

The changing faces of asthma

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Over the last 20 years, the understanding of the pathogenesis of asthma has changed dramatically. Asthma is now seen as a disease of chronic airway inflammation. Consequently, the paradigm of management has expanded from “as-needed bronchodilators” to include maintenance therapy with anti-inflammatory medications and action plans. Health care professionals are assessing medications as potential disease-modifying drugs. To do this, they must understand the natural history of asthma and identify the markers of the disease that reflect long-term outcomes. This article reviews the way in which the concept of asthma has changed, the impact of this new knowledge on the basis of medication selection, and the options for evaluating the effect of medications on long-term outcomes. Reevaluating information will continue to expand our horizon of methods to improve asthma management. (*J Allergy Clin Immunol* 2000;106:S139-43.)

Key words: Asthma therapy, leukotriene receptor antagonist, asthma management, surrogate markers, Childhood Asthma Management Program

How one looks at asthma, in relation to the method of development and use of medications, has evolved over the last few decades. Because of the substantial progress made in the understanding of the pathophysiologic features of asthma, it is no longer viewed as a disease of reversible airway obstruction, but a disease of chronic inflammation with varying degrees of severity. These new insights into the causes of asthma have impacted on the recommendations about both the prevention and the therapeutic management of the disease (Table I).¹

In the 1960s, epinephrine was the drug of choice in the treatment of asthma, and it was attractive because it relieved bronchospasm. In the 1970s, many new agents were brought to clinical trials in an effort to improve on epinephrine. Isoproterenol, metaproterenol, albuterol, and pirbuterol were developed in the search for drugs with greater bioavailability and longer in vivo half-lives than epinephrine. Because of these new longer-acting bronchodilator agents, it was realized that bronchospasm

Abbreviations used

CAMP: Childhood Asthma Management Program
COPD: Chronic obstructive pulmonary disease
FDA: Food and Drug Administration
FVC: Forced vital capacity

could be prevented. The use of methylxanthines, specifically theophylline (administered orally with extended-release formulations) also came into prominence at about this time. Because of its ability to relax bronchial smooth muscle, theophylline was the most popular drug for asthma treatment in the mid 1980s. During this period, information was gathered about methods to individualize medication dosing strategies. Through the measurement of serum theophylline concentrations, patient response could be optimized.

In the 1980s, it became apparent that theophylline's narrow therapeutic window required careful monitoring to avoid potential drug interactions and conditions that alter theophylline absorption from extended-release preparations. Although theophylline is still frequently used in the management of chronic obstructive pulmonary disease (COPD) today, its use in the treatment of asthma substantially declined by the end of the 1980s. Because of favorable features in the prevention of the pulmonary response to an allergen exposure, cromolyn was introduced as a drug that could impede the development of asthma exacerbations. Prevention of breakthrough symptoms in patients with mild-to-moderate bronchial asthma was now possible with a very safe medication.

With newfound experience in bronchoscopy, bronchoalveolar lavage, and biopsy techniques, research in the 1980s revealed new information about the pathophysiologic features of the disease, especially in adults. For example, features of chronic inflammation were recognized, which superseded the old model of viewing inflammation as consisting of eosinophils and mast cells. The new paradigm shifted to a model of chronic inflammation similar to that featured in diseases such as rheumatoid arthritis and inflammatory bowel disease. This changed the entire spectrum of how asthma was viewed in the 1990s. Attention then shifted to methods for preventing and resolving inflammation. Inhaled glucocorticoids quickly replaced theophylline and cromolyn as the preferred maintenance medications. Expert panels have emphasized the benefits of inhaled glucocorticoids as a preferred long-term controller in adults and older children, based on the concept of asthma as a disease of chronic airway inflammation.^{2,3} Inhaled glucocorticoids are known to be effective in controlling asthma symp-

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TABLE I. The changing faces of asthma

Time period	Goal of management	Preferred medication
1960s	Relieve bronchospasm	Epinephrine
1970s	Prevent bronchospasm	Albuterol, theophylline
1980s	Prevent allergen-induced bronchospasm	Cromolyn
1990s	Prevent and resolve inflammation	Inhaled glucocorticoids; leukotriene modifiers?
2000s	Prevent and reverse airways remodeling	???? disease modifiers

