Challenges in assessing outcomes for pediatric asthma

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Although progress has been made in understanding asthma, much remains unknown; as a result, diagnosis and treatment are not optimal. Information is still needed about the natural history of asthma to better understand which patients are at risk of inflammation and at what point during their disease that inflammation occurs. In the case of children, a greater understanding of the disease's natural history is needed to establish criteria for early diagnosis and to evaluate progressive aspects of the disease so that appropriate measures of progression can be defined. The safety of various medications used as long-term controllers must also be evaluated. The growing information about medication effects on asthma provides unique opportunities to design studies that will guide improvement in asthma care. A number of disease outcomes can be used as surrogate markers of clinically significant endpoints, and a number of adverse effects may serve as surrogate markers. The consequences of poor control of pediatric asthma can be observed in a variety of clinical markers, including clinical features of the disease that worsen as it progresses, pulmonary function deterioration, lung hyperexpansion, and inflammation increases. The Childhood Asthma Management Program is an ongoing clinical trial designed to improve the diagnosis and treatment of asthma in children. Its hypothesis is that anti-inflammatory treatment of childhood asthma will not only relieve morbidity but will also improve lung growth. (J Allergy Clin Immunol 2001;107:S456-64.)

Key words: *Chronic inflammation, pulmonary function, natural history, inhaled glucocorticoids, nonsteroid controller medications, surrogate markers*

Asthma, a chronic inflammatory disease of the airways, is a major health concern. Between 14 and 15 million people in the United States have this disease, including nearly 5 million children, which makes it childhood's most common chronic disease. Every year, asthma restricts activity for more than 100 million days and is the cause of 470,000 hospitalizations, with rates highest among African American individuals and children. More than 5000 people die of asthma every year, and death rates, which are consistently highest among African American individuals aged 15 to 24 years, have increased or remained stable over the past decade.[1]

Abbreviations used
CAMP: Childhood Asthma Management Program
PEFR: Peak expiratory flow rate

Although progress has been made in understanding asthma, much remains unknown; challenges remain in the assessment of treatment outcomes. Only recently have a few subcategories of the disease been elucidated, permitting a better understanding of their treatment response. By examining indicators of inadequate asthma control and surrogate markers of response to therapy, this article will provide an understanding of these subcategories. This new information has also been used in designing and managing the Childhood Asthma Management Program (CAMP).[2]

RISK FACTORS FOR PERSISTENT ASTHMA

The identified risk factors for persistent asthma include parental asthma, maternal smoking, atopic features, the presence of relevant allergens in the environment, and small lungs.[3,4] Asthma can occur early in life. Current therapy for children and adults is based on the concept that chronic inflammation is a key feature of the disease and that patients whose asthma is difficult to control show evidence of persistent inflammation.[5-8] Understanding the onset and progression of inflammation and its persistence in asthma may provide insight into the definition of appropriate strategies for treatment, depending on the stage of the disease.[4]

Relevant outcome measures in persistent asthma

Poorly controlled asthma is associated with abnormalities in a variety of clinical and objective parameters, which can be used to gauge asthma control.[9] Intervention, either through environmental control or medication, may reverse one or more of these features but usually not all of them. Because individuals with asthma can have a varying clinical course, clinicians must continually assess the risks of untreated or inadequately treated asthma versus the risk of intervention. To make an informed choice, clinicians need information not only about subcategories of disease abnormalities but also about subcategories of treatment response. When designing clinical trials, not

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only must the disease subcategory and its appropriate marker be identified, but also a primary efficacy variable must be chosen to determine whether the treatment is successful. Once the primary efficacy variable is identified, a determination must be made as to whether the variable is a true surrogate marker of the disease.

CONSEQUENCES OF POOR CONTROL OF PEDIATRIC ASTHMA

The consequences of poor control of pediatric asthma can be observed in a variety of clinical markers, including clinical features of the disease that worsen as it progresses, pulmonary function deterioration, lung hyperexpansion, and inflammation increases. Questions remain as to how these markers are related to the natural history of the disease: How are they affected by treatment, and which of the markers can predict the outcome of the disease? The clinical markers that result from poor control will be discussed and are summarized in Table I.

