effective and taken regularly, they control asthma. This term also implies that these drugs are only effective so long as they are taken. Loss of control of asthma on discontinuing inhaled steroid therapy may take a few days to a number of weeks. With our current understanding of asthma mechanisms, it is unlikely that there will be a foreseeable cure for asthma. However, approaches for prevention and for developing drugs that may induce long periods of disease remission should be contemplated. The idea of disease remission was derived from cancer therapy, whereby a protracted length of treatment with toxic cytotoxic drugs often leads to remission of the cancer for many months. Our current understanding of the inflammatory process in asthma indicates that this possibility may exist. This may also help us to determine the potential effects of certain classes of drugs in the treatment of asthma.

There is discussion regarding the best way of administering anti-asthma drugs, whether by the oral or inhaled route. While emphasis, to date, has been placed on the inhaled route, due to the use of corticosteroids and β-adrenergic agonists, it is believed that oral therapy may be better because of its simplicity and also because of greater patient adherence to such therapy. However, whether either is used is very dependent upon the best route of administration for that drug. Corticosteroids are best administered by the inhaled route with the maximal benefit/side-effect ratio and are most effective when delivered as such. Other drugs, such as leukotriene inhibitors, are not as effective when administered by the inhaled route and have acceptable side-effect profiles by the oral route. Although patients may be more compliant with oral administration, it is to be noted that patient adherence may be low with such therapies, as noted with antihypertensive therapy. There may well be advantages to using the oral route in certain patient subgroups, such as the very young and the elderly, who may have difficulties with self-administration of inhaled drugs. With either route, however, clinicians will still have to address the problem of adherence to treatment.

Many new inhaler devices have been introduced recently, including the CFC-free metered dose inhalers, multidose powder devices, inhalers triggered by inspiratory flow, new spacer devices, portable nebulizers etc. While the purpose of these new devices is to combine user friendliness with greater lower airway deposition characteristics, this plethora of devices may become confusing for both the doctor and the patient. There may be some requirement to control the introduction of different types of devices and to provide some uniformity. The new non-CFC metered dose inhalers are able to produce finer particles that penetrate deeper into the airways.[60] Whether this is an advantage to the obstructed asthmatic is unclear.

RECENT NEW APPROACHES TO THE THERAPY OF ASTHMA

Although there are specific areas of unmet clinical needs in asthma, research into new drugs for asthma has not necessarily focused on these areas. Often new treatments with potentially important side-effects have been reserved for patients with difficult severe asthma. The past 10 years have seen much research into the development of receptor antagonists such as leukotriene, platelet-activating factor and bradykinin B2-receptor antagonists. Only leukotriene antagonists have been shown to have beneficial effects. Phosphodiesterase 4 (PDE_4) is the predominant phosphodiesterase in inflammatory cells, including mast cells, eosinophils, T-lymphocytes, macrophages and epithelial cells. Inhibitors of PDE_4 have been the subject of recent clinical trials although to date no full analysis has been published.

STRATEGIES FOR INHIBITION OF EOSINOPHIL ACTIVATION AND RECRUITMENT

Eosinophils have long been implicated in the pathogenesis of asthma, being present in the airways submucosa with evidence of activation as indicated by the presence of release of eosinophil proteins such as eosinophil cationic protein and major basic protein. Eosinophils are also important sources of cysteinyl-leukotrienes. Much has been learnt about the kinetics of eosinophil traffic between the bone marrow and the airways. Eosinophilopoiesis in the bone marrow is under the control of IL-5, which regulates terminal differentiation of these cells.[61] Release of chemokines such as eotaxin in the airways may be the event that causes chemo-attraction of eosinophils to the airways, through the upregulation of adhesion molecules such as ICAM-1 and VCAM-1 on the vascular endothelium and the integrins VLA4 on the eosinophil.[62] Therefore, several strategies for inhibiting eosinophil activation and recruitment have been put into place. These include inhibition of IL-5 effects by using a neutralizing antibody or an IL-5 receptor antagonist; inhibition of chemokine effects through an antagonist or antibody to chemokine receptor CCR3; and blocking the effects of adhesion molecules with an anti-ICAM-1 or anti-VLA4 antibody. Studies in animal models indicate that anti-IL-5 antibodies can inhibit eosinophil influx into the airways of sensitized guinea-pigs or monkeys following allergen exposure and can also inhibit the increase in bronchial hyperresponsiveness.[63–65] In one study, the effect of a single administration of anti-IL-5 antibody provided protection for up to 3 months, suggesting that a state of remission may have been obtained. An anti-VLA4 antibody inhibited bronchial hyperresponsiveness but not the eosinophil influx.[66]