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toms and reducing the intensity of the inflammatory response in studies conducted in asthmatic adults. This effect lasts only as long as the treatment continues; there is no known treatment that can consistently induce a lasting remission in the disease. Inhaled glucocorticoids have a relatively slow offset of effect when compared with other long-term controller medications, which suggests that they have a significant effect on resolving chronic inflammation and improving asthma control.⁴

In 1996, 2 medications in a new leukotriene modifier class were approved for use in the treatment of asthma in the United States: zileuton (a leukotriene synthesis inhibitor) and zafirlukast (a leukotriene receptor antagonist). In 1998, the Food and Drug Administration (FDA) approved another leukotriene antagonist, montelukast.

Leukotrienes have been recognized as potent mediators of inflammation and are released in response to an allergic stimulus by cells involved in the inflammatory response, which are understood to be present in the airways of asthmatic patients. These cells are known to mediate bronchoconstriction and inflammatory changes important in the pathophysiologic features of asthma (such as microvasculature permeability, mucus secretion, and neutrophil recruitment) and may contribute to airway edema. The leukotriene modifiers are considered an attractive alternative to inhaled glucocorticoids.⁵⁻¹² These modifiers are particularly well received by some pediatricians because of the easy administration. There is, however, still some hesitancy in prescribing this class of agents, and more experience with them is needed.

An advantage of montelukast over the previous 2 medications in this class is the data that supports its use in young asthmatic children. Clinical studies have been conducted in children as young as 6 years of age^{11,12} and are presently completed in asthmatic children as young as 2 years of age. The question of concern now is whether glucocorticoids and leukotriene modifiers alter the course of the disease by preventing and reversing airway inflammation, including some of the features of chronic changes that fall under the category now labeled as "airway remodeling."

KEY MESSAGES IN ASTHMA MANAGEMENT

At least 7 major guidelines for asthma were put forth in the first 20 years. With the proliferation of these guidelines, a number of key issues in the area of asthma management have emerged. These issues include the pathophysiologic features, risk factors, optimal treatment modalities, and adverse effects associated with asthma management.

Asthma is a chronic inflammatory disease of the airways. Current therapy, even in children, is based on the concept that chronic inflammation is a key feature of asthma, but little information exists about either the time of onset of inflammation or about the mechanism for its initiation, progression, and persistence. Patients with difficulty in controlling their asthma have evidence of persistent inflammation.¹³⁻¹⁵ The disease often has its onset in early childhood, which may suggest that children who manifest persistent inflammation in the presence of anti-inflammatory therapy are at an increased risk for disease progression. If so, it will be important to recognize these patients and to provide more effective interventions at the critical stages of the disease.

Allergy is an important risk factor. There is a general belief among asthma care specialists that allergy is an important risk factor for the persistence of the disease. It is also thought to be important in terms of asthma's initiation and development; more research is needed to clarify this, however. To decrease the exposure to allergens, the patient's allergen sensitivity can be identified; exposure levels to specific allergens can be measured, and environmental control can be attempted to reduce allergen exposure. This can all be accomplished fairly effectively, provided the allergens can be defined. Unfortunately, many patients have multiple allergens. Whereas some degree of allergen control can be achieved in the home environment, it becomes more challenging to completely control the many different environments to which the patient is exposed in the course of a day. These practical limitations to environmental autonomy often result in reliance on therapeutic intervention to adequately control symptoms.

Early intervention can prevent long-term effects of inflammation. Numerous studies have shown that inhaled glucocorticoids improve asthma management and reduce inflammation in the airways. Recent observations suggest that this response is highly dependent on the time of intervention, with earlier use superior to later use.^{4,16-18} Understanding the onset and progression of the inflammation, and its persistence, could provide insight into defining appropriate treatment strategies that depend on the stage of the disease.¹⁹ Theories have developed that early intervention with inhaled glucocorticoid therapy can be effective in preventing the progression of the disease and the irreversible changes in the airways that could result in the persistence of symptoms.^{4,16-18} Thus, there appears to be a "window of opportunity" that is critical for intervention.

