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STEROID RESISTANT ASTHMA

INTRODUCTION

All patients with asthma have a specific pattern of inflammation in the airways that is characterized by degranulated mast cells, an infiltration of eosinophils, and an increased number of activated TH2 cells. This specific pattern of inflammation underlies the clinical features of asthma, including intermittent wheezing, dyspnea, cough, and chest tightness. Current guidelines of asthma therapy have therefore focused on the use of anti-inflammatory therapy, particularly inhaled corticosteroids (ICS). While the majority of patients respond to regular inhaled ICS therapy, subsets of patients are poorly responsive even when treated with high doses of oral prednisone. Patients with corticosteroid-resistant asthma, although uncommon, present considerable management problems.

DEFINITION

The definition of steroid-resistant (SR) asthma has changed over the years as ICS use has escalated in the treatment of asthma. In 1967, Schwartz et al first described SR asthma in six asthmatic patients with persistent eosinophilia despite treatment with 40 mg intravenous hydrocortisone. In 1981, Carmichael et al identified patients with SR asthma as those individuals who failed to increase their forced expiratory volume in 1st second (FEV_1) by greater than 15% after a course of prednisolone 20 mg daily for 7 days. In 1991, Corrigan et al defined SR asthma as the failure to demonstrate an increase in baseline FEV_1 by greater than 15% after a course of 20 mg daily oral prednisolone for 1 week followed by 40 mg daily for a second week. The diagnosis of SR asthma should only be made after an extensive evaluation to rule out other potential causes of wheezing or factors that contribute to the severity of asthma. Patients with steroid resistant asthma should fulfill the ATS criteria for diagnosis of asthma and have a bronchodilator response of greater than 15% improvement in FEV_1 .

The differentiating features between the two main types of SR asthma are depicted in Table 1.

Table 1: Clinical and Laboratory Features of Steroid-Resistant Asthma

Features	Type I	Type II
Morning (AM) cortisol levels	Suppressed	No
Cushingoid side effects	Yes	No
Etiological basis	Genetic or acquired	Genetic
GR ligand and DNA binding affinity	Reduced	Normal
GR number	Normal or High	Low
Reversibility of GR defect	Yes	No

GR = Glucocorticoid Receptor

GLUCOCORTICOID RECEPTORS

Corticosteroids diffuse readily across cell membranes and bind to glucocorticoid receptors (GRs) in the cytoplasm. Cytoplasmic GRs are normally bound to proteins known as molecular chaperones, such as heat shock protein-90 (hsp90) and FK-binding protein, that protect the receptor and prevent its nuclear localization by covering the sites on the receptor that are needed for transport across the nuclear membrane into the nucleus. Once corticosteroids have bound to GRs, changes in the receptor structure result in dissociation of molecular chaperone proteins, thereby exposing nuclear localization signals on GR. This exposure results in rapid transport of the activated GR-corticosteroid complex into the nucleus, where it binds to DNA at specific sequences in the promoter region of corticosteroid-responsive genes known as glucocorticoid response elements (GREs).

Interaction of GRs with GRE classically leads to an increase in gene transcription (trans-activation), but negative GRE sites have also been described where binding of GRs leads to gene suppression (cis-repression).

There is a single gene encoding human GRs, but several variants are now recognized as a result of transcript alternative splicing and alternative translation initiation. GR α binds corticosteroids, whereas GR β is an alternatively spliced form that binds to DNA but cannot be activated by corticosteroids. GR β has a low level of expression compared with GR α .

MOLECULAR MECHANISMS OF STEROID RESISTANCE IN ASTHMA

Patients who have asthma and allergic rhinitis have a specific pattern of inflammation in the airways that is characterized by degranulated mast cells, infiltration of eosinophils, and increased number of activated T helper 2 (TH2) cells.

