MEDICAL CROSSFIRE®

DEBATES, PEER EXCHANGE, AND INSIGHTS IN MEDICINE®

SPECIAL EDITION

Issues in the Management of Persistent Asthma

Looking Forward at Inhaled Corticosteroid Therapy

CE-Certified Monograph

PANELISTS

Richard J. Martin, MD
National Jewish Medical and Research Center;
University of Colorado Health Sciences Center
Denver, Colorado

Christine A. Sorkness, PharmD
University of Wisconsin
Madison, Wisconsin

Paul M. O'Byrne, MB, FRCPI, FRCP(C)
McMaster University
Hamilton, Ontario, Canada

Stanley J. Szefler, MD, FAAAAI
National Jewish Medical and Research Center;
University of Colorado Health Sciences Center
Denver, Colorado

Gary S. Rachelefsky, MD, FAAAAI
UCLA School of Medicine;
Respiratory and Allergic Disease Foundation
Los Angeles, California

MODERATOR

Peter L. Salgo, MD
National Television Medical Correspondent;
Columbia University College of Physicians and Surgeons
New York, New York

Programmed by

AMERICAN ACADEMY OF ALLERGY ASTHMA & IMMUNOLOGY

Release Date: May 2007 • **Expiration Date:** May 31, 2009

Funded through an educational grant from sanofi-aventis U.S. and ALTANA Pharma.

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Windsor Corporate Park • 50 Millstone Road, Building 400, Suite 110 • East Windsor, New Jersey 08520
(609) 918-9400 • www.medicalcrossfire.com

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Educational Overview

Asthma is one of the world's most prevalent chronic diseases, with its incidence increasing by approximately 50% every decade. Current treatment recommendations view inhaled corticosteroids (ICS) as the cornerstone of asthma anti-inflammatory treatment, and the impact of early initiation of these agents remains an important topic of discussion. Because ICS play such an important role in the control of persistent asthma, it is important to understand how to manage patients with regard to the utilization of ICS as well as differences among these agents—including pharmacodynamic and pharmacokinetic profiles—which may help predict safety and efficacy.

Through debate and authoritative peer exchange, this ***Medical Crossfire®*** activity, conducted in conjunction with the AAAAI, will confront these and other issues related to optimal inhaled corticosteroid use.

Target Audience

This educational activity is designed for allergists, immunologists, and other health care professionals interested in or involved with the management of asthma.

Learning Objectives

Upon the completion of this activity, participants should be able to:

- State the current role of ICS in the treatment of persistent asthma.
- List the limitations of current ICS therapies and the potential advantages of new and emerging ICS therapies.
- Appraise whether differences in pharmacodynamics and pharmacokinetics confer safety and efficacy advantages for inhaled corticosteroids.
- State the relative benefits and drawbacks to current inhaled corticosteroid drug and delivery technology and describe the future of ICS technology.
- Evaluate inhaled corticosteroid therapy options based on evidence as well as clinical practice parameters (best usage, number needed to treat, etc.).

Method of Instruction

Participants should read the learning objectives and review the activity in its entirety. After reviewing the material, complete the self-assessment test consisting of a series of multiple-choice questions.

The activity is complemented with references that contain the rationale for the correct answer to each self-assessment question as well as a description identifying the section of the activity that contains the correct answer, allowing participants to review the material as needed, thus finalizing their educational participation.

Upon completing this activity as designed, participants will receive a letter of credit awarding *AMA PRA Category 1 Credit(s)™* three to four weeks after receipt of the registration and evaluation materials.

Estimated time to complete this activity as designed is 1.5 hours.

Accreditation

CME

The American Academy of Allergy, Asthma and Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates this educational activity for a maximum of *1.5 AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

CE

The American Academy of Allergy, Asthma and Immunology (AAAAI) is a Provider approved by the California Board of Registered Nursing, Provider #10704, for up to 1.8 CE Contact Hours.