Markers of acute exacerbations of asthma can include death, hospitalization, emergency department visits, and courses of prednisone. Although the main objective of treatment is to reduce mortality rates, death is an infrequent outcome; in any study with death as the outcome measure, large numbers of patients would need to undergo follow-up over long periods of time. Hospitalization is another meaningful variable and probably representative of near death. Emergency department visits are also important outcomes of asthma but, like hospitalizations, are infrequent. In contrast, courses of prednisone are frequent, particularly in young children.

Mild clinical exacerbations include nocturnal asthma, breakthrough symptoms, requirements for β-agonist use, and wheezing after activity. These markers are observed more frequently over a shorter period than death or hospitalization, and smaller numbers of patients are needed to measure the effects of the treatment.

Most asthma care specialists think that early childhood asthma is underdiagnosed and undertreated. One of the consequences of undertreatment is a greater loss of pulmonary function over time, as measured by FEV_1 compared with patients without asthma. The loss of FEV_1 for undertreated asthmatic patients is similar to that observed in chronic pulmonary disease and cystic fibrosis.[10,11] Other measures of pulmonary function, such as peak expiratory flow rate (PEFR), can also be markers of treatment efficacy. In a clinical trial, however, patient adherence to repeated measures of pulmonary function may be an issue, raising other issues as to which outcome measures indicate disease progression.

The progression of asthma severity can be another consequence of poor control and should be differentiated from persistence. Progression describes events that occur either gradually or rapidly, whereas persistence describes events that have occurred and then persist. Progression can be measured by the increasing frequency or severity of symptoms or by an increasing medication requirement. Patients with severe asthma often have a history of increasing medication requirements, starting with β-agonists, moving to additional long-term control medications such as cromolyn, theophylline, long-acting β-agonists, and inhaled steroids.

TABLE I. Indicators of inadequate asthma control (ranked by increasing level of clinical significance)

- Death
- Hospitalization
- Acute exacerbations
  - Emergency department visit
  - Course of prednisone
- Nocturnal symptoms
- Breakthrough symptoms
  - β-Agonist requirement
  - Wheezing episodes that affect activity
- Peak expiratory flow
  - Morning drop
  - Variability or lability through the day
- Pulmonary function—spirometry
  - FEV_1
    - Individual measurements
    - Pattern of decline over time
  - FEV_1/FVC
  - Total lung volume to assess hyperexpansion
  - Bronchial hyperresponsiveness
    - Exercise
    - Methacholine or histamine
- Increase of medication requirement to control asthma
- Markers of inflammation
  - Induced-sputum cytologic factors (especially eosinophils) or mediators
  - Serum-eosinophil cationic protein
  - Blood eosinophils
  - Exhaled nitric oxide
- Biopsy-limited application at the present time
  - Cytologic eosinophils, mast cells, lymphocytes, and neutrophils
  - Features of airway remodeling—collagen, elastin, and tenascin deposition

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Markers of inflammation provide information about the natural history of the disease, because they indicate improvement or worsening in control. Cytologic markers may indicate airway remodeling, but these markers have not been agreed on. Possible markers include measures of collagen, tenascin, and elastin. Building models of the consequences of poor control of asthma, such as airway remodeling, however, is difficult, and the only way a useful model will be built is to develop a strong rationale for the application of measures of declining control in regular patient care. Once that rationale is accepted, it will become important for clinicians to make these measurements.