Understanding the mechanisms that give rise to corticosteroid unresponsiveness has important clinical implications for the management of these difficult to control asthmatics. Several mechanisms for corticosteroid resistance in asthma have been proposed:

1. Abnormalities in glucocorticoid receptors

There are several identified point mutations of the glucocorticoid receptor (GR) gene that may result in an abnormal GR structure, resulting in reduced corticosteroid binding affinity.

2. Inflammatory cytokines

Interleukin (IL)-2, IL-4, and IL-13, which show increased expression in bronchial biopsies of patients with SR asthma, induce a reduction in affinity of GR in inflammatory cells, such as T-lymphocytes and monocytes, resulting in local resistance to the anti-inflammatory actions of corticosteroids. The combination of IL-2 and IL-4 induces steroid resistance invitro through activation of p38 mitogen activated protein (MAP) kinase, which phosphorylates GR and reduces corticosteroid binding affinity and steroid-induced nuclear translocation of GR.

3. Glucocorticoid receptor beta

Increased expression of an alternatively spliced form of the glucocorticoid receptor, GR- β which binds to DNA but not to corticosteroids may act as a dominant negative inhibitor by competing with GR- α for binding to GRE sites or from interacting with co-activator molecules.

4. Nuclear localization of glucocorticoid receptors

In patients with SR asthma, there is a reduction in the inhibitory effect of corticosteroids on cytokine release in peripheral blood mononuclear cells which may be due to the abnormalities such as the increased activation of p38 MAP kinase described above. Reduced nuclear localization of corticosteroids is likely to reduce the anti-inflammatory action of corticosteroids.

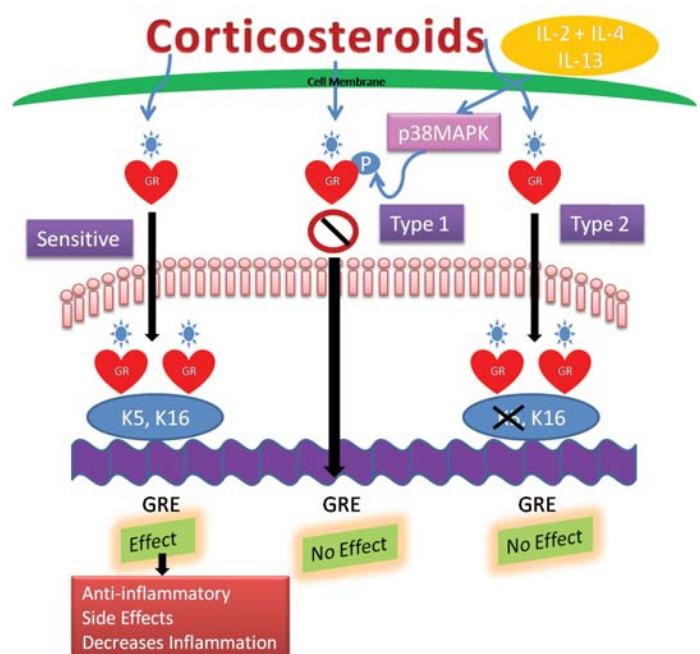
5. Interaction with transcription factors

Corticosteroids suppress the expression of inflammatory genes regulated by proinflammatory transcription factors such as activator protein-1 (AP-1) and nuclear factor- κ B (NF- κ B). There is some evidence that AP-1 activity is increased in peripheral blood mononuclear cells of patients with SR asthma and that this may counteract the anti-inflammatory action of corticosteroids.

6. Interleukin -10

Corticosteroids increase macrophage secretion of IL-10, and this may contribute to their anti-inflammatory actions. There is a reduction in T-lymphocyte secretion of IL-10 in patients with SR asthma, and this may contribute to the reduced responsiveness to the anti-inflammatory actions of corticosteroids.

The key molecular mechanisms in patients with steroid responsive and SR asthma are summarized in Figure 1 below.



MANAGEMENT OF STEROID RESISTANT ASTHMA

The management of patients suspected of having steroid resistant asthma requires a systematic, stepwise approach.