Treatment should be adjusted to maintain optimal control. One of the consequences of undertreating the asthmatic patient may be a loss of pulmonary function over time that is greater than that observed in patients without asthma. This reduction in pulmonary function with the duration of disease is similar to that observed in COPD and cystic fibrosis.¹⁹⁻²¹ Recent guidelines have suggested a step-wise approach to asthma management in both children and adults.^{3,4} Because there is no established method to monitor inflammation, indirect parameters such as symptoms and pulmonary function must be used to define optimal control. Once control is established, the maintenance medication schedule can be adjusted to the lowest daily dose that stabilizes symptoms.

Inhaled glucocorticoids may affect growth velocity. There have been issues of concern regarding the risk of long-term adverse effects with glucocorticoid therapy, and now publications support those concerns in terms of potential adverse effects on growth, bone density, and ocular disorders. Therefore, attention has been focused on the safe use of inhaled steroids, with an acceptance of the potential risk. In July 1998, an FDA panel stated that inhaled steroids are the preferred medication for long-term control of persistent asthma; they may, however, adversely affect growth.²² Several recent studies have also suggested that high dosing or long-term use of inhaled glucocorticoids may be associated with a higher risk for ocular disorders such as glaucoma or cataracts.²³⁻²⁵

GAPS IN OUR KNOWLEDGE

Although much progress has been made in the therapeutic management of asthma, gaps in our knowledge still exist.^{19,26-29} For example, although it is hypothesized that the pathophysiologic features of asthma are inflammation based, it is not known when the onset of inflammation begins or what cellular mechanisms are critical for the initiation and progression of the disease. The role of the antigen-presenting cell in the pathophysiologic features of asthma is also not well defined. This information could impact the choice of appropriate therapeutic interventions for each stage of the disease, because there may be a time when the disease is "out of control" and not dependent on allergen stimulation. For optimum therapeutic management, there needs to be criteria for initiating, titrating, and discontinuing treatment. There may be an ideal time for intervention, with well-defined treatment strategies for the choice of therapy (monotherapy or combination therapy) and criteria for the initiation, titration, and discontinuation of treatment. The appropriate time of intervention and the appropriate step-wise therapy are 2 of the most debated issues in asthma therapy today.

It is also important to determine the benefits and risks of early treatment intervention. We have very little information on the long-term effects of asthma medications, especially inhaled glucocorticoids and leukotriene modifiers when administered to young children for prolonged

periods of time. It has not been shown definitively whether glucocorticoids as a treatment strategy are the drug of choice, although they are frequently used in this population. Questions that remain to be answered include how glucocorticoids affect long-term outcome, the risks-to-benefits ratio, and the appropriate dose and method of administration. The long-term adverse effects of early intervention coupled with long-term treatment are unknown, and there is concern that this type of treatment will result in cataracts early on or adverse effects that will become apparent in the future. The recent FDA meeting of the Pulmonary and Allergy Drug and Endocrinology Advisory Panels concluded that there are no minimally effective and maximally safe doses of inhaled glucocorticoids defined for children.²² The effect of specific variables such as age, gender, race, and genetics on the risk for adverse events or lack of effects of medication also remains to be determined.

CANDIDATE SURROGATE MARKERS FOR ASTHMA

There is a need for surrogate markers for the assessment of both disease and treatment parameters. Through the use of these markers, clinical testing could be simplified with the assessment of 1 or 2 primary efficacy variables that would have some meaning in terms of disease management. We have a pretty clear picture of the indicators of poor asthma control (Table II).¹ It is now a challenge to define what markers to target that could be indicators of poor long-term outcome. Candidate surrogate markers for disease parameters include pulmonary function and asthma control measures. The severity of decline in pulmonary function can potentially be assessed through FEV₁, FEV₁/FVC (forced vital capacity), peak expiratory flow, and airway hyperresponsiveness. Markers that indicate the level or extent of asthma control include the need for rescue therapy, treatment failure, and the progression of severity. In children under the age of 5 years, FEV₁ is extremely difficult to measure for various reasons (eg, the child is unable to cooperate and/or perform forced expiration for reliable spirometry), and different ways to measure pulmonary function in this age group must be defined. Because of this inherent difficulty, disease measures such as rescue therapy, treatment failure, and episode-free days are the limited options. Presently, it is uncertain which disease markers are the most appropriate to use.

