Leukotriene receptor antagonists in asthma therapy

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In persons with asthma, the cysteinyl leukotrienes possess multiple inflammatory properties in vitro and have long been considered to be a potentially important mediator of asthma and an attractive target for therapeutic intervention. Controlled clinical trials have documented the efficacy of leukotriene receptor antagonists in asthma treatment, but reservations about their use for asthma therapy center on two main issues: the heterogeneity of patient responses and their reduced potency relative to other asthma medications. For example, leukotriene receptor antagonists also have been shown to be less efficacious than inhaled corticosteroids for several end points, including symptom relief, reduced markers of inflammation, and improved pulmonary function. This review explores several underappreciated aspects of asthma therapy: heterogeneity of patient responses to medication, the failure of symptoms to correlate with commonly used end points, and the potential of delivery to distal airways for producing important and novel benefits. (J Allergy Clin Immunol 2003;111:S62-70.)

Key words: *Leukotriene receptor antagonists, end points, asthma symptoms, pulmonary function, dyspnea, distal airways*

Because of their potent activities as smooth muscle spasmogens, mucus secretagogues, enhancers of vascular permeability, and stimuli for inflammatory cell recruitment in vivo, slow reacting substances of anaphylaxis (identified as the cysteinyl leukotrienes [CysLTs] in 1979[1]) have been considered to be potentially important mediators of asthma and thus attractive targets for therapeutic intervention.[2,3] Subsequent work has confirmed that CysLT receptor antagonists (LTRAs) produce multiple anti-inflammatory properties in patients with asthma in vivo (Table I).

Montelukast, for example, has decreased circulating eosinophils,[4-6] decreased sputum eosinophils,[7] and decreased exhaled nitric oxide in patients with asthma.[8] In addition, there are sound mechanistic reasons for using leukotriene-active drugs in conjunction with corticosteroids, the most effective class of drugs available for asthma treatment. Leukotriene production is not affected by systemic corticosteroids in some situations,[9] and the inhaled corticosteroid (ICS) beclomethasone dipropionate and the LTRA montelukast have had an additive effect in decreasing circulating eosinophils.[10]

Controlled clinical trials have documented the efficacy of LTRAs in the treatment of asthma, as shown by improvements in a variety of symptom measures (symptom score, nighttime awakenings, and mornings with asthma), several measures of pulmonary function (morning peak expiratory flow rate, [PEFR], FEV_1), rescue β-agonist use (Fig 1), and asthma exacerbations.[2-6,10-19] In many studies LTRAs have been effective both as monotherapy in mild-to-moderate asthma[4-6,11-13] and in combination with other asthma controllers.[14-16] ICS-sparing effects have been documented.[16]

Abbreviations used
CysLT: Cysteinyl leukotriene
ICS: Inhaled corticosteroid
LTD_4: Leukotriene D_4
LTRA: Leukotriene receptor antagonist
PEFR: Peak expiratory flow rate

Nevertheless, the reservations concerning the use of LTRAs for asthma therapy center on two main issues. First, not all patients respond in the same way, and the responses in a group of individuals approximate a normal distribution. Most responses are clustered around the mean, but there are some patients who appear not to respond and others who respond very well (Fig 2).[5] Second, LTRAs have been less efficacious than ICSs in controlled clinical trials for a variety of asthma end points such as symptom relief, reduced markers of inflammation, and particularly improved pulmonary function, the criterion standard for asthma therapy.[5,18,19] Nevertheless, the perception of physicians remains that the clinical benefits of improved FEV_1 or PEFR produced by LTRAs exceed the physiologic benefits in some asthmatic patients.

Several underappreciated aspects of asthma therapy include the heterogeneity of patient responses to each asthma medication, the failure of patient symptoms (a subjective measure) to correlate with several objective measures (particularly pulmonary function as reflected in the FEV_1 or PEFR), and the success of medications delivered to the distal airways, either by systemic therapy or by way of new delivery systems, to produce important and novel benefits.

HETEROGENEITY OF RESPONSES TO DIFFERENT ASTHMA MEDICATIONS

The variability in clinical response produced by the LTRA montelukast was documented in a study comparing it with low-dose beclomethasone dipropionate for the treatment of patients with mild-to-moderate asthma.[5] Whereas 34% of patients did not have an improvement in FEV_1 after treatment with the LTRA, 22% had no