UNDERSTANDING THE NATURAL HISTORY OF ASTHMA

The natural history of asthma is still not fully understood. Information is needed to understand which

TABLE II. Comparative clinical effects of asthma medications

Medication	Symptom scores*	PEFR†		Acute exacerbations*
		Morning	Evening	
β-Adrenergic				
Albuterol/terbutaline	++	+	++	++
Salmeterol	+++	++	++	++
Theophylline	++	++	++	++
Glucocorticoid	+++	+++	+++	+++
Cromolyn	++	++	++	++
Nedocromil	++	++	++	++
Leukotriene antagonists	++	++	++	++

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+++, Marked effect; ++, moderate effect; +, some effect.
*Chronic therapy results in improved symptom scores or reduced frequency of acute exacerbations.
†Chronic therapy results in improved PEFR measured in either the morning or evening.

patients are at risk of inflammation and at what point during their disease inflammation occurs. This information would help to establish preventive measures before the onset of inflammation. It is also not known whether asthma is progressive in all patients. If not, various models of the disease's natural history must be constructed. Still to be determined, however, are the appropriate outcome measures to indicate progression of the disease and whether the markers discussed earlier are reasonable indicators of progression.

MEDICATIONS FOR MANAGING CHILDHOOD ASTHMA

Inhaled glucocorticoids

Inhaled steroids currently appear to be the drug of choice in the treatment of the progression of early-onset childhood asthma, but this may be only because more data have been collected about these drugs. Although no treatment can consistently induce a lasting remission of asthma in adults, as long as treatment continues, inhaled glucocorticoids can control symptoms and reduce the intensity of the inflammatory response. Early intervention with inhaled glucocorticoid therapy may be effective in the prevention of both the progression of the disease and the risk of irreversible changes in the airways that can result in the persistence of symptoms.[12-15] Thus, there appears to be a window of opportunity that is critical for intervention. Compared with other long-term controller medications, however, inhaled glucocorticoids have a relatively slow offset of effect.[13] Chronic therapy with inhaled glucocorticoids is associated with a reduction of collagen and tenascin deposition, as previously reported.[16,17]

Nonsteroid controller medications

Nonsteroid controller medications (such as theophylline, leukotriene modifiers, long-acting β_2-agonists, cromolyn, and nedocromil) relieve and even prevent symptoms (Table II). They also improve pulmonary function, but their effect on long-term control of airway inflammation and disease progression has not been completely established. Therefore, when used concomitantly with the nonsteroid long-term controllers, the adjustment of the dose of inhaled glucocorticoids is difficult because they can mask indirect measures of inflammation such as pulmonary function.

The effects of medications in asthma

Although most medications can improve pulmonary function when administered regularly, they differ in their mechanisms of action, in their offset of effect, and particularly, in the features associated with resolution of inflammation (Table II).[9] From an examination of the symptom scores, the inhaled steroids always appear to be the most effective although other medications may approach, but never exceed, the steroids in efficacy. As a result, symptom scores alone may be misleading in terms of the individual effects of each medication.

When the performance of the medications is broken into subcategories of response, differences can be observed. Such differences include the immediate improvement of a patient's response to different bronchodilators, protection from a pulmonary response to allergens, bronchospasm induced by histamine or exercise, or the effect of the medications on the resolution of the pulmonary effects of asthma over time (Table III).

The resolution of asthma can also be used as a measure of the effects of medications. After continuous therapy, resolution is defined as a reduction of airway hyperresponsiveness, number of inflammatory cells, or thickness of the subepithelial layer below the basement membrane. The resolution can be proved by reversibility of hyperresponsiveness to a normalized state or by biopsy.

Table IV shows the effects of medications at the cellular level.[9] For example, the effect of β-agonists is to relax smooth muscle, enhance mucociliary transport, inhibit antigen-induced release of mediators, and increase mucus and water secretion into the airways, whereas the effect of theophylline is to potentiate β-agonists, adenosine blockade, and the membrane-stabilizing effect. In vitro studies identify effects of the medications on the release of cellular mediators. In vivo long-term effects of the medications can be determined by alterations in the