Step 1: Conduct a thorough clinical examination and appropriate laboratory tests to confirm the diagnosis of asthma

Concomitant medical disorders which can complicate the management of patients with chronic asthma should be ruled out. Often the diagnosis of vocal cord dysfunction, which involves abnormal vocal cord closure during inspiration, is missed. This diagnosis can only be made by direct laryngoscopy when the patient is symptomatic and should be suspected in any adolescent or adult with recent onset of steroid-dependent or steroid resistant asthma. Gastroesophageal reflux and/or aspiration, sinusitis, allergic bronchopulmonary aspergillosis, anatomical abnormalities and immunodeficiencies are some of the concomitant factors that must also be ruled out.

Step 2: Rule out psychosocial factors affecting asthma

A large proportion of patients with apparent SR asthma have an inadequate response to therapy simply due to non-compliance with recommended therapy. The basis for non-compliance is complex and can range from simple forgetfulness to the inability to pay for the medications or severe psychological problems such as depression which impair the patient's ability to function and adhere to a suggested medical regimen. In addition, it is important to keep the medication regimen as simple as possible, prioritize recommendations, educate the patient regarding their asthma management and tailor the dosing to the patient's schedule.

Step 3: Review the patient's technique of medication administration

This should be incorporated as a routine part of the follow-up as patients often forget the proper inhaler technique. Spacer devices should be used to optimize medication delivery and reduce adverse effects of medications.

Step 4: Assure appropriate environmental control for asthma at home, in school and at work

The focus should be on areas where the patient spends the greatest time, for example, the bedroom, or areas of high indoor allergen exposure. A number of studies have demonstrated that atopic patients who live with animals at

home require higher doses of steroids to maintain control of their asthma. Several studies have also implicated schools as a major source of animal dander exposure.

Step 5 : Modify inhaled corticosteroid therapy in an effort to reduce requirements for systemic corticosteroid therapy as patients with acquired SR asthma frequently develop steroid side effects

One approach is to increase the dose and frequency of inhaled ICS. This is based on the assumption that higher doses would be more effective and also that adverse effects would be less than those commonly associated with high dose systemic corticosteroid therapy. The majority of patients with steroid resistant asthma have the acquired form, which is associated with reduced GR binding affinity. Studies of their T cells indicate a shift to the right in their dose response to steroids rather than an absolute resistance. Thus, higher doses of corticosteroid or a change to a corticosteroid with a higher binding affinity is a reasonable initial approach to gain control of their asthma.

Step 6: Maximize anti-inflammatory and bronchodilator therapy for control of nocturnal asthma exacerbations.

Inhaled salmeterol administered at bedtime can be very useful in controlling nocturnal asthma. A once daily sustained-release preparation of theophylline can also be effective in the treatment of nocturnal asthma.

Step 7: Develop a written action plan for acute asthma exacerbations

Emphasis should be placed on appropriate use of rescue medications such as bronchodilators and when to notify the physician. A written care plan should also be used to summarize routine prophylactic medications including recommendations for pre-treatment programs for exercise and anticipated exposure to irritants or allergens.

Step 8: Evaluate systemic corticosteroid pharmacokinetics and receptors to maximize pulmonary function with oral corticosteroids, and assess the basis of corticosteroid insensitivity in patients with poorly controlled asthma

