

Therapy for airway inflammation in asthma

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The importance of airway inflammation in the pathogenesis of asthma has recently been emphasized.^{1, 2} One possible explanation for rising asthma mortality in the face of "improved" treatments is overreliance on symptomatic (bronchodilator) therapy and underuse of prophylactic or anti-inflammatory therapy.³

In this article, the hypothesis is presented that asthma is primarily an inflammatory disease. This hypothesis underlies the rationale for concentrating on anti-inflammatory therapeutic strategies in asthma. Methods of assessing "anti-inflammatory activity" of treatments are reviewed, and the relative "anti-inflammatory" efficacy of current asthma treatments is outlined.

OBSERVATIONS

There are four observations that are central to the development of the hypotheses on which this approach to treatment is founded.

1. The first observation is the consistency of the presence of airway inflammation in even the mildest cases of asthma.^{4, 5} Although the precise components of the inflammation have not been quantified absolutely and the genesis of the inflammation remains somewhat obscure, there are some consistent features. The inflammation underlying asthma is a particular kind of inflammation that, even when inflammation is severe and protracted, appears to cause only minor tissue damage. Although many inflammatory cell types may be increased, eosinophils, metachromatic cells (mast cells and/or basophils), and probably lymphocytes appear to be the most important cells involved.

2. The second observation is that airway hyperresponsiveness (e.g., to histamine or methacholine), well recognized as a cardinal feature of asthma,⁶ correlates in magnitude with various indices of airway inflammation.⁷⁻⁹ A number of studies now have demonstrated increased airway responsiveness to correlate with bronchial lavage eosinophils,⁷⁻⁹ metachromatic cells,^{7, 8} macrophages,⁹ and desquamated epithelial cells.⁸
3. The third observation is that of a number of "inducers" that have been demonstrated to increase both airway inflammation and airway hyperresponsiveness, generally in separate studies. Inhalant allergens,^{10, 11} chemical sensitizers,^{12, 13} and viral infections¹⁴ are examples of inducers.
4. The fourth observation, largely retrospective, is that repeated (occasionally single) exposure to inducers is associated with persistent airway hyperresponsiveness. This is particularly evident in occupational asthma in which persistent airway hyperresponsiveness relates to the duration of exposure to a sensitizer after onset of symptoms.^{15, 16} Prospective data are currently being accumulated. Several population studies have demonstrated a high statistical relationship between the degree of atopy and the prevalence of airway hyperresponsiveness.^{17, 18}

Hypotheses

These four observations lead logically to the development of a number of hypotheses that relate both to the pathogenesis and treatment of asthma. These hypotheses are as follows:

Pathogenesis. (1) Airway inflammation is the primary event in asthma, and (2) airway hyperresponsiveness, both transient and persistent, is secondary to the airway inflammation; the mechanism(s) whereby inflammation leads to airway hyperresponsiveness is currently not certain. Airway hyperresponsiveness and changes therein thus provides an indirect in vivo assessment of airway inflammation

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(and changes therein). (3) Repeated and occasionally single inflammation-inducing exposures (e.g., allergen, chemical sensitizer, and virus infection) may result in persistent airway hyperresponsiveness, that is, chronic asthma.

Therapeutic hypotheses. (1) Therapies that reduce airway inflammation should be the mainstay of both acute and chronic asthma therapy. (2) If chronic or repeated airway inflammation does lead to persistent airway hyperresponsiveness and thus permanent asthma, early anti-inflammatory treatments may improve the long-term prognosis by reducing either the prevalence of persistent disease or the future severity of the disease. (3) A third therapeutic hypothesis, for which there are as yet little or no data, is the possibility that intensive anti-inflammatory therapy might induce significant remissions.

Assessment of anti-inflammatory effects

Direct assessment of inflammation requires measurement of inflammatory cells either in peripheral blood, in the airway lumen, or in the airway mucosa. Peripheral blood,¹⁹ bronchial and bronchoalveolar lavage,⁷⁻⁹ bronchial biopsy specimens,^{4, 5} and expectorated sputum²⁰ have been used to provide evidence of airway inflammation. Other than the long-recognized suppression of blood eosinophils by systemic corticosteroids,¹⁹ there are limited data on the effect of asthma treatments on direct assessment of airway inflammation. Therefore, the evaluation of anti-inflammatory effects of asthma treatments must at present rely on indirect evidence, much of which is based on the hypotheses outlined above.