TABLE III. Comparative effects of asthma medications

Medication	Bronchodilator	Protection		Resolution*
		Allergen	Histamine/EIB	
β-Adrenergic				
Albuterol, terbutaline, pirbuterol	+++	I	+++	–
Salmeterol (long duration)	+++	I,L	+++	–
Anticholinergic	+	–	ND	ND
Theophylline	++	I,L	+	+
Cromolyn	–	I,L,AR	–	++
Nedocromil	–	I,L,AR	–	++
Inhaled glucocorticoid	–	L,AR	–	+++
Leukotriene modifiers				
Zileuton	++	I,L	ND	ND
Zafirlukast	±	I,L	ND	ND
Montelukast	++	I,L	++	ND

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I, Blocks immediate pulmonary response to allergen challenge; *L*, blocks late pulmonary response to allergen challenge; *AR*, blocks consequent airway hyperresponsiveness; *EIB*, exercise-induced bronchospasm; *ND*, no data available; +++, marked effect; ++, moderate effect; +, some effect; –, no effect; ±, variable effect.
*Defined as a reduction in airway hyperresponsiveness, number of inflammatory cells, or thickness of subepithelial layer below basement membrane after continuous therapy.

inflammatory cell infiltrate in either bronchoalveolar lavage fluid or biopsy material from the airway mucosa.

SURROGATE MARKERS IN THE EVALUATION OF THERAPEUTIC INTERVENTIONS

Information about the effects of medication on asthma provides unique opportunities to design studies that will further improve asthma care. Such studies should lead to the determination of the dosage requirements for various drugs and the identification and evaluation of surrogate markers to assess their effects.

Robert J. Temple of the Food and Drug Administration has provided the following clinical definition of a clinical trial's surrogate endpoint: "…laboratory measurement or a physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions, or survives. Changes induced by therapy on a surrogate endpoint are expected to reflect changes in a clinically significant endpoint."[18] Table V lists several possible surrogate endpoints for the assessment of response to asthma therapy, including possible adverse effects of specific treatments.

Studies could also lead to the refinement of techniques that optimize the efficacy and safety of asthma medications, which could help to define the disease and its response to medications and provide accurate markers. Studies with medications could also clarify the genetics of diseases and the role of genetics in the actions of drug receptors, drug metabolism, and behavior.[19-24]

Experience with surrogate markers

Experience with the available surrogate markers indicates that many important markers show only small changes over time. For example, with analysis of baseline data in the CAMP trial, it was observed that FEV_1 percent predicted decreases by 1% predicted FEV_1 per year.[25] Although such changes may seem small, they may be significant. Long-term studies are required to measure such small changes, but these measurements can be difficult in small children, particularly those under the

TABLE IV. Comparative cellular and tissue effects of asthma medications

Medication	Cellular*	Bronchoalveolar†	
		Lavage	Biopsy
β-Adrenergics‡			
Albuterol/terbutaline	+++	–	–
Salmeterol	+++	–	–
Formoterol	+++	ND	ND
Theophylline§	++	++	ND
Cromolyn/nedocromil	++	+	ND
Glucocorticoid	+++	+++	+++
Leukotriene modifiers			
Zileuton	+++	ND	ND
Zafirlukast	–	+	ND
Montelukast	–	+	ND

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+++, Marked effect; ++, moderate effect; +, some effect; –, no effect; *ND*, no data available.
*In vitro studies identify effects on mediator release.
†Long-term effects show alteration in inflammatory cell infiltrate, either in lavage fluid or in airway mucosal biopsy material.
‡Effect on smooth muscle relaxation, enhanced mucociliary transport, inhibition of antigen-induced release of mediators, increased mucus, and water secretion into the airways.
§Potentiates the stabilizing effect of β-adrenergics, adenosine blockade, and membrane.