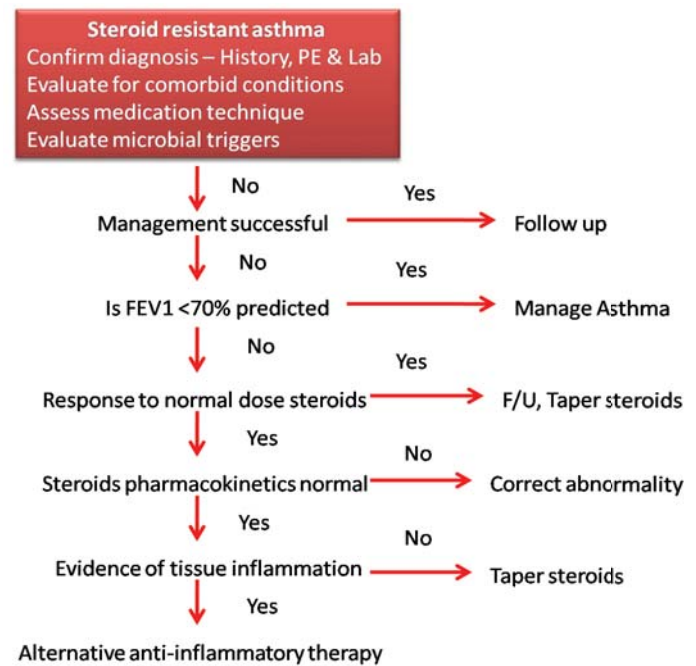
The purpose of these studies is to determine whether there is incomplete corticosteroid absorption, failure to convert to an active form, rapid elimination, reduced GR number or binding affinity, or a combination of abnormalities. This evaluation is particularly important in a patient who fails to demonstrate the anticipated adverse effects of long term, high-dose corticosteroid therapy. Patients with poor absorption of prednisone, frequently respond well to oral liquid corticosteroid preparations. In patients with rapid corticosteroid elimination, a split dosing regimen, with the

second dose of the day administered in the afternoon, should be considered. In such patients, the morning dose should be titrated, then the afternoon dose converted to a morning dose, then a reduction to alternate day therapy attempted.

Step 9: Consider alternative anti-inflammatory and immunomodulator approaches

This is of particular importance in patients with the Type II or primary form of SR asthma who have a generalized primary resistance to steroid therapy. Unfortunately, there have been no well controlled studies of alternative therapies in SR asthma. Treatment with methotrexate, gold, cyclosporine and intravenous immunoglobulin have been reported to have steroid sparing effects and may be potentially useful in patients who fail corticosteroid therapy. Recent studies suggest that T cells from SR asthma will respond to the anti-inflammatory actions of intravenous immunoglobulin and enhance their GR binding affinity thus providing a rationale for use of this agent in the management of these patients.

Figure 2 below represents an algorithm which can be used for management of patients with suspected SR asthma



SUMMARY

A correct diagnostic work up is essential prior to labeling a patient as having SR asthma.

Patients with SR asthma do respond to bronchodilator therapy and hence these medications (rescue therapy)

should be instituted early. Presence of persistent airway inflammation predisposes them to long-term effects like airway remodeling and irreversible airway obstruction. Therefore, it is of paramount importance to treat airway inflammation early and effectively.

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TARGETED THERAPY IN ASTHMA

INTRODUCTION

Asthma is a chronic inflammatory disorder of airways characterized by episodic, reversible bronchospasm resulting from an exaggerated bronchoconstrictor response to various stimuli. In the industrialized world, asthma has increased in prevalence and severity for the past two decades. Approximately 300 million people are estimated to be affected - a figure that is projected to increase to 400 million by the year 2025.¹ However, the good thing is that despite an increase in the prevalence of this disorder, significant advances have been made in the understanding of the immuno-modulatory mechanism of asthma.