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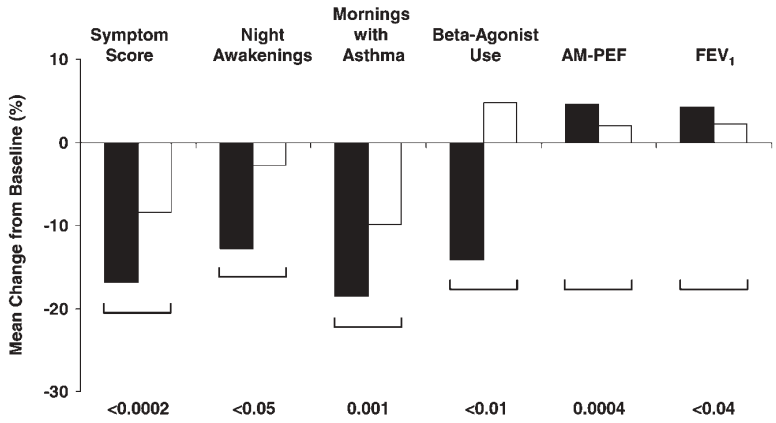


FIG 1. Effects of the LTRA zafirlukast (*black bars,* n = 514) and placebo (*white bars,* n = 248) on asthma symptoms, β-agonist use, and pulmonary function in patients with mild-to-moderate asthma. Baseline asthma characteristics were similar between groups, except for nighttime awakenings, which occurred significantly less often ($P = .02$) in the placebo group. FEV_1 was 78% of predicted. *AM-PEF,* Morning PEFR. Data from Fish JE, Kemp JP, Lockey RF, Glass M, Hanby LA, Bonuccelli CM. Zafirlukast for symptomatic mild-to-moderate asthma: a 13-week multicenter study. The Zafirlukast Trialists Group. Clin Ther 1997;19:675-90.

response to 400 μg/d of beclomethasone.[5] Similar percentages of asthmatic patients had no responses to a variety of asthma medications in a variety of other settings as well: 34% of patients with acute severe asthma had no response to 7.5 mg of albuterol in the emergency department,[20] 20% of persons with acute severe asthma admitted to the hospital had no response to systemic corticosteroids "for days,"[21] and 38% of a small group of asthmatic subjects had no response to high-dose (2000 μg/d) fluticasone.[22] Therefore, heterogeneity of patient response is characteristic of both asthma and asthma medications in general. A major challenge for improving asthma therapy is matching asthmatic patients efficiently with the medications to which they will respond robustly.

ASTHMA END POINTS AND THE IMPORTANCE OF ASTHMA SYMPTOMS AS AN END POINT

Many end points have been used in clinical trials, including wheeze, dyspnea, cough, chest tightness, nocturnal awakenings, rescue medication use, rescue medication–free days, symptom-free days, measures of pulmonary function (eg, FEV_1, PEFR variability, and airway hyperresponsiveness), asthma exacerbations, and indices of airway inflammation (eg, inflammatory cells in sputum, bronchoalveolar lavage, biopsy specimens, and exhaled nitric oxide). These end points have been used while trying to take into account patient adherence, adverse effects, and therapy costs. Physicians generally are most comfortable when evaluating measurable, "objective" end points such as pulmonary function, but patients are more concerned with symptoms and asthma exacerbations.

MODELING ASTHMA SYMPTOMS

A National Institutes of Health National Heart, Lung, and Blood Institute workshop on symptom perception and respiratory sensation in asthma has divided the many symptoms asthmatic patients have (such as wheeze, chest tightness, dyspnea, inability to exhale, cough, and nocturnal symptoms) into two general categories that can be modeled experimentally.[23] These categories are (1) wheeze (bronchospasm), which can be modeled by an external resistance (mechanical loading), and (2) the inability to exhale fully (air trapping), which can be modeled by a high-dose methacholine challenge that causes changes in inspiratory capacity (an increase in end-expiratory lung volume). In these models, 74% of the variance associated with the Borg breathing difficulty rating scale was associated with alterations in end-expiratory lung volume. With a different measure of dyspnea, the perceived change from treatment with ICSs correlated poorly with sputum eosinophils when they were 20% or fewer.[24]

TABLE I. Anti-inflammatory effects of the LTRA montelukast in vivo

Decreased circulating (blood) eosinophils
Decreased sputum eosinophils
Decreased exhaled nitric oxide

EFFECTS OF LEUKOTRIENE D_4 ON ASTHMA SYMPTOMS AND PULMONARY FUNCTION

Studies performed almost 2 decades ago examined the effects of leukotriene D_4 (LTD_4) inhalation on symptoms and pulmonary function in patients with asthma.[25,26] In one study,[25] all 6 of the challenged asthmatic patients had wheeze and chest tightness, whereas 3 of 6 had an increase in residual volume. In another study,[26] small airway function, flow at 30% vital capacity obtained from a partial flow volume curve, showed a more profound decrement than did FEV_1, the classic clinical measure of pulmonary function in asthmatic patients. Inhaled LTD_4 also caused marked changes in specific airway conduc-