TABLE V. Candidate surrogate markers for the assessment of response to asthma therapy

Disease parameters
Asthma control
Symptom-free days
Need for rescue therapy
Treatment failure
Progression of severity
Pulmonary function
FEV_1
FEV_1/FVC
Peak expiratory flow
Pulmonary resistance
Airway hyperresponsiveness
Adverse effects of treatment
Inhaled glucocorticoids
Cortisol suppression
Linear growth
Stadiometry
Knemometry
Osteopenia
Bone densitometry
Bone markers
Ophthalmologic disorders
Increased ocular tension
Cataracts
Leukotriene modifiers
Liver enzyme test
Eosinophil count, given the reports of Churg-Strauss syndrome in adults with severe asthma
Immune system, identifying any potential risk for immune system alterations

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age of 5 years. Moreover, long-term studies pose unique challenges that include the ethical aspects of study design, recruitment, and retention; medication selection; adherence to protocol; and data analyses that account for growth. Some markers, such as changes in FEV_1, occur so rarely that large numbers of patients may be needed to identify the incidence of that marker's occurrence.

Disease outcomes as surrogate markers

Asthma control. Many disease outcomes can be used as surrogate markers of clinically significant endpoints. Outcomes that indicate asthma control may be more useful in clinical trials than the infrequent or slow changes seen with other markers. Symptom-free days are a good measure of control, but its reliability depends on the patient's ability to maintain daily records. With young children, the measure's reliability depends on the caregivers' ability to recognize symptoms and to record their frequency.

Another marker is the need for rescue therapy, but that also depends on the patient and caregiver and on their ability to decide what level of symptom presentation merits treatment with a rescue therapy. Treatment failure is a marker that usually requires systemic steroid therapy and careful assessment of severity and communication with the supervising physician to decide when additional therapy is needed. A carefully designed algorithm and the education of patients, parents, and physicians are important to ensure relative uniformity in the application of this step as an outcome measure. The progression of severity is a helpful measure in long-term studies in which sufficient time is available to monitor asthma control, as indicated by the amount of rescue therapy used. As with treatment failure, an algorithm should be provided with this measure to assist in the decision process. One episode of treatment failure may not be enough to indicate disease progression, but a series of minor treatment failures such as prednisone bursts, which trigger the next level of intervention, may indicate progression.

Pulmonary function. Spirometry, generally a reliable measure in children older than 5 years of age but not in younger children, requires trained personnel to obtain reliable measures, which depend on the use of the same equipment and standards of performance for research personnel in all the centers in the study. The same age limits also apply to the use of peak flow meters. Hand-held versions of these devices are now readily available for home measurement, but the patient must perform reliable measurements and record the results. Newer devices, such as Airwatch, have internal data collection systems that eliminate the step for patient recording. The limit of these devices may be the patients' ability to produce reliable measurements in the absence of supervision by trained personnel. Measures of resistance can be obtained in young children by applying the forced oscillation technique. This can only be obtained in a clinic setting and requires trained personnel and careful analysis of the data.

ADVERSE EFFECTS OF TREATMENT AS SURROGATE MARKERS

Inhaled glucocorticoids

A number of adverse effects to therapy, especially with inhaled glucocorticoids, may serve as surrogate markers. Cortisol suppression measures and serial blood sampling require an overnight stay in a research facility with trained personnel. Although cortisol suppression is an objective measure that yields a dose response curve with increasing dosage of steroid administration, the implications of its systemic effect are not understood. For example, it is not known whether this effect is a sign of the suppression of linear growth, which can be measured by stadiometry or knemometry. Both techniques require a long-term study, a sufficient number of patients to detect significant changes, and in the case of knemometry, trained personnel. Knemometry is a controversial technique in regard to the information it provides and its clinical application. Osteopenia can be measured by bone densitometry and bone markers.

Bone densitometry requires standard equipment and performance measures, a long-term study, and a sufficient number of patients to detect significant changes. The reliability of the results can be problematic, however, if the various study sites use different types of equipment. Bone

markers have not been useful predictive indicators of alterations in bone density, the clinically significant outcome. Ophthalmic disorders include increased ocular tension and cataracts, both very difficult to measure in young children. In addition, cataracts require a long-term study to observe any effects.