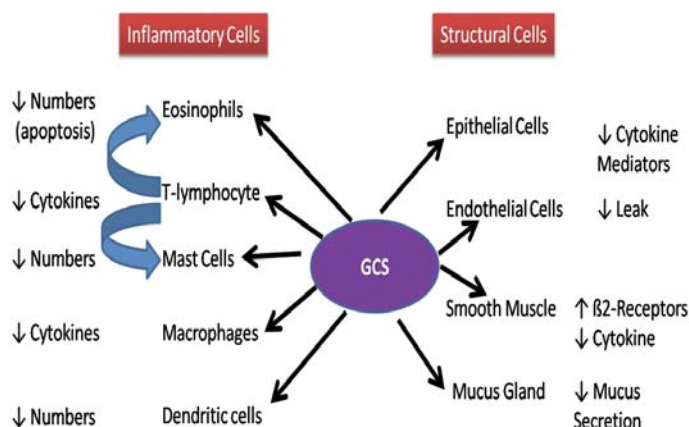
PATHOGENESIS

Airway inflammation in patients with bronchial asthma involves multiple components and is orchestrated by numerous cell types - in particular mast cells, eosinophils and CD4+ lymphocytes.^{2,3} Activation of these cells leads to the release of proinflammatory mediators and cytokines, which in turn cause vascular leakage, bronchial smooth muscle contraction, inflammatory cell infiltration, mucus hypersecretion, airway hyperresponsiveness (AHR) and ultimately airway remodeling. These changes are expressed clinically as recurrent wheezing, dyspnea, chest tightness, and cough, which are typical symptoms associated with reversible airflow obstruction. It is also known that asthma is associated with the T helper lymphocyte type 2 (TH2) cytokine profile subset of CD4+ cells. Most unaffected individuals fail to respond to inhaled allergens with a TH2 response; therefore, allergic asthma is considered to be the result of an improperly regulated immune response, with a pivotal role played by CD4+ T cells in the pathogenesis of the disease.^{4,5}

CURRENT ASTHMA THERAPIES

Current therapies for asthma are aimed at improving airflow and reducing exacerbations. Anti-inflammatory drug therapy, primarily consisting of inhaled corticosteroids (ICS), is now considered to be the first-line treatment in the management of all grades of asthma severity. The key anti-inflammatory effects of corticosteroids are depicted in figure1. Although corticosteroids are believed to be the most potent anti-inflammatory agents available, they do not suppress all the inflammatory mediators involved in the asthmatic response. Moreover, not all patients achieve control of asthma symptoms and airway inflammation with ICS therapy alone and require the use of add-on therapy

[usually, a long-acting β 2-agonist (LABA) or leukotriene modifier]. More than 25% of patients using add-on therapy, however, may remain inadequately controlled and at high risk of an exacerbation.⁶



THE NEED FOR NEW THERAPIES

The types of new drugs needed for asthma include:

- New classes effective in severe poorly controlled asthma
- Oral treatment as effective as ICS without any side effects
- Drugs that modify or even cure the disease

The newer therapies that target the various mechanisms contributing to persistent airway inflammation may have far-reaching consequences for patient care and may change our therapeutic notions. Targeted therapy has been investigated as a new tool in patients with asthma, particularly in the treatment of severe oral steroid dependent asthma and has demonstrated very promising results.⁷

New corticosteroids

Ciclesonide, a novel ICS, is essentially inactive until it is activated by esterases in the lung to a steroid with potent local anti-inflammatory activity.⁸ Thus, ciclesonide may allow targeted anti-inflammatory activity in the lung, causing only minimal local or systemic side effects and consequently permit the use of higher ICS doses. In patients with steroid-dependent asthma, administration of ciclesonide in a dose of 640 and 1280 μ g/day significantly reduced oral prednisone requirements by 47% and 63%, respectively; whereas, the oral steroid dose rose slightly in the group receiving placebo ($p < 0.0003$).⁹ Some novel corticosteroids have a greater effect on the non-genomic than genomic effect (dissociated steroids) and thus, might have a better therapeutic ratio and might even be suitable for oral administration.

New bronchodilators

Novel classes of bronchodilators have proved difficult to develop and new drugs, such as analogues of vasoactive intestinal peptide and K⁺-channel openers, have had side effects due to the fact that they are more-potent vasodilators than bronchodilators.