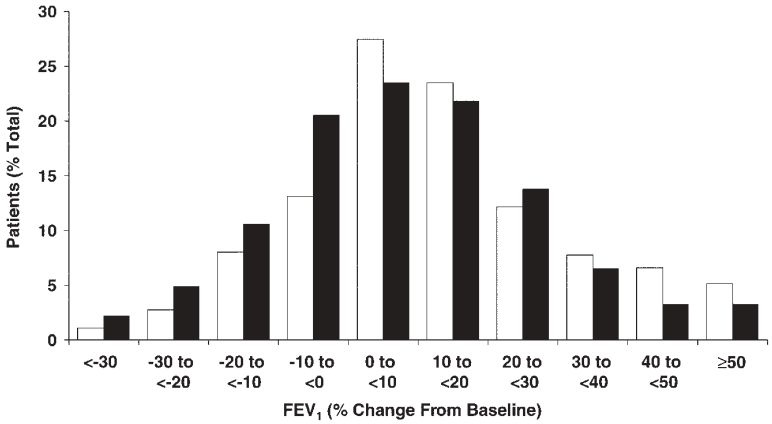


FIG 2. Distribution of treatment responses for FEV_1. In a study comparing beclomethasone with montelukast in 895 adults with persistent asthma, the distributions of discrete FEV_1 response for both groups were represented by bell-shaped curves, with about 50% of the beclomethasone group (*white bars,* n = 246) and 42% of the montelukast group (*black bars,* n = 375) showing improvement of at least 11% in FEV_1. Adapted from Malmstrom K, Rodriguez-Gomez G, Guerra J, Villaran C, Pineiro A, Wei LX, et al. Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma: a randomized, controlled trial. Montelukast/Beclomethasone Study Group. Ann Intern Med 1999;130:487-95.

TABLE II. Decrease in lung function associated with LTD_4 inhalation in patients with asthma

	Decrease (%)	
Lung function	**1 μg/L LTD_4**	**5 μg/L LTD_4**
FEV_1	8	23
Flow at 30% vital capacity obtained from partial flow volume curve	16	36
SGaw	35	55

Modified from Smith LJ, Greenberger PA, Patterson R, Krell RD, Bernstein PR. The effect of inhaled leukotriene D_4 in humans. Am Rev Respir Dis 1985;131:368-72.

tance (sGaw), a measure of large airway function (Table II). Therefore CysLTs can affect both small and large airway function, and some of these effects have not been captured in recent asthma clinical trials.

RELATIONSHIP BETWEEN DYSPNEA IN ASTHMA AND PULMONARY FUNCTION

Examination of the disparate perceptions of dyspnea in asthmatic patients before and after the administration of a β-agonist compared with measures of pulmonary function (Table III)[27] revealed that only sGaw was correlated with the Borg perception of dyspnea. In trying to interpret these disparate perceptions, it is likely that asthmatic symptoms represent some combination of large airway dysfunction, sGaw, and asthmatic hyperinflation and air trapping, which are small airway or distal lung functions. The CysLTs can affect both of these airways.

This apparent dissociation of FEV_1 and asthma symptoms is consistent with other clinical observations in the Asthma Control Questionnaire, which measures functional impairments and quality-of-life issues that are important for adults with asthma. For example, measurements of airway caliber and rescue β-agonist use were not needed to measure asthma control accurately.[28] Physicians' interpretations of this lack of association of FEV_1 with other end points, such as symptoms, is instructive. When another study[29] reported no relationship between airway obstruction and respiratory symptoms in adults with asthma, it was implied that patients' perceptions were "wrong" and that objective measures of airway obstruction were more important. Although it is necessary to assess airway obstruction objectively, the FEV_1 alone draws an incomplete picture of airway pathophysiology and does not reflect some elements of asthma that are important to patients.

SMALL AIRWAYS AND LUNG PARENCHYMA IN ASTHMA

Small airway dysfunction is important in asthma. A marked increase in peripheral airway resistance occurred in patients with mild asthma who had a normal FEV_1 and only a small decrease in forced midexpiratory flow rates.[30] More intriguing is the loss of airway-parenchymal interdependence (the ability to decrease airway resistance when increasing thoracic lung volume) measured in sleeping patients with nocturnal asthma (Fig 3).[31] Although this effect was noticed immediately after the patients fell asleep (early), resistance increased even more with the same loss of interdependence later during sleep (late), at a time when persons with nocturnal asthma have a documented increase in inflammatory cells ($CD4^+$ lymphocytes) in transbronchial lung biopsy specimens.[32]

