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Alternative agents in asthma

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Glucocorticosteroids are the backbone of asthma therapy and are administered mainly by the inhaled route. Patients with "difficult" asthma are not a single homogeneous group. Some are stable on high-dose steroid therapy but experience unacceptable side effects; others remain unstable despite receiving high doses of inhaled or oral steroids. Several different steroid-sparing and alternative agents have been tried, with varying degrees of success. Some success has been achieved with conventional immunosuppressants such as methotrexate, gold, and cyclosporin A, but these agents can be justified only in a limited range of cases. Leukotriene receptor antagonists have proved a useful addition to asthma therapy and have been shown to have a modest steroid-sparing effect. Although the existing range of alternative agents has not proved to be particularly effective, several new therapeutic agents have been developed to target specific components of the inflammatory process in asthma. These include IgE antibodies, cytokines, chemokines, and vascular adhesion molecules. Future developments might include better forms of immunotherapy and strategies targeting the remodeling of structural elements of the airways. (*J Allergy Clin Immunol* 2001;108:3-10.)

Key words: Asthma, asthma therapy, steroids, steroid-sparing agents

For many years, the treatment of asthma has depended heavily on the use of glucocorticosteroids. These agents were introduced into clinical practice in the 1940s and proved extremely effective in controlling asthma in most patients with the condition.¹ However, long-term use of oral steroids leads to significant and unacceptable side effects, so oral corticosteroid (OCS) therapy has to be restricted to those whose disease cannot be treated effectively by any other means. The introduction of inhaled corticosteroids (ICSs) in 1970 was a major advance, allowing many patients with relatively mild asthma to receive regular steroid therapy²; furthermore, the introduction of high-dose inhaled corticosteroids in the early 1980s enabled

Abbreviations used

CyA: Cyclosporin A
ICS: Inhaled corticosteroid
LTRA: Leukotriene receptor antagonist
MTX: Methotrexate
OCS: Oral corticosteroid
ODN: Oligodeoxynucleotide
sIL-4R: Soluble IL-4 receptor

many patients who had previously needed OCS therapy to discontinue their use of oral steroid preparations.^{3,4} Nevertheless, there remains a hard core of patients who continue to need OCSs to control their symptoms.

Several different alternative agents have been tried over the years, with varying degrees of success. With the arrival of the leukotriene modifiers and the expected arrival of a number of new therapies for asthma, it seems pertinent to review the evidence for these alternative therapies.

Patients with severe asthma do not form a single homogeneous group. After many years of struggle to find a workable definition, the concept is now emerging of "difficult-to-manage" asthma.⁵ Patients whose conditions are considered difficult to manage include those who have persistent symptoms despite maximum doses of standard therapy, those who have sudden, unpredictable, or catastrophic deterioration (so-called *brittle asthmatics*), those who have frequent exacerbations requiring OCS courses, and those whose asthma is perfectly well controlled but who are at high risk of side effects because they require unacceptably high doses of ICSs or OCSs to control their disease. In addition, there is a substantial group of patients whose asthma is difficult to manage because of their unreliable adherence to therapy or because they have excessive concerns about the risks of medication (ie, concerns over and above those of their medical advisers).

With respect to all of these groups, it is essential to review patients carefully, taking care to confirm that they truly have asthma and that their failure to improve is not because they have other, coexistent medical problems. Full lung function assessment is also helpful in establishing whether there is a fixed component to the airflow obstruction or any evidence of emphysema. A careful review of prior medication—in particular, a review of side effects experienced with prior medication—might reveal unexpected fears of drugs, problems of compliance, or a lack of understanding about asthma.

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Once the diagnosis is firmly established and issues of compliance with current therapy have been addressed, there are a number of steroid-sparing strategies that can be considered.

STERIOD-SPARING STRATEGIES

Safer steroids

Much effort has gone into the search for safer inhaled steroids. Whether these are truly necessary depends on the view taken of whether current ICSs pose any real risk. It is undoubtedly true that inhaled beclomethasone is absorbed and has detectable systemic effects in terms of reductions in short-term linear growth rates,⁶ but at present it remains uncertain whether these effects have any long-term adverse consequences for final height or any other aspect of health.⁷ This is in stark contrast to the evidence for the adverse effects of OCSs, which clearly stunt growth and have significant effects on bone and skin integrity.⁸ It is also well established that uncontrolled asthma has adverse effects on growth. Physicians need to strike a balance between protecting their patients from the theoretic risks of ICSs and managing the effects of poor control of asthma. A detailed discussion of the relative indications for the different ICS formulations lies outside the scope of this review, but the introduction of inhaled fluticasone and mometasone offers a chance to achieve the same therapeutic effect that is achievable through use of beclomethasone with considerably less systemic bioavailability.^{9,10}

Troleandomycin

Troleandomycin is a macrolide antibiotic that was formerly used quite widely in asthma exacerbations. In addition to its antibacterial action, troleandomycin inhibits the hepatic metabolism of methyl prednisolone,¹¹ and it now seems likely that the beneficial effects result from this mechanism. Claims that treatment with troleandomycin allowed the use of smaller OCS doses have been investigated in 2 clinical trials.^{12,13} The first of these used a placebo-controlled crossover design and showed a greater improvement in FEV₁ and symptom control as well as a reduced requirement for OCSs when troleandomycin was added to the therapy.¹² In contrast, the second study used a parallel group design and found no difference in the ability to withdraw OCS therapy over a 2-year period.¹³ However, there were significantly more steroid-related side effects in the troleandomycin group, consistent with the effect of troleandomycin on OCS metabolism. Thus the benefit from this agent has not been established.