Leukotriene modifiers

Liver enzyme tests and eosinophil counts are easily obtained but must be followed for a sufficient period of time to identify the effect. In regard to immune system effects, the relevant test must be identified, and a sufficient time period for observation to detect an effect must be allotted.

GOALS IN PEDIATRIC ASTHMA THERAPY

To advance the effectiveness of asthma therapy in children, a number of goals must be pursued. A greater understanding of the natural history of the disease is needed to establish criteria for early diagnosis and to evaluate progressive aspects of the disease so that appropriate measures of progression can be defined. The safety of various medications used as long-term controllers must be evaluated, specifically in relation to inhaled steroids and leukotriene modifiers. The efficacy in young children of certain medications (including cromolyn, nedocromil, leukotriene modifiers, and inhaled steroids) needs to be examined. The selection of medications for early intervention should be refined, which requires a careful assessment of the balance between efficacy and safety. In various age groups and with various levels of asthma severity, it is important to define the maximally safe dose and the minimally effective dose for the available inhaled steroids and the respective delivery devices. The benefits and risks of the new delivery devices must be addressed, including chlorofluorocarbon replacements and dry powder, breath-actuated delivery devices, and nebulizers.

CAMP

CAMP is an ongoing clinical trial designed to improve the diagnosis and treatment of asthma in children by seeking progress toward some of the goals mentioned earlier.[25,26] The underlying hypothesis for this randomized, placebo-controlled trial is that anti-inflammatory treatment of childhood asthma will not only relieve morbidity but will also improve lung growth. In children with asthma, then, the trial will evaluate the relative efficacy of 3 treatment strategies on asthma control and on lung growth and development.

CAMP was initiated in 1991; 1041 participants aged 5 through 12 years were enrolled between November 1993 and September 1995 at 8 clinical centers. Almost one third of the participants were members of minority groups. This was probably CAMP's biggest contribution because minorities have not been adequately represented in most pharmaceutic trials. Participation of minorities usually has been approximately 5% and rarely more than 10%.

In CAMP, the primary outcome measure was lung growth as indicated by postbronchodilator FEV_1 as a percent of the predicted volume observed over a 5- to 6-year period. CAMP also assessed differences between treatment groups with respect to airway responsiveness, morbidity, and physical and psychologic growth and development. The participants' inclusion was based, in large part, on their ability to perform spirometry, which can measure the drugs' effect on lung growth.

Participants were randomized into 1 of 3 treatment groups (budesonide, nedocromil, or placebo) and were followed for a minimum of 5 to 6.5 years. Budesonide is a well-characterized inhaled glucocorticoid delivered in a device that is emerging as the delivery device of the future.[27] Nedocromil, an inhaled nonsteroid controller, is an emerging nonsteroid inhaled medication that may eventually replace cromolyn. The metered-dose inhaler with cromolyn has not been found to be consistent in its effect, however. For the ease of patients, the use a nebulizer for 5 years was considered inconvenient. Even though placebo groups are not allowed in European clinical trials, the inclusion of the placebo group was important because it provides important information about asthma's natural history.

Each participant was given recourse to rescue therapy by means of a metered-dose inhaler that contained the short-acting β_2-agonist, albuterol, to be used for relief of symptoms or pretreatment of exercise-induced asthma. To treat significant asthma exacerbations, prednisone was initiated according to specific guidelines. In most clinical trials, prednisone use indicates a treatment failure, and the patient is removed from the study. If that procedure had been followed in this 5-year trial, more than one half of the trial population would have been lost, but by retaining participants who used prednisone, the frequency of prednisone bursts could be followed. In addition to prednisone courses, data on hospitalizations and emergency department visits were collected for the first time in any study. This trial provided not only measures of the reduction in β-agonist use or changes in peak flow but also profiles of the medications' performance.

Beclomethasone was also available for poorly controlled asthma. Because patients needed to follow certain criteria before they could receive beclomethasone, information on its use will be an indicator of disease progression or treatment failure.