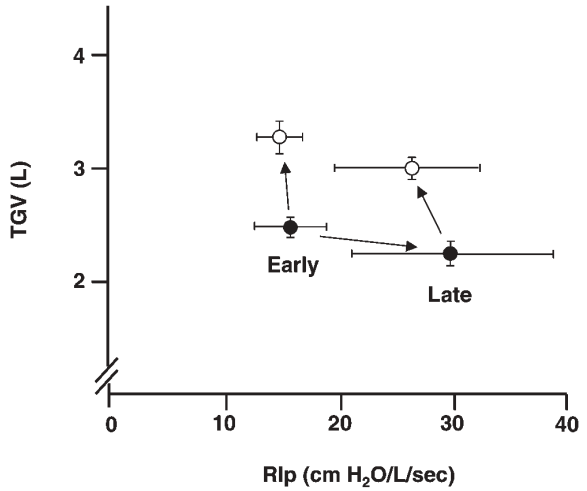


FIG 3. Effect of sleep on airway-parenchymal interdependence in patients with nocturnal asthma. *Black circles* represent the lower airway resistance *(RIp)* and thoracic gas volume during early (approximately 0.5 hours) and late (approximately 2.5 hours) sleep at baseline. *White circles* represent data obtained when the thoracic gas volume *(TGV)* was increased by approximately 1 L with negative extrathoracic pressure. In both situations, increasing the thoracic gas volume did not decrease airway resistance, suggesting a loss of airway-parenchymal coupling. With increasing sleep time, there was an additional increase in lower airway resistance, which occurred when increased markers of inflammation have been shown to be present in patients with nocturnal asthma. Data points are ± SEM. Adapted from Irvin CG, Pak J, Martin RJ. Airway-parenchyma uncoupling in nocturnal asthma. Am J Respir Crit Care Med 2000;161:50-6.

TREATMENT STRATEGIES TO TARGET ASTHMA SYMPTOMS AND THE DISTAL LUNG

If asthmatic symptoms are a result of the dysfunction of both large airways (as reflected by changes in sGaw) and the distal lung, LTRAs could be effective in both areas. These possibilities should be tested experimentally. First, it should be determined whether a relationship exists between LTRAs and sGaw on asthma symptoms as it does for β-agonists.[27] Second, the effects of LTRAs on distal lung pathophysiology, including air trapping, peripheral airway resistance, and the loss of airway-parenchymal interdependence, should be determined. An agent that does target the distal airways, a hydrofluoralkane formulation of beclomethasone dipropionate, has decreased air trapping produced by methacholine inhalation in asthmatic persons.[33]

CONCLUSIONS

The CysLTs produce many of the pathophysiologic manifestations associated with asthma, and leukotriene-active drugs have shown clinical benefits in many different aspects of asthma therapy. The heterogeneity of patients' responses to different asthma medications is an issue that appears to be common to most, if not all, asthma medications. Some asthma end points that might be affected by LTRAs, such as those associated with specific aspects of asthma symptoms and some associated with the pathophysiology of the distal lung, are not captured in traditional clinical trials. Studies with the LTRAs have the ability to provide information in these areas as well as to improve our understanding of the importance of different aspects of distal pulmonary function, which should lead to improved asthma therapy.

TABLE III. Relationship between perception of dyspnea (Borg) before and after a β-agonist and different measures in lung function in patients with asthma

Lung function	*r* Value	*P* value
Change in sGaw	0.47	.007
Change in airway resistance	0.31	.086
Airway resistance before β-agonist	0.17	Not significant
Change in PEFR	0.31	.094
FEV_1 before β-agonist	0.15	Not significant
Change in functional residual capacity	0.13	Not significant
Change in FEV_1	0.09	Not significant

Modified from Lavietes MH, Matta J, Tiersky LA, Natelson BH, Bielory L, Cherniack NS. The perception of dyspnea in patients with mild asthma. Chest 2001;120:409-15.

QUESTIONS AND DISCUSSION

Qutayba Hamid: Stephen, is there a good way to measure peripheral airway obstruction?

Stephen Peters: The short answer to this question is no, in that all the commonly used techniques have disadvantages. For example, one of the most direct and accurate techniques involves measuring flow and pressure through a wedged bronchoscope, but this is an invasive technique. One could look at peripheral airway obstruction more indirectly, for example, by quantitating air trapping before and after methacholine inhalation by computed tomographic scanning, but this technique is both indirect and involves the use of radiation, which limits its general applicability. Although some pulmonary function tests, such as changes in residual volume, may also provide important clues to the presence of peripheral airway obstruction, other tests, such as changes in vital capacity and forced midexpiratory flow rate, are nonspecific and useful only in limited situations. A more general issue raised by this question is, "What aspects of distal lung structure and function are most important in the pathogenesis of asthma?" Are they, in fact, those changes associated with increases in resistance? Or increases in air trapping? Or loss of airway-parenchymal interdependence? Or all of the above? And how are the key physiologic alterations related to the inflammatory and structural changes that we observe in the distal lung?

Redwan Moqbel: How will intrapatient and interpatient differences in response affect our understanding of the response and nonresponse to various agents used to treat asthma?

Stephen Peters: One of the key unanswered questions in all asthma therapeutics is why some patients with asthma have responses to an asthma medication, whereas others do not. Although this was most prominently pointed out with leukotriene modifiers, it seems to be a phenomenon common to most if not all asthma medications, in varying degrees. Defining molecular reasons for such interpatient and intrapatient variability would have an important, practical patient care benefit. It also has the potential to define key molecular asthma phenotypes so that we could better understand the several molecular routes by which asthma is expressed in different patients.