Antimetabolites

Methotrexate (MTX) is a folic acid antagonist that inhibits thymidine synthesis and thereby interferes with DNA synthesis. MTX is mainly used in cancer chemotherapy, but it can also be used in lower doses as an anti-inflammatory agent for rheumatoid arthritis and psoriasis. MTX has predictable side effects on bone mar-

row function, especially neutrophil production, but can also cause nausea, anorexia, hair loss, liver dysfunction, and fibrosis. In vitro studies have demonstrated increased sensitivity of lymphocytes to the inhibitory effects of GCS in patients with asthma after MTX treatment.¹⁴ In 1988, Mullarkey et al¹⁵ reported a significant reduction in OCS dose with MTX, but the trial was both short and small (13 subjects completed the study). More significantly, no attempt was made to taper OCS dosage before the trial. Subsequent studies have reported variable findings,¹⁶⁻²⁴ and there is no real consensus on the use of MTX in asthma. A recent meta-analysis of 11 controlled studies has indicated a definite steroid-sparing effect in OCS-dependent patients with asthma.²⁵ The effect was seen to reduce prednisolone usage by an average of 4.73 mg/day. The greatest effect was seen in those patients in whom baseline steroid usage was reduced, and for the benefit to be seen, MTX use had to continue for 24 weeks. Conversely, a meta-analysis of 12 randomized, double-blinded, placebo-controlled trials that included a total of 250 patients showed that MTX allowed a modest reduction of 3.3 mg/day in OCS dose in comparison with placebo. This was at the expense of significantly more complications.²⁶ On balance, it is reasonable to conclude that even in studies showing a benefit of MTX, the reduction allowed in daily OCS dose was insufficient to lead to a substantial reduction in steroid side effects. The benefits are thus outweighed by the potential problems associated with MTX use.

The only other published trial of an antimetabolite in asthma appeared in 1971; this was a trial of azathioprine, which is incorporated into DNA and affects cell-mediated immune responses. In a controlled trial of 2 doses of azathioprine in asthma, 20 patients were treated for up to 4 weeks without any demonstrable benefit on lung function or symptoms.²⁷ As expected, patients receiving the higher dose of azathioprine had reduced neutrophil counts. No further trials of azathioprine in asthma have been reported in the past 30 years.

Cyclosporin A

Cyclosporin A (CyA) is a fungal metabolite that has proved to be an extremely useful immunosuppressant agent in the prevention of rejection after organ transplantation. The principal action of CyA is to inhibit T-cell activation and suppress the production of cytokines associated with activation. CyA also has inhibitory effects on a number of other kinds of cells, including mast cells, monocytes, neutrophils, and basophils. CyA is associated with a number of unwanted sequelae, including hypertrichosis and adverse effects on renal function, which mean that its use requires very careful monitoring. The decision to test CyA in patients with steroid-dependent asthma was based on the new appreciation of asthma as a T-cell-driven disorder. CyA both blocks the late asthmatic reaction and inhibits eosinophil-associated cytokines after allergen challenge.^{28,29}

Trials have addressed both the efficacy and the steroid-sparing properties of CyA. Unfortunately, all controlled

trials have been both short-term and small. Alexander et al³⁰ conducted a placebo-controlled crossover study to assess efficacy. The 12-week trial was not designed to assess any steroid-sparing effect, but it showed that CyA treatment led to an improvement in FEV₁ and peak flow rates as well as a reduction in exacerbations requiring extra OCS. However, there was no detectable change in bronchodilator use or symptoms. Lock et al³¹ examined the steroid-sparing effect of CyA in 39 patients and found that a significant (25%) reduction in OCS dose was possible in the CyA-treated group. Comparisons were made between the lowest steroid dose on CyA and placebo during the treatment period. Significant improvement was also seen in morning peak expiratory flow rate but not in FEV₁, forced vital capacity, or symptom scores. It should be noted that the actual reduction in daily steroid dose in the CyA-treated patients does not appear to have been clinically significant.

Nizankowska et al³² conducted a trial of CyA in a group of 34 steroid-dependent patients and reported no significant differences in either lung function or steroid-sparing effect in the CyA-treated group. A number of case reports and open studies of CyA have been reported, but there have been no other randomized trials of the use of CyA in asthma. Although other methods of administration of CyA look promising, at present there appears to be insufficient evidence of benefit to recommend its use, especially given the potential severity of side effects.

Leukotriene receptor antagonists

The introduction of leukotriene receptor antagonists (LTRAs) was the first truly new therapy for asthma in nearly 30 years. The bulk of patients treated with LTRAs have had mild to moderate asthma, but in a significant proportion of them the disease has been imperfectly controlled on their previous ICS therapies. LTRAs have proved effective when added to low- and high-dose ICSs^{33,34} and have been shown to have an ICS-sparing effect.³⁵⁻³⁷ In a study comparing montelukast 10 mg/day with placebo, patients were assisted in reducing their ICS dosage to the minimum required before starting the trial drug. Once on the trial drug, those in the active group were able to reduce their mean ICS dose from 976 to 526 µg/day (a 46.1% average reduction); in contrast, those in the placebo group were able to reduce their mean ICS dose from 1079 to 727 µg/day (a 30% average reduction). In a second study, which compared zafirlukast 20 mg bd with placebo, the dose of inhaled corticosteroids was stepped down progressively over 6 weeks according to a predetermined schedule and adjusted according to symptoms thereafter; the mean morning peak flow was maintained above the baseline level throughout a 20-week period.³⁶ The final dose of inhaled corticosteroids was 30% of the baseline dosage, demonstrating that the addition of an LTRA allows the reduction of inhaled steroid dosages while maintaining asthma control over at least 4 months. The placebo group achieved a similar reduction in ICS dosage, but their mean peak flow rate remained 10 to 15 L/min lower than that of the LTRA

group throughout, and the final lung function measurements were significantly below the baseline. As in other zafirlukast/placebo trials, the improvements in lung function were seen within 1 week of the beginning of therapy and were maintained throughout the course of the trial.³⁶ In a third trial, pranlukast 50 mg bd or placebo was given to patients who were receiving at least 1500 µg/day of beclomethasone. The ICS dose was then halved. Those on pranlukast tolerated this reduction in ICS without any fall in lung function or increase in daytime or nocturnal asthma symptoms over a 6-week period, whereas the placebo group showed a substantial reduction in lung function that was accompanied by an increase in asthma symptoms and in the use of β₂-agonists.³⁷ These studies encouraged physicians to use LTRAs in patients with more severe asthma who were receiving OCSs. Formal clinical trials assessing the ability of LTRAs to facilitate reduction of OCS dosages have not been reported; however, in clinical practice LTRAs have been used to cover withdrawal or reduction of oral steroids, and some formal trials would be welcome.