This treatment could be used to reverse established disease and could be tried in patients with severe asthma, in particular. The idea of inducing remission of disease would also be an exciting prospect. It could also be administered as a prophylaxis for asthma. Inherent in this approach is the idea that inhibiting a single target may be sufficient. However, studies in animals indicate that

IL-5 and chemokines such as regulated on activation, normal T-cells expressed (RANTES) and eotaxin cooperate in eosinophil recruitment and activation.[67,68] This suggests that a combined inhibition of IL-5 and chemokine effects may be more effective.

MODULATION OF TH-1/TH2 T-CELL ACTIVATION

The concept of interfering with the imbalance of the Th-1 and Th-2 T cell activities derives from the observations that Th-2 derived cytokines such as IL-4 and IL-5 are over-expressed in asthma, and that Th-2 T cells may be suppressed by enhancing Th-1 responses. Cytokines from Th-1 cells, notably IFNγ and IL-12, can prevent or reverse Th-2 responses. There is an inverse association between a positive tuberculin test indicating a Th-1-mediated response and the development of atopy.[69] Apart from inhibiting the Th-2 response, it would be possible to enhance Th-1 T-cell function. Interleukin-12 and IFNγ are both potential candidates for use as treatment in asthma, and can inhibit allergic eosinophilia and bronchial hyper-responsiveness in the ovalbumin-sensitized mouse.[70–73] A reduction in IL-12 expression in airway biopsies of patients with allergic asthma has been reported, supporting a reduction in Th-1 response.[74] Other approaches would include the use of vaccination to induce a Th-1 response. Approaches aimed at restoring the Th-1/Th-2 imbalance (e.g. Bacille Calmette-Guerin (BCG) vaccination) may be used early in the disease process, and perhaps targeted towards those at risk of developing asthma. However, ways of identifying such people at risk are needed.

More classical immunomodulators such as cyclosporin A have been tried in asthma and found to possess oral steroid-sparing effects in severe asthma.[58] It is likely that such T cell inhibitors inhibit both Th-1 and Th-2 cells and, therefore, do not reset the imbalance in T-helper subsets. The mechanisms by which Th-2 cells are selectively activated involve the costimulatory molecule B7.2, which is expressed on antigen-presenting cells that interact with CD28 on T cells.[75] Blocking this costimulatory molecule may yield novel therapies.

TARGETING IgE RECEPTORS WITH AN ANTI-IgE APPROACH

IgE is an important mediator of allergic airways disease and a relationship between IgE levels and airway hyper-responsiveness, and between IgE levels and asthma symptoms has been reported.[76,77] Allergen exposure of sensitized asthmatics may cause both early and late bronchoconstrictor responses which are considered to be both IgE and mast cell dependent. The late response is associated with airway inflammation characterized by eosinophil influx, airway edema and activation of adhesion molecules.

A recombinant humanized monoclonal antibody that binds to IgE recognized by the high-affinity IgE receptor FcϵR1 has been developed. This antibody blocks the binding of IgE to mast cells and inhibits mediator release.[78] This antibody (rhuMAb-E25) reduces free IgE levels in serum,[79] and inhibits both the early and late responses to allergen exposure.[80,81] Which categories of patients should such a potential treatment be targeting? From its properties, this novel approach should be more preventive (similar to the use for sodium cromoglycate). For example, it could be used as prophylaxis for seasonal rhinitis or asthma, or for preventing the onset of symptoms in allergic patients. In the latter group, however, we have no diagnostic methods for predicting allergic patients at risk of developing asthma. This approach is now being tested in symptomatic patients with allergic asthma.