The hypothesis that airway hyperresponsiveness reflects, and is caused by, airway inflammation leads directly to the hypothesis that sustained improvement in airway hyperresponsiveness likely indicates an improvement in airway inflammation. In this context, sustained improvement in airway hyperresponsiveness indicates that which occurs beyond the pharmacologic duration of action of the therapeutic agent in question, and therefore does not represent a pharmacologic inhibition, either specific or nonspecific, of the agent used to measure the airway responsiveness. This finding thus excludes the transient reduction in airway response to bronchoconstrictors induced by bronchodilators (e.g., β -agonist) or by specific inhibitors (e.g., H_1 blockers versus histamine).

A second method of indirectly assessing anti-inflammatory or prophylactic effects of medication is the inhibition (or reversal) of induced airway hyperresponsiveness, particularly hyperresponsiveness caused by allergen. Allergen-induced airway hyper-

responsiveness in the laboratory¹⁰ and during allergen seasons²¹ may thus be used as clinical models for the assessment of anti-inflammatory effects of drugs.

A third way in which anti-inflammatory effects of asthma drugs can be indirectly assessed is that of a corticosteroid-sparing effect. This sparing effect, of course, is based on the unproven, but plausible, hypothesis that the beneficial effect of corticosteroids in the management of bronchial asthma is primarily anti-inflammatory. Treatments that produce a sustained reduction in minimum corticosteroid requirements outside of those that suppress symptoms (e.g., bronchodilators) or those that alter corticosteroid metabolism (e.g., troleandomycin)²² may be hypothesized to be anti-inflammatory.

Applying these models to standard asthma therapeutic strategies, the following observations have emerged: Treatments that are either active or passively "anti-inflammatory" include environmental control, inhaled cromolyn sodium, and both inhaled and ingested corticosteroids. By contrast, bronchodilators, either β -agonists, anticholinergics, or theophylline preparations, alone or in combination, appear to exert no "anti-inflammatory" effect. Evidence for these claims will be reviewed, and additionally, a brief review of newer or unusual therapeutic approaches will be presented.

Therapeutic strategies that are anti-inflammatory

Environmental control. Reduction of exposure to either allergen²³⁻²⁵ or low-molecular-weight chemical sensitizers²⁶ results in marked improvement in airway responsiveness occurring gradually during weeks to months. Evidence for allergen avoidance comes chiefly from studies involving house dust mite, both controlled²³ and uncontrolled²⁴; there is some evidence dating back almost one fourth of a century.²⁵ The spontaneous improvement of seasonal airway hyperresponsiveness in seasonal studies²¹ is also supportive. Numerous studies in occupational asthma document that avoidance strategies can be associated with marked gradual improvement (during several months to 2 years) in airway responsiveness.²⁶ Early avoidance has the potential to result in complete resolution.

Cromolyn sodium. Cromolyn has the ability to inhibit allergen-induced increase in airway responsiveness both in the laboratory^{27, 28} and during natural seasonal exposure.²⁹ Its effect on airway responsiveness in various populations of subjects with asthma is variable³⁰ and likely depends on patient selection.