One unexpected hazard of introducing steroid-sparing therapy in patients on OCS is revealed by the fact that a small number of individuals have been found to have previously undiagnosed Churg-Strauss syndrome after the reduction in steroid dose that was achieved once they had begun therapy with zafirlukast.³⁸ Thus far, a case-by-case analysis of these episodes suggests that these were cases of previously undiagnosed Churg-Strauss syndrome rather than true drug-induced Churg-Strauss syndrome. In other words, it seems that the Churg-Strauss syndrome responded to the initial treatment with OCSs and then relapsed when the addition of LTRA allowed the OCS dose to be decreased. Further vigilance is required, however.

Gold

Gold is used in the treatment of aggressive forms of rheumatoid arthritis, and though the immunopathologic character of asthma and that of rheumatoid arthritis are quite different, it is known that gold can inhibit some of the processes implicated in asthma, including IgE-dependent histamine release and neutrophil chemotaxis. The side effects of gold therapy, which have been described principally in patients with rheumatoid arthritis, include neutropenia, thrombocytopenia, nephropathies, rashes, and gastrointestinal upset. Three controlled trials of gold therapy have been published; oral gold was used in 2 of them^{39,40} and an injectable preparation in the other, which was a small study.⁴¹ All 3 studies found a reduction in OCS requirements. In the largest study,⁴⁰ 136 patients received active therapy, and by the end of the 28-week trial, 56 (41.2%) of these were able to reduce their OCS dose by at least 50% of the starting dose; this compared with 37 (26.6%) of the 139 patients who received placebo. When the patients were assessed on an intention-to-treat basis, the figures were 55.9% and 32.4%, respectively. There was no difference in objective measures of lung function, but the gold-treated group showed a much more marked improvement in patients' subjective assess-

ments, presumably reflecting the reduction in OCS dosage. The gold-treated group also showed a reduction in total serum IgE concentrations.

OTHER AGENTS WITH ANTI-INFLAMMATORY ACTIVITY

Several other agents with anti-inflammatory activity have been tried in severe chronic asthma. These include dapsone, colchicine, and chloroquine, all of which have been used in various rheumatologic conditions. Dapsone inhibits neutrophil activity, has antibacterial activity, and is useful in leprosy; it was used to treat severe chronic asthma in 1 small open trial.⁴² Although the dapsone allowed a reduction in OCS dose, side effects were unacceptable. Colchicine was at one time a very useful agent for treating hyperuricemic gout, and it has been evaluated in asthma. An open study suggested that colchicine was useful,⁴³ but a more recent study found no benefit with regard to ICS requirements.⁴⁴ Like dapsone, colchicine caused a high level of side effects. Chloroquine is an antimalarial agent that has disease-modifying properties in rheumatoid arthritis. Chloroquine inhibits phospholipase A2 and reduces the release of histamine and leukotrienes. In an early controlled trial, chloroquine was ineffective in asthma.⁴⁵ After further open studies that reported improved symptom scores and lung function when hydroxychloroquine was given for more than 6 months to patients on moderate ICS doses, a placebo-controlled study confirmed a beneficial effect of hydroxychloroquine on airflow and serum IgE levels.⁴⁶ Intravenous immunoglobulin was reported to induce a reduction in symptoms and OCS requirements in 2 open studies in children with chronic steroid-dependent asthma,^{47,48} but subsequent double-blinded, controlled studies have provided conflicting results.^{49,50} Some insight has been obtained into the possible mechanisms of action of intravenous immunoglobulin in asthma with evidence of reduced lymphocyte infiltration in the airways and altered lymphocyte responsiveness to steroids.^{51,52}

THE FUTURE OF ALTERNATIVE AGENTS

Although the existing range of alternative agents has not proved particularly effective, there are a number of new therapeutic agents coming through the pipeline that will offer entirely new approaches to the treatment of asthma.

Most of these have been developed to target specific components of the inflammatory process that has been demonstrated in the airways of all patients with asthma. These include IgE antibodies, the cytokines involved in IgE production (IL-4 and IL-13) or in eosinophilia (IL-5), and various components of the cellular recruitment process, such as vascular adhesion molecules and chemokines.

Anti-IgE

The role of IgE in the etiology of asthma remains surprisingly controversial. It is well established that IgE sensitizes mast cells and that on exposure to common

inhaled allergens (or food allergens) IgE molecules are cross-linked, leading to the release of inflammatory mediators. High-affinity IgE receptors are present on mast cells and basophils, and quite recently it has been shown that there are also high-affinity IgE receptors on eosinophils and antigen-presenting cells. The low-affinity IgE receptor (CD23) is present on monocytes, macrophages, and B cells and might play an important role in triggering IgE production. In vitro work with anti-IgE has shown that IgE itself can regulate the IgE receptor, so in addition to its traditional role in triggering mast cell mediator release, IgE also plays a part in antigen presentation and in focusing the development of T cells and B cells.

The role of allergy in the causation of asthma is still a matter of some controversy. There is no doubt that being atopic is a risk factor for the development of asthma in childhood, but in adults, there is a clearly discernible pattern of nonallergic asthma that typically starts in the fourth or fifth decade with a normal total IgE level and no evidence of specific sensitization. It seems likely that the importance of allergy in asthma wanes as patients get older. Some individuals with asthma become increasingly unresponsive to bronchodilators as they get older, and these people seem to be less responsive to allergic triggers as well. Nevertheless, there is a minority who do not lose their allergy and remain quite sensitive to allergic triggers throughout their lives.