Another approach to inhibiting mast cell activation is the use of heparin, which may act by inhibiting IP3-mediated calcium release. Inhaled heparin has been shown to protect against exercise-induced asthma[82] and attenuate allergen-induced early and late responses.[83] The anti-allergic effect of heparin was found to be within the nonanticoagulant fraction.[84]

ANTI-INFLAMMATORY CYTOKINES AND INHIBITION OF PRO-INFLAMMATORY CYTOKINES

A number of cytokines expressed in asthma appear to have anti-inflammatory properties, for example interleukin-10 (IL-10) and interleukin-1 receptor antagonist (IL-1ra). IL-10, which is produced by CD4+ and CD8+ T cells and activated monocytes, is a potent inhibitor of monocyte/macrophage function, of IL-4 and IL-5 production by Th2 T cells, of eosinophil survival and of IL-4 induced IgE synthesis. There is a reduced capacity for alveolar macrophages to produce IL-10 in asthma, a defect which is reversed by inhaled corticosteroid therapy.[85] IL-10 inhibits eosinophilia induced by ovalbumin in immunized mice.[86,87] IL-10 has been administered to normal volunteers inducing a fall in circulating T cells with suppression of T-cell proliferation and a reduction of TNFα and IL-1β production by mononuclear cells.[88] IL-1ra can block the proliferation of Th-2 cell clones but

not of Th-1 cell clones,[89] and in the ovalbumin-sensitized model, there is an inhibition of allergen-induced bronchial hyperreactivity and pulmonary eosinophilia.[90] Other approaches include the inhibition of effects of pro-inflammatory cytokines such as TNFα and IL-1β, which may be overexpressed in chronic severe asthma. These cytokines may play a role as amplifying mechanisms, through the activation of NF-κB and other transcription factors. Blocking antibodies may be used or soluble TNF receptors or IL-1ra. These approaches should probably be directed towards established diseases, particularly those which do not respond to currently available therapies.

POTENTIAL FOR NEW CORTICOSTEROIDS

While currently available inhaled corticosteroids are highly effective and have a good margin of safety, there is still room for improvements. Development of even more potent corticosteroids with lesser potential for systemic side-effects continues. However, this raises several issues as to whether more potent steroids will provide more clinical benefits, particularly for the more difficult asthmatic patients. In addition, some contribution of systemic effects of inhaled corticosteroids in suppressing eosinophilopoiesis in the bone marrow has been raised. The potential prolongation of effects of topical steroids delivered by liposomes in the airways may be useful. These improvements may lead to the use of a once daily inhaled steroid dosage.

Corticosteroids may control airway inflammation through suppression of transcription factors largely through a direct interaction of the activated glucocorticoid receptor with transcription factors such as AP-1 and NFκB (trans-repression).[91] It seems likely that the side-effects of corticosteroids are mostly the result of trans-activation of genes through binding of glucocorticoid receptors to DNA. Some steroids may have greater potency against trans-repression than trans-activation,[92] which may translate into less side-effect profile, while increasing anti-inflammatory potency. Other approaches would be to develop specific transcription factor blockers.

CONCLUSIONS

Although there have been new advances in the treatment of asthma, the search for new targets to aim at in the hope of developing novel asthma treatments continues as long as research into the inflammatory and immuno-logical mechanisms of asthma progresses. However, this search must be combined with the clinical needs of patients with asthma, and of the particular needs of certain subgroups. It should be on the basis of their properties that novel drugs be considered for use as pre-ventors, inducers of remission, controllers or relievers. The long-term aim of any new asthma treatment is to prevent the disease from occurring, which means target-ing susceptible persons, and to provide better controllers or drugs that cause remission in those at the more severe spectrum of the disease. Current treatments for asthma are very effective for those with mild to moderate disease severity.

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