CME Activity Advisor

Christopher C. Randolph, MD, FAAAAI
Clinical Professor of Pediatrics
Section of Allergy and Clinical Immunology
Yale University School of Medicine
New Haven, Connecticut;
Private Practice
Center for Allergy, Asthma, and Immunology
Waterbury, Connecticut

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Faculty Disclosure Declarations

Dr. Martin has received grant/research support from ALTANA Pharma, GlaxoSmithKline Pharmaceuticals, and Ivax Corp.; and has received honoraria from and has been a consultant for ALTANA Pharma, Early Sense, Genentech, GlaxoSmithKline Pharmaceuticals, Merck & Co., Novartis, sanofi-aventis U.S., Schering Corp, and Teva.
Dr. Rachelefsky has received grant/research support from ALTANA Pharma, Genentech, GlaxoSmithKline Pharmaceuticals, Ivax Corp., Medpointe, sanofi-aventis U.S. and Schering Corp.; has served on the speakers' bureaus of AstraZeneca Pharmaceuticals, GlaxoSmithKline Pharmaceuticals, Ivax Corp., Medpointe, Merck & Co., and Schering Corp; is a member of the board of directors of Starbright Starlight; and is the National Program Director for Pediatric Asthma for the Robert Wood Johnson Foundation.
Dr. O'Byrne has received grant/research support from ALTANA Pharma, AstraZeneca Pharmaceuticals, Dynamax, GlaxoSmithKline Pharmaceuticals, Merck & Co., and Ono Pharmaceutical Co.; has been a consultant for AstraZeneca Pharmaceuticals and GlaxoSmithKline Pharmaceuticals; and is the Chair and Executive of the Global Initiative for Asthma.
Dr. Sorkness has received grant/research support from GlaxoSmithKline Pharmaceuticals, the National Heart, Lung, and Blood Institute, and the National Institute of Allergy and Infectious Diseases; and has served on the speakers' bureau of and has been a consultant for GlaxoSmithKline Pharmaceuticals.
Dr. Szefler has received grant/research support from Ross, a division of Abbott Laboratories; and has been a consultant for AstraZeneca Pharmaceuticals, GlaxoSmithKline Pharmaceuticals, Merck & Co. and sanofi-aventis U.S.
Dr. Salgo has no financial arrangements or affiliations to disclose.
Dr. Randolph has no financial arrangements or affiliations to disclose.

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This activity contains discussion of unlabeled and non-FDA-approved uses of commercial products. No treatments are approved for influencing the long-term outcome of asthma. The fixed dose combination of budesonide/formoterol is not approved in the United States. The FDA has granted an approvable letter for ciclesonide, an inhaled corticosteroid, for the treatment of persistent asthma and allergic rhinitis.

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It should be noted that the recommendations made herein, with regard to the use of therapeutic agents, varying disease states, and assessments of risk, are based upon a combination of clinical trials, current guidelines, and the clinical practice experience of the participating panelists. The drug selection and dosage information provided in this activity are believed to be accurate. However, the participants are urged to consult the full prescribing information on any drug mentioned in this activity for recommended dosage, indications, contraindications, warnings, precautions, and adverse effects before prescribing any medication. This is particularly important when a drug is new or infrequently prescribed.

Issues in the Management of Persistent Asthma

Looking Forward at Inhaled Corticosteroid Therapy

PANELISTS

Richard J. Martin, MD
Professor and Chair, Department of Medicine
National Jewish Medical and Research Center;
Professor of Medicine
University of Colorado Health Sciences Center
Denver, Colorado

Christine A. Sorkness, PharmD
Professor of Pharmacy and Medicine
School of Pharmacy
University of Wisconsin
Madison, Wisconsin

Paul M. O'Byrne, MB, FRCPI, FRCP(C)
E.J. Moran Campbell Professor
Chairman, Department of Medicine
McMaster University
Hamilton, Ontario, Canada

Stanley J. Szefler, MD, FAAAAI
Helen Wohlberg and Herman Lambert Chair in Pharmacokinetics
Head, Pediatric Clinical Pharmacology
National Jewish Medical and Research Center;
Professor of Pediatrics and Pharmacology
University of Colorado Health Sciences Center
Denver, Colorado

MODERATOR

Gary S. Rachelefsky, MD, FAAAAI
Professor of Allergy and Immunology
Director, Center for Asthma, Allergy, and Respiratory Disease
UCLA School of Medicine;
President, Respiratory and Allergic Disease Foundation
Los Angeles, California

Peter L. Salgo, MD
National Television Medical Correspondent;
Clinical Professor of Medicine and Anesthesiology
Columbia University College of Physicians and Surgeons
New York, New York