Treatment with humanized monoclonal anti-IgE antibodies is extremely effective in reducing the serum concentration of free IgE (Fig 1). Anti-IgE also reduces responses to inhaled allergen.^{53,54} A limited amount of published data is available on the use of anti-IgE in clinical asthma. This suggests that patients who are dependent on high-dose inhaled corticosteroids or OCSs can substantially reduce their steroid doses once they have been stabilized on anti-IgE.⁵⁵ The fact that many patients who received placebo injections in this study were also able to reduce their steroid doses does not detract from the overall message that anti-IgE might prove a useful steroid-sparing therapy.

Cytokines

Several cytokines have been implicated in the regulation of asthma. IL-5 is a potential target for immunotherapeutic intervention because it is intimately involved in the development, recruitment, and activation of eosinophils. This has been shown in human nasal biopsy studies,⁵⁶ human inhalation studies,⁵⁷ and animal models. In animal models, anti-IL-5 antibodies have proved capable of blocking the development of airways eosinophilia and the increased bronchial hyperresponsiveness that accompanies allergen exposure.^{58,59} Interestingly, in a mouse model, anti-IL-5 prevented airway inflammation and airway hyperresponsiveness whereas anti-IgE was ineffective.⁶⁰ Clinical trials of an anti-IL-5 monoclonal antibody were able to reduce the eosinophilic response to allergen inhalation but had little effect on the functional response (ie, bronchospasm was not affected).⁶¹

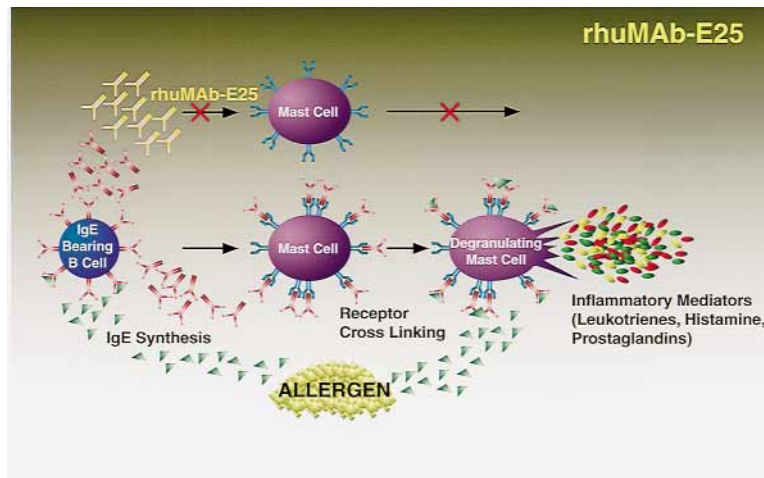


FIG 1. Recombinant monoclonal allergen stimulates B cells to synthesize and release IgE, which binds to receptors on mast cells. Exposure of these sensitized mast cells to allergen causes release of inflammatory mediators. Monoclonal anti-IgE binds free IgE, preventing mast cell sensitization.

The cytokine IL-4 is also implicated in asthma through its effects on IgE class switching and other effects, most notably adhesion molecule expression by endothelial cells. Inhalation of recombinant IL-4 induces increases in sputum eosinophilia and nonspecific bronchial responsiveness.⁶² However, in animal models, strategies directed against IL-4 have not been as effective as those directed against IL-5. Although IL-4 is clearly proinflammatory, it has recently been shown in mice that the development of eosinophilic airway inflammation and airway hyperresponsiveness can be independent of B lymphocytes and IgE.⁶³ An alternative approach is to use soluble IL-4 receptor (sIL-4R) molecules to interrupt the biological actions of IL-4 (Fig 2). sIL-4R inhibits mucus production and eosinophil recruitment in animal models and has had beneficial effects on lung function in short-term clinical studies. This approach has now been tried in the field and shows considerable promise in clinical asthma.⁶⁴

On the basis of its antagonism to IL-4 in the regulation of B cells, it has been suggested that IFN- γ might be effective against allergic inflammation. However, when parenteral IFN- γ was given to patients with steroid-dependent asthma, there was no benefit in terms of lung function or oral steroid requirements, though blood eosinophil numbers did reduce after treatment.⁶⁵ Other potential cytokine targets include the pro-T_H1 cytokine IL-12, which attenuates airway eosinophilia in animal models,^{66,67} and the pro-T_H2 cytokine IL-10, which is released in experimental human asthma.⁶⁸

Adhesion molecules

Strategies directed against adhesion molecules have also been considered, though there are some concerns that it might prove difficult to find targets that are not also involved in aspects of antigen presentation and recognition which are critical for normal host defense. In

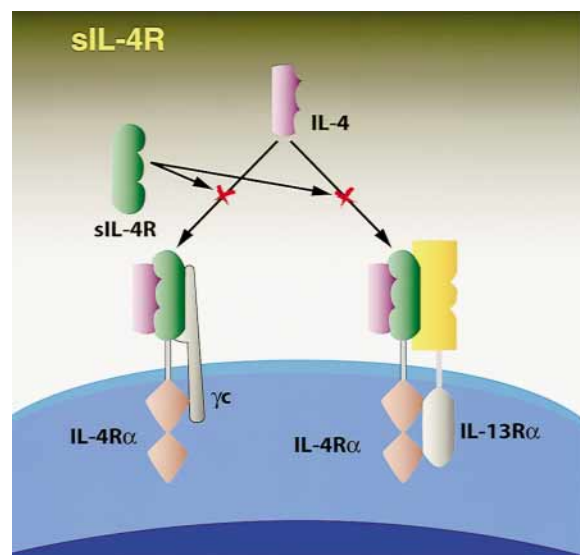


FIG 2. Recombinant human IL-4 receptor sIL-4R interacts with free IL-4, preventing its binding to the 2 IL-4 cell surface receptors.

a primate model of asthma, anti-intercellular cell adhesion molecule-1 blocked the development of airway eosinophilia and the increase in bronchial responsiveness that usually follows allergen challenge,⁶⁹ but this effect was most clear-cut when the animal had been sensitized by multiple allergen inhalations but the airways were not inflamed at the time of challenge. In contrast, anti-E-selectin was more effective when a single challenge was given to an airway that was already inflamed.⁷⁰ Adhesion molecule antagonists that can be used in humans have not yet reached clinical trials.