Anthony Sampson: From Jeff Drazen's study on the 5-lipoxygenase promoter, in which he looked at the response to an agent acting on the pathway at four points in time, 75% of the variability could be accounted for by general and biologic variation *between* the patients, and only 25% of the variability resulted from random variations in individual patients with time. Thus, it was at a high level of biologic consistency that the good responders early on remained good responders throughout the 12-week study. This is a surprising amount of consistency for a variable disease. Therefore, both interpatient and intrapatient events appear to be important in the variability of responses to asthma medications.

DISCUSSION OF IMPORTANT CLINICAL MEASUREMENTS FOR MANAGING ASTHMA (MARC PETERS-GOLDEN, CHAIRMAN)

Marc Peters-Golden: In this discussion, let us try to propose practical clinical recommendations for what is important to measure and how the measurements can be used to better manage the asthmatic patient. In other words, in a clinical study or in patient care, what are the things we need to know?

Stephen Peters: Looking at asthmatic patients on 2 different days shows a lack of correlation between patient symptoms and FEV_1, which is not surprising. Juniper et al[28] used the asthma control questionnaire, which comprises five questions and two objective measures, FEV_1 and rescue β-agonist use. When the FEV_1 or rescue β-agonist use was disregarded, the five questions showed the same sensitivity and specificity. Therefore, there is a lack of connection between what we doctors think is important (objective measures) and what may be closer to the real world (subjective measures).

Marc Peters-Golden: I do not think that anyone would argue with the concept that symptoms and quality of life are important. Exacerbation would probably be another end point, because it is the most important factor that affects the patient's life. The challenge is that with subjective measures, patients vary in their perceptual abilities; perceptions are influenced by social, psychologic, and ethnic factors. Consequently, some objective measurements do provide additional information useful in asthma management, and pulmonary function represents such an objective measure that can hopefully supplement patient-centered outcomes.

Stephen Peters: I think pulmonary function measures are most important in assessing the long-term decline of pulmonary function rather than short-term changes.

Jon Leff: If symptoms do not correlate with pulmonary function, it would appear scientifically that the symptoms are measuring another characteristic of the disease that we do not understand. Pulmonary function measures alone are not valuable unless declines with time lead to clinically important outcomes (cost measure, some symptoms, exacerbation rate) that matter to the patient. If the decline in pulmonary function has not affected the patient, I do not think that it matters. It only matters when it leads to clinically important outcomes. I do not feel the same about small airway function, which is the part of the lung in which the pathologist says we ought to be looking.

Marc Peters-Golden: It would be fair to say, then, that the true importance of measuring pulmonary function may be realized in only a minority of cases or circumstances where the long-term monitoring may capture information that we do not get from patients. I think we have said that spirometry is more useful than peak flow, but we also have heard a lot about how FEV_1 correlates poorly with subjective measurements. Therefore, there is a need for further description and validation of other physiologic or imaging measures that would provide information that was better than spirometry alone.

Redwan Moqbel: What are the questions that we are actually asking? Basically, we use them to tell the patient, "Yes, you have asthma because we measured those parameters." When you include biomarkers in the same list of needed measurements, it is not necessarily for diagnosis but for determining whether a patient will have a response to specific therapies.

Marc Peters-Golden: Let us group together bronchial hyperreactivity (BHR) and biomarkers. There is a perception that BHR is a clinically relevant marker of inflammation or remodeling. Better asthma control is obtained if BHR is considered with other measurements. But is the use of methacholine the most appropriate challenge?

Stephen Peters: BHR may be useful to predict which patients with asthma have a high likelihood of exacerbation. In our steroid withdrawal trial with colchicine, patients with asthma who had a PC_{20} of 2 mg/mL or less and had their ICSs withdrawn or stopped had a 40% likelihood of having an exacerbation within 2 months. Those with a PC_{20} greater than 2 did not. Therefore BHR may be useful in predicting exacerbations.

Hans Bisgaard: Again, we need to consider the heterogeneity of the disease. In pediatrics, we do BHR testing every day for the reason that lung function is normal in most of our patients. They have normal lung function because we treat early and aggressively. The increase in asthma prevalence is among the patients with mild asthma. Therefore, we are looking for sensitive measures, and exercise-induced asthma is sensitive. In children, it probably is a useful indicator of a clinical problem. In our pediatric patients, BHR is a physiologic measure that is more useful than spirometry.

Redwan Moqbel: How early does BHR occur in children, and does it get worse as they grow older?

Hans Bisgaard: We measure it as young as 2 years of age with cold air hyperventilation. It is useful in separating children with asthma from those without asthma. It does not seem to get worse with age.