Targeting IgE in Asthma

Asthma is recognized to be IgE-mediated, with an allergic basis in most patients. IgE triggers the allergic cascade by binding to mast cells. On initial exposure, inhaled allergens are presented to TH2 lymphocytes, resulting in the secretion of IL-4 and IL-13, and, in turn, the stimulation of immunoglobulin class-switching in B cells to allow IgE production. Subsequent binding to high-affinity IgE receptors (Fc ϵ RI) on mast cells and basophils results in sensitization to allergen exposure.¹⁰

Omalizumab (Xolair; Genentech; San Francisco, CA) is a recombinant humanized monoclonal antibody that is recommended for the treatment of patients with moderate-to-severe persistent asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with ICS therapy.⁶ Omalizumab (administered subcutaneously every 2 or 4 weeks per serum IgE levels and body weight) has been assessed in randomized controlled trials. In pooled analyses of clinical trials, omalizumab significantly reduced asthma exacerbations by 38% ($p < 0.0001$), emergency department visits by 61% ($p < 0.013$), hospital admissions by 52% ($p < 0.041$), and unscheduled doctor visits by 47% ($p < 0.0003$) vs. control subjects and provided clinically meaningful improvements in asthma-related quality of life.^{6,11} The benefits of adding omalizumab were particularly evident in patients receiving high-dose ICS therapy, those with frequent asthma exacerbations, and those with poor lung function. Patients treated with high-dose ICS plus a LABA who had reduced lung function and a recent history of clinically significant exacerbation were evaluated in a separate trial. Adding omalizumab to therapy significantly reduced severe exacerbations by 50% ($p < 0.002$) and emergency department visits by 44% ($p < 0.038$) vs. placebo and improved lung function ($p < 0.05$), asthma symptoms ($p < 0.05$), and asthma-related quality of life ($p < 0.001$).¹²

AGENTS IN CLINICAL DEVELOPMENT

Neutralizing Th2 Cytokines

TH2 lymphocytes promote airway inflammation in asthma patients through the release of several key cytokines

(i.e., IL-4, IL-5, and IL-13).^{4,5} IL-4, which is required for the differentiation of naive T cells into TH2 cells in the presence of an allergen, is the primary factor driving B-cell isotype switching from IgM to IgE.

Soluble IL-4 receptor

A recombinant human soluble IL-4 receptor (sIL-4R), which inactivates IL-4, was evaluated in steroid dependent asthma patients following the withdrawal of ICS therapy. Anti-inflammatory activity was shown by a reduction in exhaled nitric oxide after a single sIL-4R dose; stabilization of asthma symptoms also occurred, despite ICS therapy withdrawal. However, the study discontinuation rate due to asthma exacerbation was similar between the sIL-4R and placebo groups.¹³

Anti-IL-5 monoclonal antibody

A humanized IL-5 monoclonal antibody (Mepolizumab) that inactivates IL-5 reduced eosinophil levels in the blood, bone marrow, sputum, and bronchial tissue of patients with mild asthma who were not receiving ICS therapy.¹⁴ Nevertheless, blocking IL-5 did not significantly affect late-phase bronchospasm, AHR, or lung function vs. placebo. Similarly, adding anti-IL-5 to high-dose ICS therapy reduced blood eosinophil levels in patients with severe asthma but produced no clinical improvement in symptom score or lung function.¹⁵

Anti-IL-13 monoclonal antibody

IL-13 induces airway hyperresponsiveness, mucus production, secretion of eotaxin, and changes in airway remodeling. At least 3 different humanized mAbs under development, specific for human IL-13 are either in phase I or phase II human clinical trials.¹⁶

TNF- α blockade

TNF- α may also be up-regulated in asthma patients, particularly in those with severe, steroid-dependent asthma.¹⁷ TNF- α promotes the recruitment of neutrophils and eosinophils into the airways, and may be important in both phenotypes of severe asthma.

Etanercept, a recombinant fusion protein that blocks TNF- α , produced marked and significant improvement in asthma control ($p < 0.001$) when added to high-dose ICS therapy in patients with treatment-resistant asthma.¹⁸ AHR and all measured lung function parameters improved significantly ($p < 0.03$). Reductions in sputum eosinophils and neutrophils were seen in 8 of 11 patients with paired samples. Similar results were obtained in a 10-week crossover trial of patients with refractory asthma.