Chemokines

The recent discovery of soluble chemoattractant proteins (chemokines) has provided a molecular basis for many of the phenomena that have been described in the chemotaxis and cell-activation literature. Chemokines are much less specific than cytokines in terms of their receptor binding, and several chemokines can bind to 1 receptor type whereas each individual cytokine can bind to more than 1 receptor.⁷¹ The development of antagonists to chemokine receptors offers another strategy for preventing the recruitment and activation of inflammatory cells, but again the issue of selectivity is crucial. Modified chemokines have been synthesized; these include MET-RANTES and AOP-RANTES.⁷² In animal models, neutralization of RANTES decreases lymphocyte and eosinophil infiltration, whereas neutralizing monocyte chemoattractant protein 1 dramatically reduces bronchial hyperresponsiveness and inflammation. In contrast, blocking monocyte chemoattractant protein 5 abolishes bronchial hyperresponsiveness not by any effect on accumulation of leukocytes in the airways but through an effect on eosinophil trafficking.⁷² Other chemokine antagonists are stimulated by viral infections, such as vMIP-II.⁷³ These might represent viral strategies to avoid the human inflammatory response. Within model systems, it has been possible to test the receptor specificity of the RANTES variants, and it turns out that AOP-RANTES acts as an inhibitor via CCR5 but as an agonist via CCR3. This means that AOP-RANTES inhibits the effects of RANTES on T cells but mimics the effects of RANTES on eosinophils. If appropriate selective antagonists can be developed, it should eventually be possible to achieve selective blockade of cellular recruitment.

Immunotherapy

When a single antigen such as house dust mite or cat dander has been implicated in the triggering of asthmatic attacks, it might be possible to modulate the individual's response to that antigen by specific allergen immunotherapy. Allergen extracts and treatment regimens have been substantially improved in the last 15 years, and though doubts have been cast on the validity of this form of therapy,⁷⁴ it remains viable as a treatment for those patients whose asthma is driven by allergic triggers.^{75,76}

Other forms of vaccination are also being considered as strategies for asthma. From epidemiologic and experimental studies, we know that vaccination with mycobacteria has antiallergic properties. In Japan, early vaccination with BCG was associated with a substantial reduction in the risk of developing allergy,⁷⁷ though similar associations were not evident in Sweden.⁷⁸ In the laboratory it has been shown that administration of BCG before or during sensitization to ovalbumin reduces the degree of airway eosinophilia that follows subsequent challenge with ovalbumin. This effect is not mediated through any direct effect on IgE production or blood eosinophil numbers; instead, it is mediated through IFN- γ and can be reversed by exogenous IL-5.⁷⁹

Two new approaches using DNA vaccines are now undergoing serious consideration. The first of these is a general approach to allergy involving the use of CpG oligodeoxynucleotides (ODNs). This technology is essentially a refinement of the old vaccination adjuvant technique, inasmuch as CpG ODNs have been shown to be the principal activity from Freund's Complete Adjuvant. Preadministration of CpG ODNs prevented both airway eosinophilia and bronchial hyperresponsiveness in a mouse model of asthma.⁸⁰ Moreover, these effects were sustained for at least 6 weeks after CpG ODN administration.⁸¹ A contrasting approach is to use allergen-specific naked DNA sequences as vaccines. This is still in its infancy, but preliminary data suggest that giving naked DNA leads to production of allergens from within the airways' epithelial cells. Because of the different handling pathways for endogenous and exogenous allergens, it seems that the endogenously produced allergen elicits a T_H1-type response; it is hoped that if this can be reproduced in an allergic individual, it might overcome the existing T_H2-pattern response and eliminate the allergy. However, the potential for generating a powerful T_H1-type response to ubiquitous agents means that this approach will need careful evaluation in animal models before it can be pursued in human beings.

Finally, it is important to remember that it is the interaction of the inflammatory cells with the fixed elements of the airways that produces the substrate in which the excessive bronchospasm occurs. Historically, there has been a tendency to regard the epithelium, tissue matrix, and smooth muscle as victims of an uncontrolled allergic process mediated by mast cells and infiltrating leukocytes. Evidence is now emerging that the structural elements of the airway might play an important role in the development of the airway inflammation, either by producing chemotactic cytokines such as IL-8 or by releasing growth factors that lead to the deposition of collagen in the airway, remodeling of the tissue matrix, and impaired relaxation of the airways.⁸² Future work to improve the treatment of therapy-resistant asthma should include strategies to address these aspects of the pathobiology of asthma and the factors that determine the persistence of the asthma process.

REFERENCES

1. Bordley JE, Carey RA, McGhee HA, Howard JE, Kattus AA, Newman EB, et al. Preliminary observations on effect of adrenocorticotrophic hormone (ACTH) in allergic diseases. *Bull Johns Hopkins Hosp* 1949;85:396-8.
2. Medical Research Council. Double-blind trial comparing two dosage schedules of beclomethasone dipropionate aerosol with a placebo in chronic bronchial asthma. *Br J Dis Chest* 1979;73:121-32.
3. Smith MJ, Hodson ME. High dose beclomethasone inhaler in the treatment of asthma. *Lancet* 1983;1:265-9.
4. Lacroix J, Renon D, Georges D, Henry-Amar M, Marsac J. High dose beclomethasone: oral steroid-sparing effect in severe asthmatic patients. *Eur Respir J* 1991;4:807-12.
5. Ind PW. Definition of difficult asthma. *Eur Respir Rev* 2000;10:2-4.
6. Wolthers OD, Pedersen S. Short-term growth during treatment with inhaled fluticasone and beclomethasone dipropionate. *Arch Dis Child* 1993;68:673-6.
7. Silverstein MD, Yunginger JW, Reed CE, Petterson T, Zimmermann D, Li JTC, et al. Attained adult height after childhood asthma: effect of glucocorticoid therapy. *J Allergy Clin Immunol* 1997;99:466-74.