John Edelman: Are all BHR challenges considered to indicate the same thing? Are the results from all challenge substrates interpreted to mean the same thing? Are exercise-induced and cold, dry air–induced BHR the same as BHR obtained with methacholine or adenosine monophosphate (AMP) or histamine? I am uncomfortable thinking that a methacholine challenge gives the same information that exercise or AMP does.

Emilio Pizzichini: Bronchoprovocation with AMP is more predictive than methacholine challenge for eosinophilic inflammation in the lungs, as measured by induced sputum. If we think that eosinophilic inflammation is the criterion standard, then it might be more useful. There is only one study of which I am aware that shows that treating BHR improves several asthma outcomes. Because of its design, however, the main conclusion of the study was that if you give more steroids, patients get better. Currently there are two ongoing studies evaluating the use of sputum examination as an additional outcome of asthma treatment.

Bill Henderson: To what degree do you use AMP response, versus some other physiologic function, as a reflection of the inflammatory state of the airways you are trying to assess? Are there other ways of looking at the inflammatory state of the airways?

Marc Peters-Golden: Steve, would you use AMP? Would that be measuring something that you think would be more useful?

Stephen Peters: It certainly does things that methacholine does not do. If you think that mast cell triggering is an important trigger of the asthmatic response, that is the way to go.

Mark Liu: There are different forms of asthma, and there are different forms of BHR that depend on the challenge. The mechanisms are likely to be different. One question still asked is whether BHR is truly a phenomenon of the hyperreactivity of the airways or actually an aberration of the bronchodilating effect of a deep breath that occurs in healthy persons but that seems to be lost in asthma. If you take a healthy person and do not allow him or her to take a deep breath between inhalation of increasing concentrations of methacholine, the dose-response to methacholine in terms of a change in FEV_1 and the forced vital capacity of those partial curves will actually be exactly the same as for patients with asthma. When the healthy person is allowed to take deep breaths between doses of methacholine, there is no response to methacholine. There is clearly a protective phenomenon involved, and BHR is not from a hypersensitive airway but from a loss of a bronchoprotective mechanism that normally dilates the airway. The bottom line is that BHR can be a marker of inflammation but in general is probably not. I think that exercise and cold air are probably much more specific tests of an underlying asthma diathesis than is the response to methacholine.

Jon Edelman: I would like to be provocative and suggest that in fact the data are really mounting to say that BHR is not an indication of inflammation. The two phenomena are true but unrelated. One can be abrogated, yet the other phenomenon remains. This would be a good time to break the perceptual connection between BHR and inflammation, because inflammation itself is such a difficult concept to grasp, and its meaning is so varied that we might do better describing what we have and what BHR is. If it is a marker of inflammation, then what is the evidence for that? And if it is not, then it is time to stop linking them without thought.

Hans Bisgaard: I would tend to agree with that. As one example, we completed more than 100 exercise-induced asthma tests and looked at the nitric oxide before that exercise test. There was no good correlation. Whether a subject had high or low nitric oxide, he or she would react to exercise. Different mechanisms are at work.

Mark Liu: If you treat people with ICSs and do methacholine challenges on them, they produce little change. However, if you use bradykinin as the provocative agent, it produces a huge change. So bradykinin reactivity may be a marker more consistently linked with inflammation.

Marc Peters-Golden: Are there other circumstances, as in small children, where BHR captures information that we could not capture otherwise? The consensus seems to be that methacholine has not really proved itself to be useful in that way. Is there a sense that some other source of challenges or a battery of two or three different challenges would be helpful?

Emilio Pizzichini: Methacholine challenge can be used to effectively exclude asthma as a diagnosis because it has a high predictive negative value. We need more evidence from well-designed long-term studies to determine whether methacholine and other markers (eg, sputum examination) are useful outcomes of asthma treatment and control.

Jon Edelman: I am not prepared to completely give up on BHR as a valuable measure, because it passes the test that Stephen Peters mentioned. When a patient says, "I'm worried about my exercise level," or "I'm worried about my cold air tolerance when I go out in the winter time," there are things that could be tested. Therefore I am encouraged to push that forward.

Marc Peters-Golden: The consensus seems to be that we should disband the notion that BHR is an indicator of inflammation but rather view it as an indicator of asthma control. There may be room to improve the ability to tailor therapy and monitor patients on the basis of what other challenges may tell us more than methacholine tells us.

Let us move to other biomarkers. We have talked about sputum, cells, mediators, and exhaled nitric oxide. The general idea has been that these biomarkers are not necessarily telling us something about asthma but about inflammation. The question is, do we need to know about inflammation? Does knowing about inflammation get us further down the road in terms of treating asthmatic patients?

Qutayba Hamid: I think that it is going to be difficult to dissociate inflammation from asthma. The general practitioners now understand that asthma is a chronic inflammatory disease. It took many years for them to accept this, and now to say that asthma is not an inflammatory disease would be confusing at the least.