The efficacy and safety of various treatments can also be assessed through the use of surrogate markers. Common markers for inhaled glucocorticoids include cortisol and linear growth suppression, knemometry, bone density, and ophthalmic disorders. It is unclear whether long-term growth measures must be used or if knemometry is an adequate surrogate marker for adverse effects on growth. Similarly, it is unknown whether there are quick measures for bone density that can be performed in the short term and whether ophthalmologic markers exist. Leukotriene modifiers may also be assessed through

TABLE II. Indicators of asthma control, ranked by level of clinical significance

Death
Hospitalization
Acute exacerbations
Emergency Department visit
Course of prednisone
Nocturnal symptoms
Breakthrough symptoms
β -agonist requirement
Wheezing episode affecting activity
Peak expiratory flow
Morning drop
Variability or lability through the day
Pulmonary function (spirometry)
FEV ₁ (an indicator of airway obstruction)
Individual measurements
Pattern of decline over time
FVC (necessary to assess reliability of FEV ₁ measurement)
FEV ₁ /FVC (another indicator of airway obstruction)
Total lung volume (indicator of hyperexpansion)
Bronchial hyperresponsiveness (marker of airway sensitivity to activity or irritants)
Exercise
Methacholine or histamine
Markers of inflammation
Induced sputum (cytologic features, especially eosinophils, neutrophils, or mediators)
Blood (total eosinophils; activated eosinophils)
Serum (eosinophilic cationic protein)
Exhaled nitric oxide (requires special instrument; at present time, limited to research applications)
Biopsy (limited application at the present time)
Cytologic features (eosinophils, mast cells, lymphocytes; and neutrophils)
Features of airway remodeling (collagen, elastin, and tenascin deposition)

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liver function tests, eosinophil count, and possibly through effects on the immune system. Because the lungs and immune systems are still developing in young children, there is additional concern for toxicities and adverse effects on the developing child.

Experience with available surrogate markers indicates that important markers show small but significant changes, such as FEV₁ decline over time, and thus are indicative of a pattern.¹⁹⁻²¹ Because these changes are small, a long-term study is required to reach statistical significance. Clinical studies have reported a potential decline in FEV₁ over time of about 0.7% to 1% predicted per year, which indicates that 3 or more years would be necessary to detect a significant change.^{30,31} Long-term studies pose unique challenges, including the ethical aspects of study design, recruitment, and retention of study subjects, medication selection, adherence to proto-

col, and the analysis of data.³¹

CHILDHOOD ASTHMA MANAGEMENT PROGRAM: MEETING THE CHALLENGES

Long-term studies in children pose other challenges, including a high cost and the requirement of long-term planning; unlike short-term studies, they do not provide immediate answers to urgent questions. There are also questions about how to analyze the data. For example, it is not clear how to best analyze measures of lung growth.

The Childhood Asthma Management Program (CAMP), which is sponsored by the National Heart, Lung, and Blood Institute, was assembled in 1991 and is the most comprehensive study in childhood asthma to date.³¹ Over 1000 children, 5 to 12 years of age at enrollment, have now been followed for an average of 4 to 5.5 years in this multicenter study. Unlike the typical clinical study, minority populations comprised one third of the participants of this study, as required by the National Institutes of Health guidelines for clinical research. This is an extremely important group in which to assess for therapeutic intervention, based on the well-known impact of the disease on this patient population. Measurements included in CAMP were spirometry to assess lung development and measures of airway hyperresponsiveness. Three different treatment arms are being evaluated: the inhaled glucocorticoid budesonide, the inhaled nonsteroid long-term control medication nedocromil, and placebo. Medication selection was based on the anticipated interest in these medications at the time of completion of the first phase of this study in 1999.