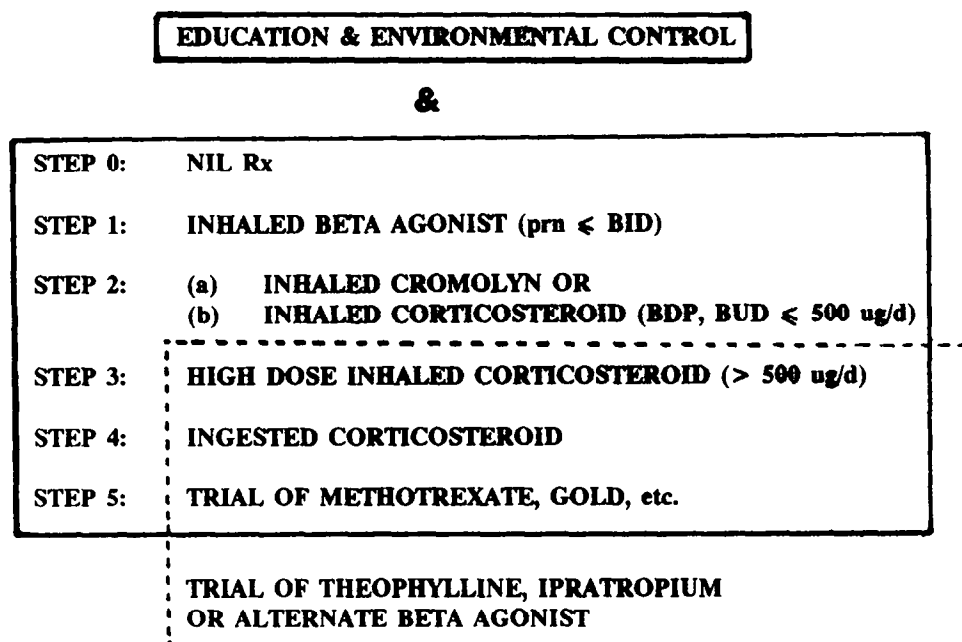


FIG. 1. Outline of a stepwise predominantly anti-inflammatory approach to outpatient asthma treatment modified from Hargreave et al.⁶⁰ Education and environmental control are followed by increasing anti-inflammatory therapy (*solid line large rectangle*); steps 0 and 1, no anti-inflammatory; steps 2 and 3, inhaled anti-inflammatory; steps 4 and 5, ingested anti-inflammatory. Bronchodilator manipulation, including theophylline or ipratropium trial(s) (*dotted line rectangle*) is tried at level step 3 or higher; *prn*, as needed; *b.i.d.*, twice daily; *BDP*, beclomethasone dipropionate; *BUD*, budesonide.

There appears to be little effect in subjects not exposed to allergen.³¹ Although cromolyn can inhibit some noninflammatory triggers of bronchospasm (e.g., exercise), the evidence that cromolyn is anti-inflammatory outside the setting of current allergen exposure is, as yet, uncertain.

Corticosteroids. Both inhaled and ingested corticosteroids, particularly the former, appear to be the most potent anti-inflammatory agents of the commonly used asthma drugs. Corticosteroids inhibit allergen-induced increase in airway responsiveness, both experimental²⁷ and natural.³² Both of these corticosteroids, but particularly inhaled corticosteroids, produce consistent marked and sustained improvement in airway hyperresponsiveness in unselected subjects with asthma.³³⁻³⁶ When treatment with moderate- to high-dose inhaled corticosteroids is continued (often beyond that required for symptom control), airway responsiveness continues its gradual improvement (during months), often to normal or near normal.³⁶ If such improvement can be sustained, the benefits are obvious.

Drugs that are not anti-inflammatory

The other commonly used drugs in the management of asthma are bronchodilators. Despite some claims

of an anti-inflammatory effect in some models for theophylline,³⁷ it appears likely that none of the currently available three classes of bronchodilators is anti-inflammatory in human asthma in vivo.

β_2 -Agonists. Inhaled β_2 -agonists do not prevent allergen-induced airway hyperresponsiveness in the laboratory²⁷ or during seasonal exposures.²⁹ The regular use of β -agonists in naive subjects does not improve airway responsiveness^{33, 34, 38, 39}; in fact, some studies have demonstrated small increases in airway responsiveness that occur within a few weeks of commencing a β_2 -agonist, terbutaline, and that does not appear to progress thereafter.^{33, 34} It has been hypothesized that such a small shift in the magnitude of airway responsiveness induced by β_2 -agonists in the general population (subjects with asthma) might significantly increase the number of individuals with severe airway hyperresponsiveness, thus being one possible explanation for increase in asthma mortality.⁴⁰

Theophylline. Likewise, theophylline does not inhibit allergen-induced increases in airway responsiveness,²⁸ nor does it produce any sustained improvement in airway responsiveness when it is administered chronically.^{35, 41} This finding suggests that, in conventional doses in the model of human asthma, theophylline is not anti-inflammatory.