An estimated 300 million people worldwide suffer from asthma, with a trend toward an increasing incidence in developed nations.[1] The high morbidity and mortality associated with this chronic inflammatory disease have led recent guidelines to identify the achievement and maintenance of long-term control as the primary goal of asthma treatment.[2,3] For patients with persistent asthma of all severities, inhaled corticosteroids (ICS) are the cornerstone of treatment and confer long-term control with appropriate prescribing and adherence. "In this ***Medical Crossfire***, we are going to discuss management issues in persistent asthma, with a focus on optimizing therapy with inhaled corticosteroids," began Peter L. Salgo, MD, the moderator of this live event convened before an audience of pulmonologists and other clinicians interested in asthma care. "We are pleased to have with us a panel of international experts to discuss this important topic and offer their insights. In addition, we will be bringing today's attendees into the debate through our ***Medical Crossfire*** audience response system."

The Role of Available and Emerging Inhaled Corticosteroids

Current Clinical Landscape

"In the early 1990s, there was a major movement away from bronchodilator-type therapy to inhaled corticosteroid therapy, which rapidly became the cornerstone of asthma management," stated Stanley J. Szefler, MD, FAAAAI, to launch this ***Medical Crossfire***. The extensive literature on ICS has confirmed the efficacy of these agents in reducing asthma symptoms, bettering quality of life, improving lung function, decreasing airway hyperresponsiveness, controlling airway inflammation, reducing both the frequency and the severity of exacerbations, and lowering asthma mortality.[2]

As the armamentarium of inhaled corticosteroids increases, continued Dr. Szefler, "the challenge over the past 10 years has become the appropriate selection of the different products and formulations that have evolved and the respective dosages to use. In addition, concerns have arisen about long-term use and adverse effects of inhaled steroids." Nonetheless, Dr. Szefler urged participants to "refer to current guidelines,[2,3] which acknowledge ICS as the cornerstone of therapy. We are awaiting new guidelines, which should only strengthen this position."

Agreeing that the introduction of ICS has been "nothing short of a revolution," Dr. Salgo wondered, "Is everybody happy with this revolution?"

In response, Christine A. Sorkness, PharmD, observed, "Death rates from asthma in the United States seem to be going down, and much of that may be attributed to inhaled corticosteroids."

"ICS is the cornerstone of therapy," concurred Gary S. Rachelefsky, MD, FAAAAI, "and it is the cornerstone of therapy based on science and disease control."

A different perspective was offered by Richard J. Martin, MD. "Although I do believe that inhaled steroids are indeed the backbone of treatment for asthma, we are learning that not all our patients respond well to inhaled corticosteroids. Therefore, we must individualize patient care and perhaps look to additional treatments in the future."

The reputation of ICS is compromised by concerns about safety and tolerability as well as a related reluctance to increase dosages.[4] "We will be touching on this topic later in this ***Medical Crossfire***," noted Paul M. O'Byrne, MB, FRCPI, FRCP(C), "but in most countries in the world there is a debate about how much ICS to use. Yet, I believe that ICS are still greatly underutilized, which means a lot of patients do not get the opportunity to benefit from their use."

"Do you think they are underutilized in the United States?" queried Dr. Salgo.

"Without doubt," asserted Dr. O'Byrne. "Certainly, Australia, New Zealand, Canada, the United Kingdom, and many countries in Europe use ICS more widely than does the United States. There is a longer history of both their use and acceptance of their safety profile in these countries. It is worthwhile to bring an international perspective to this issue."

Optimizing ICS: Adjunctive Therapy or Higher Doses?

Dr. Salgo turned the panelists' attention to the FDA's recent alert regarding long-acting bronchodilators containing beta 2-adrenergic agonists (LABA).[5] The alert addressed a finding from the Salmeterol Multi-center Asthma Research Trial [SMART] that severe asthma exacerbations and asthma-related deaths increased among patients who took LABA in combination with usual asthma care.[6] "What do you think the impact of the FDA alert is going to be?" queried Dr. Salgo. "How is it going to affect clinical practice?"

"The impact has begun, but I am not sure how significant it has been," offered Dr. Rachelefsky, explaining that "the FDA put a black-box warning on long-acting beta agonists with the recommendation that they should be used in the appropriate patients and not in everybody who coughs or wheezes. Further, the FDA encourages more emphasis on monotherapy with inhaled corticosteroids." Only when these strategies are unsuccessful should add-on therapy be considered, he advised. "Whether add-on therapy should be a long-acting beta agonist, a leukotriene modifier, or theophylline is a significant topic of debate in the realm of the clinical management of asthma."