8. Allen DB, Mullen M, Mullen B. A meta-analysis of the effect of oral and inhaled corticosteroids on growth. *J Allergy Clin Immunol* 1994;93:967-76.
9. Barnes NC, Marone G, Di Maria GU, Visser S, Utama I, Payne SL. A comparison of fluticasone propionate 1 mg daily with beclomethasone dipropionate 2 mg daily in the treatment of severe asthma. *Eur Respir J* 1993;6:877-84.
10. Bernstein DI, Berkowitz RB, Chervinsky P, Dvorin DJ, Finn AF, Gross GN, et al. Dose-ranging study of a new steroid for asthma: mometasone furoate dry powder inhaler. *Respir Med* 1999;63:603-12.
11. Szeffler SJ, Brenner M, Jusko WJ, Spector SL, Flesher KA, Ellis EF. Dose and time-related effect of troleandomycin on methyl prednisolone elimination. *Clin Pharmacol Ther* 1982;32:166-71.
12. Spector SL, Katz FH, Farr RS. Troleandomycin: effectiveness in steroid-dependent asthma and bronchitis. *J Allergy Clin Immunol* 1974;54:367-79.
13. Nelson HS, Hamilos DL, Corsello PR, Levesque NV, Buchmeier AD, Bucher BL. A double-blind study of troleandomycin and methyl prednisolone in asthmatic subjects who require daily corticosteroids. *Am Rev Respir Dis* 1993;47:398-404.
14. Vrugt B, Wilson S, Bron A, Shute J, Holgate ST, Djukanovic R, et al. Low dose methotrexate treatment in severe glucocorticoid-dependent asthma: effect on mucosal inflammation and in vitro sensitivity to glucocorticoids of mitogen-induced T-cell proliferation. *Eur Respir J* 2000;15:478-85.
15. Mullarkey MF, Blumenstein BA, Andrade WP, Bailey GA, Olasen I, Wetzel CE. Methotrexate in the treatment of corticosteroid-dependent asthma. A double blind crossover study. *N Engl J Med* 1988;318:603-7.
16. Shiner RJ, Nunn AJ, Chung KF, Geddes DM. Randomised, double-blind, placebo-controlled trial of methotrexate in steroid-dependent asthma. *Lancet* 1990;336:137-40.
17. Dyer PD, Vaughan TR, Weber RW. Methotrexate in the treatment of steroid-dependent asthma. *J Allergy Clin Immunol* 1991;88:208-12.
18. Erzurum SC, Leff JC, Cochran JE, Ackerson LM, Szeffler SJ, Martin RJ, et al. Lack of benefit of methotrexate in severe steroid-dependent asthma. A double-blind, placebo-controlled study. *Ann Intern Med* 1991;114:353-60.
19. Trigg CJ, Davies RJ. Comparison of methotrexate 30 mg/week with placebo in chronic steroid-dependent asthma: a 12 week double-blind crossover study. *Respir Med* 1993;87:211-6.
20. Coffey MJ, Sanders G, Eschenbacher WL, Tsien A, Ranesh S, Weber RW, et al. The role of methotrexate in the management of steroid-dependent asthma. *Chest* 1994;105:117-21.
21. Shiner RJ, Katz I, Shulimzon T, Silkoff P, Benzaray S. Methotrexate in steroid-dependent asthma: long term results. *Allergy* 1994;49:565-8.
22. Stewart GE, Diaz JD, Lockey RF, Seleznick MJ, Trudeau WL, Ledford DK. Comparison of oral pulse methotrexate with placebo in the treatment of severe glucocorticoid-dependent asthma. *J Allergy Clin Immunol* 1994;94:482-9.
23. Ogirala RG, Sturm TM, Aldrich TK, Meller FF, Pacia EB, Keane AM, et al. Single high dose intramuscular triamcinolone acetate versus weekly oral methotrexate in life-threatening asthma: a double blind study. *Am J Respir Crit Care Med* 1995;152:1461-6.
24. Hedman J, Seideman P, Albertioni F, Stenius-Aarniala B. Controlled trial of methotrexate in patients with severe chronic asthma. *Eur J Clin Pharmacol* 1996;49:347-9.
25. Marin MG. Low dose methotrexate spares steroid usage in steroid-dependent asthmatic patients: a meta-analysis. *Chest* 1997;112:29-33.
26. Aaron SD, Dales RE, Phan B. Management of steroid-dependent asthma with methotrexate; a meta-analysis of randomised clinical trials. *Respir Med* 1998;92:1059-65.
27. Hodges NG, Brewis RAL, Howell JBL. An evaluation of azathioprine in severe chronic asthma. *Thorax* 1971;26:734-9.
28. Sihra BS, Kon OM, Durham SR, Walker S, Barnes NC, Kay AB. Effect of cyclosporin A on the allergen-induced late asthmatic reaction. *Thorax* 1997;52:447-52.
29. Khan LN, Kon OM, MacFarlane A, Meng Q, Ying S, Barnes NC, et al. Attenuation of the allergen-induced late asthmatic reaction by Cyclosporin A is associated with inhibition of bronchial eosinophils, interleukin-5, granulocyte macrophage colony-stimulating factor and eotaxin. *Am J Respir Crit Care Med* 2000;162:1377-82.
30. Alexander AG, Barnes NC, Kay AB. Trial of cyclosporin in corticosteroid-dependent chronic severe asthma. *Lancet* 1992;339:324-8.
31. Lock SH, Kay AB, Barnes NC. Double-blind, placebo-controlled study of cyclosporin A as a corticosteroid-sparing agent in corticosteroid-dependent asthma. *Am J Respir Crit Care Med* 1996;153:509-14.