We must find a true marker of inflammation. One of the ways would be to show that some markers respond better to one treatment than another.

Marc Peters-Golden: Inflammation is present and important in asthma; it is part and parcel of asthma. However, the direction of an arrow connecting asthma and inflammation must go in both directions. We do not necessarily know which one comes first.

We agreed earlier that the only reason to measure a biomarker is if it reveals something that we do not get from conventional measurements. Therefore, do we need to measure inflammation per se? Do we learn something from measuring eosinophils or nitric oxide or exhaled leukotrienes that we do not know from conventional measurements?

Qutayba Hamid: The biomarkers could indicate the response to treatment. It provides a clearer way to determine whether the patient is responding to specific treatment. A biomarker is more likely to show a consistent change than are some of the physiologic measurements.

Marc Peters-Golden: Because of the heterogeneity of asthma phenotypes and the fact that none of the biomarkers necessarily correlate with others, there will be some patients for whom control can be measured by symptoms and not by lung function. There will be other patients for whom control can be measured from exhaled nitric oxide and not symptoms. My guess is that there are patients for whom some end points are more revealing than others. So one could argue that the more types of end points one uses, the more likely one is to capture useful information.

Redwan Moqbel: I agree that the real reason that we should use biomarkers is we are going to tell the patient that he or she is very likely to have a response to a particular treatment because of this biomarker of inflammation. For example, the leukotriene C_4 synthase polymorphism is a good example. It should indicate whether or not there would be a response to an LTRA.

Jon Edelman: Perhaps we need diagnostic biomarkers to help diagnose a particular kind of the disease, therapeutic choice biomarkers that would indicate whether a specific therapy is working, and therapeutic effect biomarkers that would indicate whether all therapies together are working.

Anthony Sampson: You may well want to monitor the changing levels of inflammation and titrate different dosages of corticosteroids, but with an LTRA, the same dose regimen applies to all patients irrespective of severity. The only major decision is, do you treat with LTRAs or not? It would be a one-off genetic test of the likelihood of responding well, not a test to monitor whether the treatment is working. However, none of the genetic polymorphisms have been sufficiently proved to think that they will be available for clinical use in the foreseeable future.

Marc Peters-Golden: As we try to relate this to current clinical practice, a similar outcome would be obtained through an empiric trial with an LTRA.

Qutayba Hamid: I think what is needed are publications showing that a biomarker specifically responds to a particular therapy. If you can say, for example, that an LTRA causes decreased airway remodeling, practitioners would understand exactly what is being said and it would affect their use of specific drugs. They are not going to try to measure airway remodeling in every patient, but the reported results would help to decide which drug to use. I do not agree that they would routinely need to use those biomarkers in individual patients in the clinical setting.

Marc Peters-Golden: Finally, I want us to consider the concept of *remodeling,* by which some people mean histologic changes in the airway and other people mean irreversible airway obstruction. We do not know whether remodeling and airway obstruction consistently correlate with each other. Are the things that lead to irreversible airway obstruction likely to be different than those that lead to, for example, airway hyperresponsiveness?

Stephen Peters: Yes. There are data suggesting that subepithelial changes occur early and that they correlate with hyperresponsiveness, but that is not what causes irreversible airway obstruction.

Jon Edelman: The prevalence of the pathologic changes is high among patients with asthma, although the proportion with irreversible airway obstruction is very small.

Marc Peters-Golden: This is something that still remains a problem, and rightly or wrongly, these are the two ways that the term gets used. There is probably some degree of correlation, but it is certainly imperfect. Does anybody have any recommendations about how to use the term *remodeling* in our therapeutic decisions?

Qutayba Hamid: I think the generic observation about steroids is that they do not affect airway remodeling. There are many studies, both long and short term, that show that steroids have no effect. I think the effect of LTRAs on airway remodeling in human beings is unknown, and there may be an opportunity to design some studies for that purpose. Most available data, some in vitro data on collagen formation, are more on airway remodeling and steroids than on anything else.

Redwan Moqbel: Is it possible to reverse fibrosis? It is a major part of remodeling. I do not think that it is possible; to reverse it completely is most uncertain.

Qutayba Hamid: Is it possible to decrease it and also to stop it? The fibrosis in asthma is not like fibrosis in other diseases. It is an active fibrosis with some activity still going on.

Mark Liu: There is little evidence to suggest that the fibrosis, the thickening of the basement membrane, contributes significantly to the pathophysiology or clinical course of asthma. There have been studies that try to correlate various aspects of the disease to the basement membrane thickening and the results are mixed. Most studies do not show correlations.

Stephen Peters: However it varies, its presence correlates with the existence of asthma.

Mark Liu: Yes, but I would argue that it is a nonspecific indicator, because other diseases, including allergic rhinitis and interstitial lung disease, can produce some basement membrane thickening.