Dr. O'Byrne pointed out that the use of LABA as monotherapy is not an accepted practice in much of the world. "Interestingly, the United States was a little unusual in approving the use of LABA as monotherapy. Certainly, in Canada, LABA were never approved as monotherapy; they were only approved for use with inhaled corticosteroids. I don't think anybody would debate that LABA, when used as the only therapy for asthma, do pose risk; whether that same risk exists when they are used together with inhaled corticosteroids is a compelling issue."

Dr. Salgo pursued this point further. "Are you comfortable saying that inhaled corticosteroids, when given with LABA, provide protection from the adverse effects of LABA?"

"I am comfortable saying that the combination of inhaled steroids and LABA improve every important outcome, exacerbations, and, particularly, severe exacerbations, in every properly conducted clinical trial,[7,8]" declared Dr. O'Byrne.

Dr. Sorkness reminded her colleagues of a public statement in support of the use of LABA as adjunctive therapy recently published by the Canadian Asthma Guideline Group.[9] "The statement reinforced that they were not going to change their guidelines and position regarding LABA based on the SMART trial. Instead, they would look at the large body of evidence documenting their value."

Dr. Martin approached the issue from a different direction, pointing out the problem with increasing the dose of ICS. "Do we just ratchet up the dose of inhaled corticosteroids? Remember, the dose response to ICS is not very impressive, so if we were to increase the dose, in most individuals, all we would do is increase the systemic effects." Until there are newer ICS with less systemic absorption and more local activity, he suggested, "we need to understand which individuals are going to respond to a higher dose, which individuals are not going to respond to a higher dose, and how to best treat those individuals who do not respond."

Seeking clarification, Dr. Salgo asked, "Are you saying that simply cranking up the ICS is not going to substitute for LABA? Are you saying that, until we have better ICS, we should use LABA but use them appropriately?"

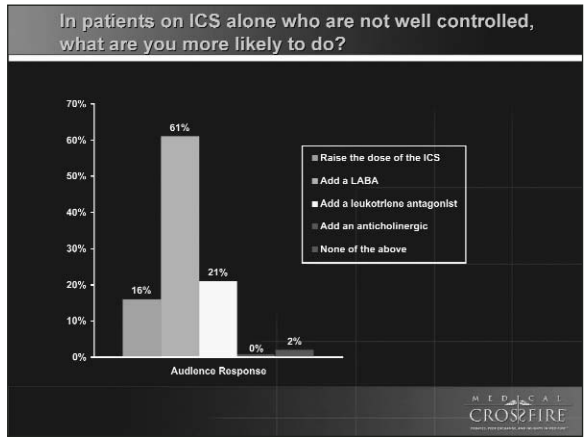

Figure 1.

"That is correct," confirmed Dr. Martin. "I agree with Dr. O'Byrne and the guidelines that LABA should not be used as monotherapy—there is no doubt about that. Therefore, the combination is, indeed, appropriate because we cannot always just ratchet up doses of ICS. Coming back to those individuals who do not respond to higher doses of ICS, we really have to think of new therapies to treat them."

Dr. Szefler expressed an additional concern. "There are special issues in children, in terms of ratcheting up doses and increasing the risk of adverse effects. The critical issue comes not so much in the escalation of doses from low to medium but in the maintenance of patients on high doses—particularly, high doses of very potent inhaled corticosteroids for long periods of time."

"A lot of physicians are using combination therapy as a first-line treatment in everyone with asthma," lamented Dr. Rachelefsky, who advised against this practice. Instead, he recommended, "Low-dose inhaled corticosteroids should be the primary treatment in the majority of patients with mild and moderate persistent asthma."

"Let's bring the audience into this debate," suggested Dr. Salgo. He invited participants to weigh in on this issue by using the handheld controllers of the ***Medical Crossfire*** audience response system to provide their answers to the following question: In asthma patients on ICS alone who are not well controlled, what are you most likely to do? The audience responses to this question are tallied in **Figure 1**.