Most studies in asthma with long-term control medications define treatment failure as the first significant exacerbation leading to prednisone treatment. Removing the patient from the study consequently results in problems in data analysis for the projection of long-term outcome. In CAMP, to account for both the patient declining and improving in health, algorithms were built in for medication reduction and rescue. Immediate rescue for breakthrough symptoms is albuterol, to be used as needed. Prednisone is available for a severe exacerbation after communication with the study physician to assess the indications. Specific criteria were also defined for intervention with additional long-term control therapy. Beclomethasone was used for poorly controlled asthma. This in itself and the time between each step-wise increment in therapy may be very important endpoints.

The CAMP research team developed a Patient Education Center and carefully selected participants to ensure adherence to the study protocol.³² To minimize measurement variability, strict procedures were used to certify the staff, and the equipment was standardized. Ancillary studies were built into the protocol to address specific questions in smaller populations. Because of the length of the study, it was designed to have flexibility in addressing current issues. It was important, particularly with the emergence of organized health care systems,

that the primary care physician was kept involved.

Analysis of data derived from a long-term study such as CAMP poses many unique problems and challenges. In long-term studies that involve children, the impact of medication on disease modification must be assessed. In the final data analysis, growth and development must be accounted for. For example, with measures of linear growth, it is preferred that the final height be measured, and it is unclear how accurate intermediate measures can be projected. Rescue therapy also affects the final analysis, because it can affect the primary measure.

As illustrated by the CAMP study, there are many challenges in conducting childhood asthma studies. These include identifying meaningful outcomes, determining appropriate measures, defining relevant inclusion and exclusion criteria, supporting recruitment and retention and medication adherence, considering growth and development in the analysis, and assessing the safety and benefit. Many important lessons that can be applied to future long-term pediatric studies will also be identified through CAMP. These types of studies require a multidisciplinary team, and a coordinating center is crucial for trial management. The questions posed must be focused and timely; for example, unique features of the study population must be considered. Great emphasis should also be placed on education because cooperation is crucial to maintain the quality of the study. Most important for the future direction of asthma management is the selection of parameters that reflect the long-term impact of an intervention.