The preliminary results from CAMP support the concept that asthma severity is related to the duration of the disease.[25] The data include information on asthma duration, lung function (including airway responsiveness to methacholine), and symptoms. Although the choice of the best method of quantitation of asthma severity is controversial, relationships can be shown between several variables that reflect severity and the time of physician-diagnosed asthma to entry into CAMP. For example, after potential explanatory variables (which include atopy, levels of the household allergen Der p 1, anti-inflammatory medication use, and other variables) were controlled, regression models showed that the longer the duration of asthma, the lower the lung function. The association was

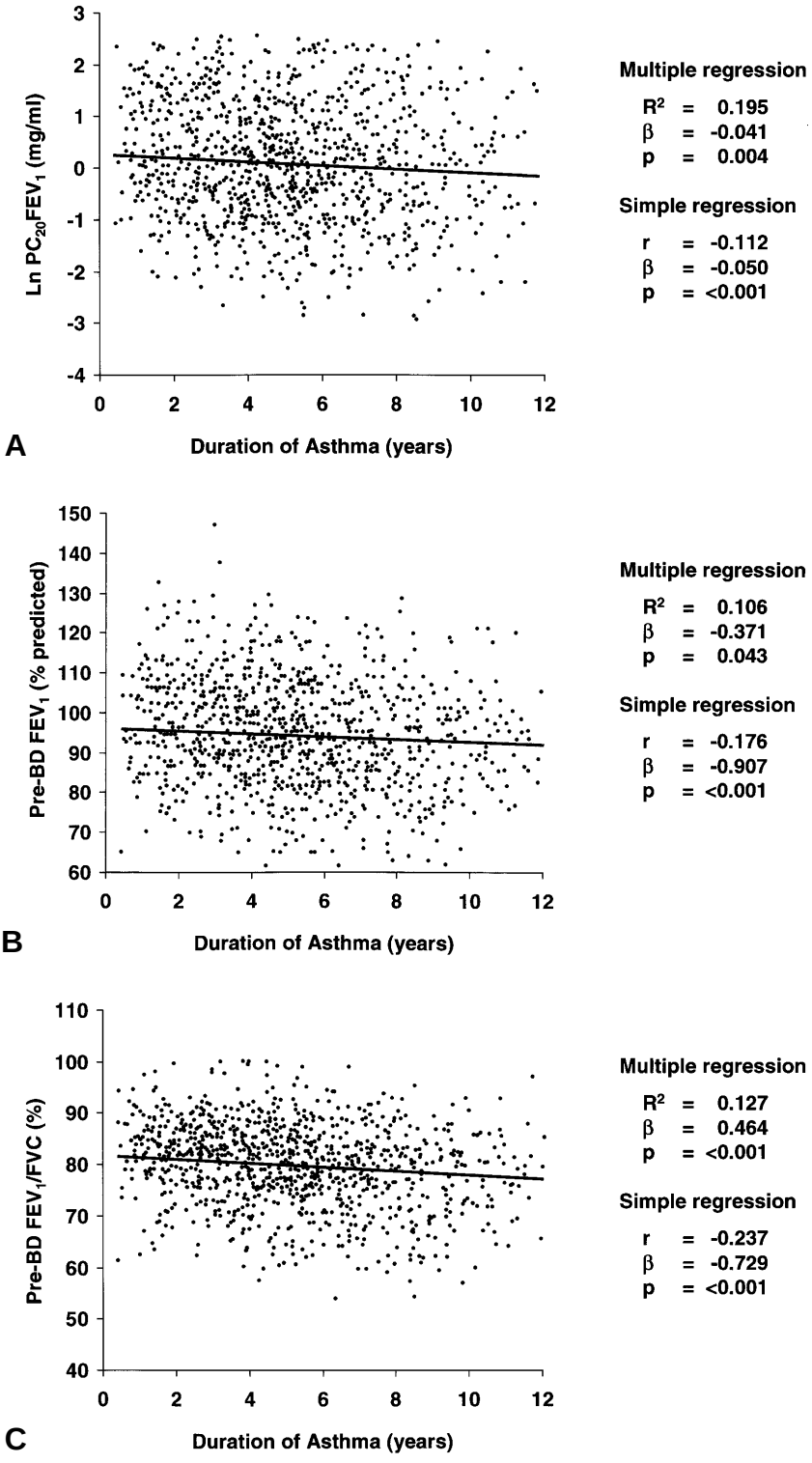

FIG 1. Relationship between (**A**) natural logarithm PC_{20} FEV_1, (**B**) prebronchodilator FEV_1, and (**C**) prebronchodilator FEV_1/FVC (%) and asthma duration determined by multiple regression analyses adjusted for the following potential confounding parameters: age at randomization, sex, serum log IgE level, number of positive skin prick test responses, total blood eosinophil count, asthma severity, household Der p 1 level, prior use of inhaled corticosteroids and cromolyn, and clinical center. *R*, Spearman rank coefficient for unadjusted bivariate analysis of this relationship by simple linear regression; *Pre-BD*, prebronchodilator. (From Zeiger RS, Dawson C, Weiss S. 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. With permission.)

significant and independent of the other variables that were studied. This lower function was reflected in greater methacholine responsiveness, expressed as the natural log of FEV_1PC_{20} (Fig 1, *A*), prebronchodilator percent predicted FEV_1 (Fig 1, *B*), prebronchodilator FEV_1/FVC (Fig 1, *C*), and postbronchodilator FEV_1/FVC.[25] More asthma symptoms and a greater use of albuterol on an as-needed basis also indicated lower function with longer duration during the 4-week screening period. Duration was significantly associated with assessments by physicians and nurses of asthma severity and other historic measures of medication use. Thus, CAMP has established a relationship between the duration of the disease and multiple criteria that, taken together, reflect the severity of the disease.