Cholinergic antagonists. Antimuscarinic agents are effective bronchodilators. The late asthmatic response to allergen is not inhibited by these agents, and some data,⁴² largely unpublished, have documented that these do not prevent allergen-induced increase in airway responsiveness in the laboratory. A recent investigation has confirmed that the regular use of ipratropium does not improve airway responsiveness.³⁹

New and alternative therapies

A number of new or less traditional asthma therapies have possible or probable anti-inflammatory effects. Some examples are listed.

Methotrexate. Methotrexate (and other cancer chemotherapeutic agents) has been used in asthma for its corticosteroid-sparing effect.⁴³ The corticosteroid-sparing effect suggests an anti-inflammatory action.

Gold. Parenteral gold salts are used as an anti-inflammatory in rheumatic diseases. Studies from Japan have documented a corticosteroid-sparing effect of intramuscular gold on the course of asthma.⁴⁴ Substantial improvement in airway hyperresponsiveness has been observed.⁴⁵ In one open trial, an ingested gold preparation had a modest corticosteroid-sparing effect.⁴⁶

Hydroxychloroquine. Hydroxychloroquine is also used as an anti-inflammatory therapy in the rheumatic diseases. A preliminary open trial in corticosteroid-dependent subjects with asthma is optimistic regarding its efficacy as an anti-inflammatory agent in asthma.⁴⁷

Nedocromil. Nedocromil is a new, inhaled prophylactic agent distantly related to cromolyn. It is believed to have a spectrum of activity that is at least as broad, if it is not broader, than cromolyn.⁴⁸ It may improve airway responsiveness in nonallergic subjects with asthma.⁴⁹

Ketotifen. Ketotifen is an H₁ blocker that is widely used as an antiallergic or prophylactic medication in the management of asthma.⁵⁰ Its effect on direct or indirect measures of airway inflammation is not certain.

Single mediator inhibitors. The complexity of the mediators involved in asthma inflammation makes it unlikely that inhibition of a single mediator or of its synthesis is likely to exert a major beneficial influence on airway inflammation. Many agents have been investigated in asthma, and there are a few provocative glimpses. Inhibition of the cyclooxygenase pathway with indomethacin has a modest inhibiting effect on allergen-induced increase in airway responsiveness.⁵¹ Although this effect could not be reproduced by inhibition of thromboxane synthesis,⁵² some studies suggest that thromboxane synthetase inhibitors may improve airway responsiveness⁵³; further investigation is necessary. Platelet-activating factor is an interesting

candidate for an inflammatory mediator in asthma⁵⁴; investigations as to its importance in inflammation in asthma are pending. Leukotriene antagonists and newer antihistamines are also being investigated.

Long-acting β_2 -agonists. New ultralong-acting β_2 -agonists, such as salmeterol and formoterol, demonstrate sustained bronchodilating effects. There are preliminary claims regarding anti-inflammatory effects of these new agents, particularly salmeterol,^{55, 56} unlike their shorter-acting relatives. Further studies are necessary.

Allergen-injection treatment. The efficacy of allergen injections in the management of asthma is too large and controversial a topic to be covered in depth in this article. There is a theoretic rationale to suggest the possibility of an anti-inflammatory effect analogous to that which might be achieved by environmental control, and indeed one study demonstrating reduction in late asthmatic responses after immunotherapy with mite⁵⁷ would support this possibility. Nevertheless, there are other studies⁵⁸ and some anecdotes⁵⁹ that suggest allergen-injection therapy can be "proinflammatory" and increase airway responsiveness.

PRACTICAL APPLICATION

The importance of inflammation in the pathogenesis of asthma and possibly in the persistence of asthma has led logically to development of therapeutic plans in which anti-inflammatory treatments are used more aggressively and earlier in asthma management. One such approach, the result of a consensus conference in Canada, has recently been published⁶⁰ and is summarized in Fig. 1. Education regarding the nature of the disease, the nature and use of medications, the goals of treatment, and both early recognition and self-treatment of worsened asthma is stressed. Anti-inflammatory treatments, particularly environmental control, inhaled cromolyn, and inhaled corticosteroids, are essentially front-line therapy; symptoms and bronchodilator (β -agonist) requirements are minimized, the latter ideally to twice a day or less. It is hoped that the aggressive and early use of anti-inflammatory therapy in the management of asthma will reduce morbidity and mortality and perhaps even improve the overall prognosis of asthma.

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