REFERENCES

- Szeffler SJ. Asthma: the new advances. *Adv Pediatr* 2000;47:273-308.
- Global Initiatives for Asthma. Global strategy for asthma management and prevention, NHLBI/NIH workshop report. Publication no. 95-3659. Bethesda (MD): National Institutes of Health, National Heart, Lung, and Blood Institute; 1995.
- National Asthma Education and Prevention Program Expert Panel Report 2. Guidelines for the diagnosis and management of asthma. Publication no. 97-4051. Rockville (MD): National Institutes of Health, National Heart, Lung, and Blood Institute; 1997.
- Hahtela T, Jarvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K, et al. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med* 1994;331:700-5.
- Spector SL. Leukotriene inhibitors and antagonists in asthma. *Ann Allergy Asthma Immunol* 1995;75:463-70,473-4.
- Holgate ST, Bradding P, Sampson AP. Leukotriene antagonists and synthesis inhibitors: new directions in asthma therapy. *J Allergy Clin Immunol* 1996;98:1-13.
- Liu MC, Dube LM, Lancaster J, and the Zileuton Study Group. Acute and chronic effects of a 5-lipoxygenase inhibitor in asthma: a 6-month randomized multicenter trial. *J Allergy Clin Immunol* 1996;98:859-71.
- Spector SL, Smith LJ, Glass M. Effects of 6 weeks of therapy with oral doses of ICI 204,219, a leukotriene D4 receptor antagonist, in subjects with bronchial asthma. *Am J Respir Crit Care Med* 1994;150:618-25.
- Reiss TF, Altman LC, Chervinsky P, Bewtra A, Stricker WE, Noonan GP, et al. Effects of montelukast (MK-0476), a new potent cysteinyl leukotriene (LTD4) receptor antagonist, in patients with chronic asthma. *J Allergy Clin Immunol* 1996;98:528-34.
- Israel E, Cohn J, Dube L, Drazen JM. Effect of treatment with zileuton, a 5-lipoxygenase inhibitor, in patients with asthma: a randomized controlled trial: zileuton clinical trial group. *JAMA* 1996;275:931-6.
- Knorr B, Matz J, Bernstein JA, Nguyen H, Seidenberg BC, Reiss TF, et al. Montelukast for chronic asthma in 6- to 14-year-old children: a randomized, double-blind trial: pediatric montelukast study group. *JAMA* 1998;279:1181-6.
- Kemp JP, Dockhorn RJ, Shapiro GG, Nguyen HH, Reiss TF, Seidenberg BC, et al. Montelukast once daily inhibits exercise-induced bronchoconstriction in 6- to 14-year-old children with asthma. *J Pediatr* 1998;133:424-8.
- Leung DYM, Martin RJ, Szeffler SJ, Sher ER, Ying S, Kay AB, et al. Dysregulation of interleukin-4, interleukin-2, and interferon- γ gene expression in steroid-resistant asthma. *J Exp Med* 1995;181:33-40.
- Wenzel SE, Szeffler SJ, Leung DYM, Sloan SI, Rex MD, Martin RJ. Bronchoscopic evaluation of severe asthma: persistent inflammation despite high dose glucocorticoids. *Am J Respir Crit Care Med* 1997;156:737-43.
- Lee TH, Brattsand R, Leung D. Corticosteroid action and resistance in asthma. *Am J Respir Crit Care Med* 1996;154 (suppl):S1-S79.
- Agertoft L, Pedersen S. Effects of long term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994;88:373-81.
- Selroos O, Pietinalho A, Lofroos AB, Riska H. Effect of early vs late intervention with inhaled corticosteroids in asthma. *Chest* 1995;108:1228-34.
- Overbeek SE, Kerstjens HAM, Bogaard JM, Mulder PGH, Postma DS, and the Dutch CNSLD study group. Is delayed introduction of inhaled corticosteroids harmful in patients with obstructive airways disease (asthma and COPD)? *Chest* 1996;110:35-41.
- Peat J. Asthma: a longitudinal perspective. *J Asthma* 1998;35:235-41.
- Weiss ST. Early life predictors of adult chronic obstructive lung disease. *Eur Respir Rev* 1995;5;31:303-9.
- Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998;339:1194-200.
- Food and Drug Administration. Pulmonary and Allergy and Endocrinology Advisory Committees meeting, July 30-31, 1998; Bethesda, Md.
- Garbe E, LeLorier J, Boivin J-F, Suissa S. Inhaled and nasal glucocorticoids and the risks of ocular hypertension or open-angle glaucoma. *JAMA* 1997;277:722-7.
- Cumming RG, Mitchell P, Leeder SR. Use of inhaled corticosteroids and the risk of cataracts. *N Engl J Med* 1997;337:8-14.
- Garbe E, Suissa S, LeLorier J. Association of inhaled corticosteroid use with cataract extraction in elderly patients. *JAMA* 1998;280:539-43.
- Silverman M, Taussig L. Early childhood asthma: What are the questions? *Am J Respir Crit Care Med* 1995;151(suppl):S1-S42.
- Busse W, Banks-Schlegel SP, Larsen GL. Childhood- versus adult-onset asthma. *Am J Respir Crit Care Med* 1995;151:1635-9.
- Silverman M, Pedersen S. Outcome measures in early childhood asthma and other wheezing disorders. *Eur Respir J* 1996;9(suppl):1s-49s.
- Woolcock AJ, Barnes PJ. Asthma: the important questions: part 3. *Am J Respir Crit Care Med* 1996;153(suppl):S1-S32.
- Zeiger RS, Dawson C, Weiss S, and the Childhood Asthma Management Program Research Group. Relationships between duration of asthma and asthma severity among children in the Childhood Asthma Management Program (CAMP). *J Allergy Clin Immunol* 1999;103:376-87.
- Childhood Asthma Management Program Research Group. Design, rationale, and methods: Childhood Asthma Management Program. *Control Clin Trials* 1999;20:91-120.
- Childhood Asthma Management Program Research Group. Design and implementation of a patient education center for the Childhood Asthma Management Program (CAMP). *Ann Allergy Asthma Immunol* 1998;81:571-81.