The anti-TNF- α monoclonal antibody Infliximab reduced diurnal PEF variability ($p = 0.02$), but not morning PEF, in a trial of symptomatic patients with moderate asthma despite receiving ICS therapy. Fewer patients receiving infliximab had exacerbations during the 8-week study compared to those receiving placebo ($p = 0.01$).¹⁹

PDE-4 Inhibitors

In the lungs, cyclic adenosine monophosphate (cAMP) is inactivated by phosphodiesterase E-4 (PDE-4), and consequently the selective inhibition of this enzyme has anti-inflammatory effects. Roflumilast, an orally active PDE-4 inhibitor, produced dose-related inhibition of late-phase bronchospasm following allergen challenge in patients with mild asthma. In a subsequent study, therapy with roflumilast, 500 μg once daily, produced similar improvements in lung function and asthma symptoms, and reductions in rescue medication use vs. therapy with beclomethasone, 200 μg twice daily.²⁰

A second PDE-4 inhibitor under clinical development is ciclesonide. Studies in murine models have suggested that this agent mediates AHR through the inhibition of PDE-4D messenger RNA expression and the down-modulation of PDE-4 activity, with reduced inflammation and mucus hypersecretion.²¹

Chemokine antagonists

Chemokines are small peptides that attract inflammatory cells, including mast cells, eosinophils and TH2 cells into the airways and are therefore appropriate targets for new therapies for asthma, particularly because they signal via G-protein-coupled receptors for which small-molecule inhibitors can be developed.²² The major focus of interest has been the chemokine (C-C motif) receptor 3 (CCR3), which is predominantly expressed on eosinophils and mediates the chemotactic response to the CC-chemokine eotaxin, which is secreted in asthma.²³ Several small-molecule inhibitors of CCR3 are under clinical development but their effects in asthma have not yet been reported. Other chemokine receptors that are also targeted for asthma therapy are CCR2 on monocytes and T cells and CCR4 on Th2 cells

Transcription-factor blockade

Transcription factors have a crucial role in regulating the expression of inflammatory genes in asthma. Small-molecule inhibitors of the key enzyme inhibitor of NF- κ B kinase (IKK2) blocks inflammation that is induced by NF- κ B activation and are now under preclinical testing.²⁴ P38 mitogen-activated protein (MAP) kinase activates inflammatory genes similar to those activated by NF- κ B and several small-molecules inhibitors are now under

clinical development for the treatment of other inflammatory diseases.²⁵ Another approach to inhibit inflammation is to block the adhesion molecules that are involved in the recruitment of inflammatory cells from the circulation into the airways. Although many different adhesion molecules have been identified, there has been particular interest in very late antigen-4 (VLA-4, $\alpha 4\beta 1$), which is involved in the recruitment of eosinophils and T cells.²⁶ Small-molecule inhibitors have been effective in animal models and are currently being tested in asthma patients, although there have been concerns about long-term safety.

Toll-like receptors (TLRs)

Therapeutic targeting of Toll-like receptors (TLRs) as either antagonists or agonists have enormous potential to prevent inflammation, change the pattern of allergic disease or improve responses to infection. These agents have modulated inflammatory cell function and/or reduce airway inflammation in experimental models.²⁷

CONCLUSIONS

Airway inflammation, a prominent feature in asthma, needs to be targeted with effective medication to achieve asthma control. Increasing knowledge of asthma pathophysiology and the various inflammatory phenotypes may make it possible to target anti-inflammatory therapy to the various pathways of the disease, thereby improving asthma control. A number of other approaches that are currently in clinical development, which show promise in targeting specific cytokines, inflammatory cells, or inflammatory mechanisms, may become available for clinical use in the future.

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