32. Nizankowska E, Soja J, Pinis G, Szczeklik A. Treatment of steroid-dependent bronchial asthma with cyclosporin. *Eur Respir J* 1995;8:1091-9.
33. Laviolette M, Malmstrom K, Lu S, Chervinsky P, Pujet JC, Peszek I, et al. Montelukast added to inhaled beclomethasone in treatment of asthma. *Am J Respir Crit Care Med* 1999;160:1862-8.
34. Virchow JC, Prasse A, Naya I, Summerton L, Harris A. Zafirlukast improved asthma control in patients receiving high-dose inhaled corticosteroids. *Am J Respir Crit Care Med* 2000;162:575-85.
35. Lofdahl CG, Reiss TF, Leff JA, Israel E, Noonan MJ, Finn AF, et al. A leukotriene receptor antagonist, montelukast, allows tapering of inhaled steroid corticosteroids while maintaining asthma control: a randomised, placebo-controlled trial. *BMJ* 1999;319:1-4.
36. Bateman ED, Holgate ST, Binks SM, Tams IP. A multicentre study to assess the steroid-sparing potential of Accolate (zafirlukast; 20mg BD) [abstract]. *Euro J Allergy Clin Immunol* 1995;50:26:320.
37. Tamaoki J, Kondo M, Sakai N, Nakata J, Takemura H, Nagai A, et al. Leukotriene antagonist prevents exacerbation of asthma during reduction of high dose inhaled corticosteroid. *Am J Respir Crit Care Med* 1997;155:1235-40.
38. Wechsler ME, Garpestad E, Flier SR, Kocher O, Weiland DA, Polito AJ, et al. Pulmonary infiltrates, eosinophilia, and cardiomyopathy following corticosteroid withdrawal in patients with asthma receiving zafirlukast. *JAMA* 1998;279:455-7.
39. Nierop G, Gijzel WP, Bel EH, Zwinderman AH, Dijkman JH. Auranofin in the treatment of steroid-dependent asthma: a double-blind study. *Thorax* 1992;47:349-54.
40. Bernstein IL, Bernstein DI, Dubb JW, Faerman I, Wallin B. A placebo-controlled multicenter study of auranofin in the treatment of corticosteroid-dependent chronic severe asthma. *J Allergy Clin Immunol* 1996;98:317-24.
41. Klaustermeier WB, Noritake DT, Kwong FK. Chrysotherapy in the treatment of corticosteroid-dependent asthma. *J Allergy Clin Immunol* 1987;79:720-5.
42. Berlow BA, Liebhaber MI, Dyer Z, Spiegel TM. The effect of dapsone in steroid-dependent asthma. *J Allergy Clin Immunol* 1991;87:710-5.
43. Schwarz YA, Kivity S, Ilfeld DN, Schlesinger M, Greif J, Topilsky M, et al. A clinical and immunologic study of colchicine in asthma. *J Allergy Clin Immunol* 1990;85:578-82.
44. Newman K, Mason UG, Buchmeier A, Schmaling KB, Nelson HS. Failure of colchicine to reduce inhaled triamcinolone dose in patients suffering with asthma. *J Allergy Clin Immunol* 1997;99:176-8.
45. Roberts JA, Gunneberg A, Elliott JA, Thomson NC. Hydroxychloroquine in steroid-dependent asthma. *Pulm Pharmacol* 1988;1:59-61.
46. Charous BL, Halpern EF, Steven GC. Hydroxychloroquine improves airflow and lowers circulating IgE levels in subjects with moderate symptomatic asthma. *J Allergy Clin Immunol* 1998;102:198-203.
47. Mazer BD, Gelfand EW. An open study of high dose intravenous immunoglobulin in severe childhood asthma. *J Allergy Clin Immunol* 1991;87:976-83.
48. Jakobsson T, Croner S, Kjellman MPA, Vassella C, Bjorksten B. Slight steroid-sparing effect of intravenous immunoglobulin in children and adolescents with moderately severe bronchial asthma. *Allergy* 1994;49:413-20.
49. Salmun LM, Barlan I, Wolf HM, Eibl M, Twarog FJ, Geha RS, et al. Effect of intravenous immunoglobulin on steroid consumption in patients with severe asthma: a double-blind, placebo-controlled, randomised trial. *J Allergy Clin Immunol* 1999;103:810-5.
50. Kishiyama JL, Valacer D, Cunningham-Rundles C, Sperber K, Richmond GW, Abramson S, et al. A multicenter, randomized, double-blind, placebo-controlled trial of high-dose intravenous immunoglobulin for oral corticosteroid-dependent asthma. *Clin Immunol* 1999;91:126-33.
51. Vrugt B, Wilson S, van Velzen E, Bron A, Shute JK, Holgate ST, et al. Effects of high dose intravenous immunoglobulin in two severe corticosteroid-insensitive asthmatic patients. *Thorax* 1997;52:662-4.
52. Spahn JD, Leung DYM, Chan MTS, Szeffler SJ, Gelfand EW. Mechanisms of glucocorticoid reduction in asthmatic subjects treated with intravenous immunoglobulin. *J Allergy Clin Immunol* 1999;103:421-6.
53. Boulet LP, Chapman KR, Cote J, Kalra S, Bhagat R, Swystun VA, et al. Inhibitory effects of an anti-IgE antibody E25 on allergen-induced early asthmatic response. *Am J Respir Crit Care Med* 1997;155:1835-40.
54. Fahy J, Fleming HE, Wong HH, Liu JT, Su JQ, Reimann J, et al. The effect of an anti-IgE monoclonal antibody on the early and late-phase responses to allergen inhalation in asthmatic subjects. *Am J Respir Crit Care Med* 1997;155:1828-34.
55. Milgrom H, Fick RB, Su JQ, Reimann JD, Bush RK, Watrous ML, et al.