Observing that no one in the audience responded that they would add an anticholinergic, Dr. Sorkness affirmed, "They are absolutely right. There are no good trials to support chronic use of an anticholinergic in asthma. As far as choosing a leukotriene antagonist, we have far less data regarding the addition of that to ICS than we have for adding LABA to ICS."

"There are some fairly well-done studies in adults that found adding LABA is more effective than adding a leukotriene antagonist,[10]" commented Dr. O'Byrne. "Dr. Szefler made a good point earlier in this ***Medical Crossfire***, which is that the evidence of efficacy of the combination of steroids and LABA is much less satisfactory in children than it is in adults. In children, therefore, leukotriene antagonists may be a viable option."

Reviewing the multiple-choice answers of the question posed to the audience, Dr. Szefler chose the fifth option—none of the above—as his own response. Compliance and adherence with the proper usage technique of the prescribed product would be his first concern, he offered. Before adding a second agent to ICS, "I would confirm that the patient had filled the prescription and was taking the ICS the right way," declared Dr. Szefler.

"Dr. Szefler is absolutely right," seconded Dr. Rachelefsky. "Before escalating the dose, ensure that the patient is adherent and knows how to perform the skills. Review everything with the patient and make sure the treatment is being taken in the way it is intended."

"Wonderful drugs are being brought to the marketplace, but if physicians cannot be convinced to prescribe them and patients to take them, we are just not going to get very far," lamented Dr. Sorkness.

Reaching the New Goal: Asthma Control

Asthma guidelines have recently moved from disease severity to asthma control as the primary goal of asthma management.[2,3] Asthma control is defined as the control of the clinical manifestations of asthma, including symptoms, sleep disturbances, limitations of daily activity, impairment of lung function, and use of rescue medication.[2] Asthma is said to be controlled when recurrences of symptoms are occasional and severe exacerbations are rare.[2] The future NAEPP/NHLBI guidelines will focus on patient outcomes and

"Before escalating the dose, ensure that the patient is adherent and... make sure the treatment is being taken in the way it is intended."

—Dr. Rachelefsky

control but emphasize that the evaluation of baseline severity should be used as a guide to treatment. Dr. Salgo queried the panel, "How does this emerging emphasis on a new way to look at asthma—control—impact your clinical practice?"

Taking the question was Dr. Rachelefsky. "Control means reducing the impairment of disease and also reducing the risk. Therefore, control requires getting the patient and their family involved in decision-making. We are finally spending time asking what the patient wants—rather than what the physician wants—to get out of treatment." Sharing the goal of control makes it more likely that the patient will fully participate in the treatment protocol, he added. "When included as part of the decision-making, the patient is adherent as opposed to compliant. Adherence is a form of partnership, where the patient and the physician discuss treatment together. By involving the patient, we are going to get a much better outcome."

"Isn't the subtle distinction of asthma control that you are not treating symptoms but, rather, treating the underlying disease process?" inquired Dr. Salgo, adding, "hasn't that distinction spearheaded the movement toward maintenance therapy with ICS as opposed to rescue therapy for exacerbations?"

"Control of impairment and risk allows us to step back and look at the bigger picture," suggested Dr. Sorkness, drawing a parallel with the early guidelines for the treatment of hypertension. "When the guidelines talked about mild, moderate, and severe hypertension, this led people to reason, 'Well, why would I bother treating my mild hypertension? It's not going to hurt me.' Ultimately, however, hypertension of any severity can lead to cardiovascular disease and end-organ damage." Focusing on control of a symptom rather than the severity of the disease, she emphasized, "is a different philosophy. If you are controlling, for example, inflammation, then you may be preventing downstream risk."

"Another problem with focusing on severity is that it is poorly done," added Dr. O'Byrne, explaining that definitively establishing the severity of disease requires conducting a number of tests and measurements that are seldom completed in general medicine. "But for control, there are very objective parameters that should be easy to measure. In my view, this approach provides much better care overall."

"Is the key phrase then—and I hear this a lot, especially among people dealing with asthma—*patient-centered disease* as opposed to *physiology-centered disease*, if you will?" inquired Dr. Salgo.

"That is what it has become," confirmed Dr. Rachelefsky. The Global INitiative for Asthma (GINA) guidelines, for example, recommend an approach called patient-guided self-management, in which patients assume a major role in the management of their asthma, reaching a consensus with their health-care professionals on treatment goals and plans and actively engaging in monitoring asthma control. The guidelines are based on high-level clinical evidence that this approach reduces asthma morbidity in both adults and children.[2] Commented Dr. Rachelefsky, "Clinicians are finally thinking about the patient and getting the patient involved in the equation, whether that patient is a two-year-old or a 70-year-old."