SUMMARY (MARC PETERS-GOLDEN)

Endpoints. A variety of end points are used to monitor asthma in clinical practice and in clinical trials, but the correlation among these various end points is at best imperfect, and at worst, downright poor. This underscores the importance of monitoring multiple end points.

Symptoms. Indisputably important to patients, symptoms are perceived through variables in psychosocial factors (influencing the recognition of symptoms and the willingness to report them), perceptual ability, and lifestyle (eg, level of activity and thus the degree of challenge that patients face in their daily lives). Therefore, symptoms may not be sufficiently sensitive.

Exacerbations. Exacerbations are indisputably important to patients and health care costs, but chronic symptoms do not necessarily predict them.

Physiologic measures. Appropriate measures are expected to provide objective data that capture some important information about asthma control that may be missed by purely subjective and experiential end points. However, peak flow is of limited utility and is not commonly used in practice. Moreover, FEV_1 does not correlate well with symptoms, may not adequately reflect small airway involvement, and may be particularly insensitive to leukotriene-mediated effects. Although there is a need for better physiologic measures, there is a lack of consensus regarding the best test (flow at low lung volumes, sGaw, measures of air trapping). To be useful, a physiologic test must be readily performed. Imaging (high-resolution computed tomographic scan) may be able to provide similar information.

Hyperresponsiveness. Apart from the obvious utility of this test in differential diagnosis of difficult cases, the importance of BHR in follow-up of patients and in making treatment decisions is unclear. Incorporating routine measures of BHR may alter treatment (ICS dose) and outcomes; however, few physicians have implemented them in clinical care. Although it has been suggested in both human and animal studies that BHR is a measure of airway inflammation, a dissociation exists between inflammation and BHR. It is probably preferable to consider BHR as a reflection of asthma control. In that context, it is probably more sensitive than other measures of lung physiology. There is a consensus that responsiveness to methacholine may be less meaningful than responsiveness to exercise (which is a clinically relevant challenge) or to AMP (which triggers and is dependent on relevant mechanisms, such as mast cell activation). Widespread investigation into the utility of more relevant measures of BHR needs to be undertaken. Appropriate BHR determination may represent a useful alternative to physiologic measures, as discussed previously.

Biomarkers. Biomarkers include measurements of mediators or markers of relevant pathophysiologic processes in accessible body compartments (eg, sputum, exhaled breath, bronchoalveolar lavage fluid, plasma, or urine). Commonly studied examples include numbers of particular cell types (eg, eosinophils or neutrophils) and concentrations of particular molecules (nitric oxide, peroxynitrite, leukotrienes, eosinophil peroxidase). Some of these measures are inherently variable and insensitive (eg, urinary leukotriene E_4), whereas others (eg, sputum eosinophils and exhaled nitric oxide) appear to be more reliable in correlating with or predicting level of asthma control or exacerbations. Assessment of local activation of leukotriene synthesis on the basis of the intracellular locale of immunodetectable 5-lipoxygenase in sputum cells may have potential. Finally, genetic polymorphisms represent another biomarker that may be useful in discerning phenotypes of patients and individually tailoring therapy.

The assumption behind the use of biomarkers is that they may provide useful information that correlates with and presages changes in conventional parameters. This assumption in turn is predicated on inflammation as the central driving force of relevant events in asthma. That paradigm is currently in question. It is clear that inflammation exists in asthma, but it is less clear to what extent it is the cause or the consequence of asthma. It is less certain that measuring markers of inflammation will predict other events in this disease. It may be more appropriate to view biomarkers such as eosinophils or nitric oxide as markers of disease control rather than as mediators of inflammation (as argued previously for BHR); the largely bronchoprotective and anti-inflammatory actions of nitric oxide in particular argue against it being a mediator of inflammation. Ultimately, the most important question is whether biomarkers provide information about asthma control and responses to therapy that cannot be ascertained by measuring other end points.

Heterogeneity. It is now clear that asthma is not a single disease. Heterogeneity probably exists among patients with asthma in terms of relevant pathophysiologic mechanisms, the end points that most sensitively reflect their level of control, and the pharmacologic agents to which they will be the most responsive. This emphasizes the need to monitor multiple end points that may provide complementary information and to continue the investigative efforts that seek to predict therapeutic responsiveness to various agents.

Remodeling. The term *remodeling* is used to refer to (1) the development of fixed airflow obstruction in physiologic testing and (2) histologic alterations in the airway, such as mucus gland hyperplasia, smooth muscle cell hyperplasia, basement membrane thickening, and subepithelial fibrosis. It is often assumed that these two uses of the term reflect two parallel aspects of the consequences of chronic airway injury that correlate well with each other, but the nature of this relationship is poorly defined. Although there is undoubtedly overlap between these aspects, histologic changes can be seen relatively earlier in the course of disease than is irreversible

obstruction. The frequency, determinants, and functional consequences of histologic airway alterations, as well as the potential for pharmacologic intervention, require a great deal more investigative effort.

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