- Treatment of allergic asthma with monoclonal anti-IgE. *N Engl J Med* 1999;341:1966-73.
56. Durham SR, Ying S, Varney VA, Jacobson MR, Sudderick RM, Mackay IS, et al. Cytokine messenger RNA expression for IL-3 IL-4 and GM-CSF in the nasal mucosa after local allergen provocation: relationship to tissue eosinophilia. *J Immunol* 1992;148:2390-4.
 57. Shi HZ, Chen YQ, Qin SM. Inhaled IL-5 increased concentrations of soluble intracellular adhesion molecule-1 in sputum from atopic asthmatic subjects. *J Allergy Clin Immunol* 1999;103:463-7.
 58. Mauser PJ, Pitman A, Witt A, Fernandez X, Zurcher J, Kung T, et al. Inhibitory effect of the TRFK-5 anti-IL-5 antibody in a guinea pig model of asthma. *Am Rev Respir Dis* 1993;148:1623-7.
 59. Mauser PJ, Pitman AM, Fernandez X, Foran SK, Adams GK 3rd, Kreutner W, et al. Effects of an antibody to IL-5 in a monkey model of asthma. *Am J Respir Crit Care Med* 1995;152:467-72.
 60. Hamelmann E, Cieslewicz G, Schwarze J, Ishizuka T, Joetham A, Heusser C, et al. Anti-IL-5 but not anti-IgE prevents airway inflammation and airway hyperresponsiveness. *Am J Respir Crit Care Med* 1999;160:934-41.
 61. Leckie MJ, ten Brinke A, Khan J, Diamant Z, O'Connor BJ, Walls CM, et al. Effects of an IL-5-blocking monoclonal antibody on eosinophils, airway hyperresponsiveness and the response to allergen in patients with asthma. *Lancet* 2000;356:2144-8.
 62. Shi H-Z, Deng JM, Xu H, Nong ZHX, Xiao CQ, Liu ZM, et al. Effect of inhaled IL-4 on airway hyperreactivity in asthmatics. *Am J Respir Crit Care Med* 1998;157:1818-21.
 63. Hamelmann E, Takeda K, Schwarze J, Vella AT, Irvin CG, Gelfand EW. Development of eosinophilic airway inflammation and airway hyperresponsiveness requires IL-5 but not IgE or B lymphocytes. *Am J Respir Cell Mol Biol* 1999;21:480-9.
 64. Borish L, Nelson HS, Lanz MJ, Claussen L, Whitmore JB, Agosti JM, et al. IL-4 receptor in moderate atopic asthma: a phase 1/2 randomised, placebo-controlled trial. *Am J Respir Crit Care Med* 1999;160:1816-23.
 65. Boguniewicz M, Schneider LC, Milgrom H, Newell D, Kelly N, Tam P, et al. Treatment of steroid-dependent asthma with recombinant interferon-gamma. *Clin Exp Allergy* 1993;23:785-90.
 66. Iwamoto I, Kumano K, Kasai M, Kurasawa K, Nakao A. IL-12 prevents antigen-induced eosinophil recruitment into mouse airways. *Am J Respir Crit Care Med* 1996;154:1257-60.
 67. Bryan SA, O'Connor BJ, Matti S, Leckie MJ, Kanabar V, Khan J, et al. Effects of recombinant human interleukin-12 on eosinophils, airway hyperresponsiveness, and the late asthmatic response. *Lancet* 2000;356:2149-53.
 68. Robinson DS, Tscopoulos A, Meng Q, Durham SR, Kay AB, Hamid Q. Increased IL-10 messenger RNA expression in atopic allergy and asthma. *Am J Respir Cell Mol Biol* 1996;14:113-7.
 69. Wegner CD, Gundel RH, Reilly HN, Letts GL, Rothlein R. Interleukin adhesion molecule-1 (ICAM-1) in the pathogenesis of asthma. *Science* 1990;247:416-8.
 70. Gundel RH, Wegner CD, Torcellini CA, Clarke CC, Haynes N, Rothlein R, et al. ELAM-1 mediates antigen-induced acute airway inflammation and late-phase obstruction in monkeys. *J Clin Invest* 1991;88:1407-11.
 71. Nickel R, Beck LA, Stellato C, Schleimer RP. Chemokines and allergic disease. *J Allergy Clin Immunol* 1999;104:723-42.
 72. Gonzalo JA, Lloyd CM, Wen D, Albar JP, Wells TNC, Proudfoot A, et al. The co-ordinated action of CC chemokines in the lung orchestrates allergic inflammation and airway hyperresponsiveness. *J Exp Med* 1998;188:157-67.
 73. Chen S, Bacon KB, Li L, Garcia GE, Xia Y, Lo D, et al. In vivo inhibition of CC and CX3C chemokine-induced leukocyte infiltration and attenuation of glomerulonephritis in Wistar-Kyoto (WKY) rats by vMIP-II. *J Exp Med* 1998;188:193-8.
 74. Barnes PJ. Is immunotherapy for asthma worthwhile? *N Engl J Med* 1996;334:531-2.
 75. Abramson M, Puy R, Weiner J. Immunotherapy in asthma: an updated systematic review. *Allergy* 1999;54:1022-41.
 76. Walker SM, Pajno GB, Lima MT, Wilson DR, Durham SR. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. *J Allergy Clin Immunol* 2001;107:87-93.
 77. Shirakawa T, Enomoto T, Shimazu SI, Hopkin JM. The inverse association between tuberculin responses and atopic disorder. *Science* 1997;275:77-9.
 78. Strannegård IL, Larsson LO, Wennberg G, Strannegård O. Prevalence of allergy in children in relation to prior BCG vaccination and infection with atypical mycobacteria. *Allergy* 1998;53:249-54.
 79. Erb KJ, Holloway JW, Sobeck A, Moll H, Le Gros G. Infection of mice with M bovis-BCG suppresses allergen-induced airways eosinophilia. *J Exp Med* 1998;187:561-9.
 80. Kline JN, Waldschmidt TJ, Businga TR, Lemish JE, Weinstock JV, Thorne PS, et al. Modulation of airway inflammation by CpG oligodeoxynucleotides in a murine model of asthma. *J Immunol* 1998;160:2555-9.
 81. Sur S, Wild JS, Choudhury BK, Sur N, Alam R, Klinman DM. Long-term prevention of allergic lung inflammation in a mouse model of asthma by CpG oligodeoxynucleotides. *J Immunol* 1999;162:6284-93.
 82. Bousquet J, Jeffery PK, Busse WW, Johnson M, Vignola AM. Asthma: from bronchoconstriction to airways inflammation and remodelling. State of the art. *Am J Respir Crit Care Med* 2000;161:1720-45.