In CAMP, the long-term effects of the medications that are used and the impact of medications on disease modifications are being studied, including measurement of final height and full development as measured by bone density, which are crucial issues in children. CAMP also measured the effects of drugs on lung growth, including their effects on the maintenance of and the potential harm to lung growth. The results were recently published.[28]

The management of the trial was coordinated with the participants' primary care physicians, acknowledgment of the impact of managed care, and insurance companies. In addition, the trial dealt with the adverse effects of the selected medications and the publicity sometimes associated with such effects. The treatment phase was completed between February and June 1999, and the washout phase was completed in October 1999. A 5-year follow-up observational study has begun in which maximum lung growth and other outcomes will be followed.

The experience with CAMP will provide some important lessons for the future. Effective studies of pediatric asthma require the use of a multidisciplinary team; a coordinating center, as set up in CAMP, is crucial for study management. The questions posed in studies must be focused and timely and should consider the unique features of the study population by means of effective patient and clinician education. Studies should be designed so that the results have long-term impact; the possible future direction of asthma management should be considered.

CONCLUSIONS

Inadequate asthma control is a serious, widespread problem among children. Although death and hospitalization from asthma are not common, the disease, if uncontrolled, can produce debilitating symptoms that interfere with normal life. Usually, asthma can be controlled with therapy, and possible surrogate markers that permit the assessment of patients' response to therapy have been identified. These include disease parameters that measure the clinical effects of treatment, such as the number of symptom-free days and pulmonary function (ie, FEV_1 and PEFR). The adverse effects of treatment can also be used as markers of patient response to treatment.

Clinical trials, such as CAMP, can advance the diagnosis and treatment of asthma in children. One third of the children enrolled in CAMP are from minority groups, the populations that are disproportionally affected by asthma, and their experience in the trial will be particularly important. While evaluating the relative efficacy of 3 treatment strategies on asthma control, CAMP will also provide information on the effect of anti-inflammatory treatment not only on morbidity but also on lung growth and development.

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