Dr. Sorkness, however, sought to emphasize a continuing role for objective measurements like forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and peak expiratory flow (PEF), lamenting, "To the extent that we have given up on objective measurements—"

"We have to get objective measurements," interjected Dr. Rachelefsky, "but is it more important to get a patient's FEV_1 up to 85% of predicted value, or is it more important to ensure that the patient is satisfied with their asthma control, is not missing work or school, and is adherent to the treatment plan?"

"If I had a child with an FEV_1 of 78% predicted value I would be very concerned," objected Dr. Sorkness. "Sometimes objective measurements are very important."

Dr. Martin jumped into the exchange, suggesting that both his colleagues had presented valid arguments. "Obviously, the combination of both objective data as well as patient involvement is important." He opined that in switching to an emphasis on control, the new guidelines "are just catching up to all of us clinicians who have been talking with our patients about control for a long time."

"Control is now going to focus people's attention on achieving certain objectives," pointed out Dr. Szefler. "Both the patient and the physician will have to think about the risks they take in terms of achieving control. How far should the inhaled steroids be escalated? How many treatments should be added on? What additional risk is incurred in terms of gaining control?"

Returning to the value of objective measurements versus patient satisfaction in determining asthma control, Dr. O'Byrne posited that patients' perceptions might sometimes be inaccurate. "A patient with an FEV_1 of 78% predicted value might claim to feel normal, but put that person—particularly a child—on an exercise bike and they will not do as well as a person with an FEV_1 of 100% predicted value. That is impairment, and I believe it does lead to handicap." Suggesting that "patients may not perceive it as such because, with long-standing asthma, they get acclimated to having handicaps in their lives," Dr. O'Byrne declared, "I agree with Dr. Sorkness on this point. We must be patient centered, but we need to use objective measurements to ensure that the patient's perceptions are accurate."

"I do not agree," declared Dr. Rachelefsky. "If the patient can do all they want to do, then they do not have hidden asthma. Take an eight-year-old child, for example. If the child is exercising, sleeping through the night, growing properly, not missing school, and is satisfied with the care given, are there any data to show that a 78% FEV_1 is detrimental to their long-term future?"

Dr. O'Byrne objected, countering, "There are very good data in the short term that patients do not do as well.[11]"

Dr. Rachelefsky defended his position, asking his fellow panelists and audience members to consider how reluctant many parents are to place children on ICS therapy. "Let's say the asthma is under control, the patient and the parent are satisfied with the care, and then the patient shows an FEV_1 of 78% predicted value. If the physician suggests a higher dose of steroids, the parent might say, 'I do not want to give my child any more steroids.' " In this scenario, continued Dr. Rachelefsky, "are clinicians better off trying to force the patient to take more medicine—potentially prompting more adverse effects and possibly making the patient less adherent—or should we accept the 78% FEV_1 and carefully follow the patient? Remember, asthma is not a fixed disease."

"But the issue is control today," emphasized Dr. Sorkness. "A patient who has impairment in pulmonary function tests is not likely to be controlled in the future. If we cannot deal with the issue of prevention of risk in exacerbations—"

"I know what you are saying in theory," interjected Dr. Rachelefsky, "but I really do not think there are any data in children to support that statement."

"But you are not going to find out if the patient has hidden asthma unless you do more measurements," argued Dr. Sorkness. "You have to raise the bar."

Dr. O'Byrne interrupted the exchange to suggest a compromise position. "The art of clinical care in asthma is negotiation," he posited. "You say to the parent, 'We have this combination device, a long-acting bronchodilator and a steroid. Let's put your child on it and try it for six weeks.' If there is no improvement, and the child does not want to use it, that is fair enough. But very often,

when the FEV_1 goes from 78% to 100% predicted value, the impairment associated with that poorer lung function is lost."

Therapeutic Strategies in ICS Treatment

"Let's bring our audience into this debate," suggested Dr. Salgo, who posed the next question directly to the audience members: "Do you believe that all patients with mild persistent asthma should receive ICS?" See **Figure 2** for a summary of the audience response.

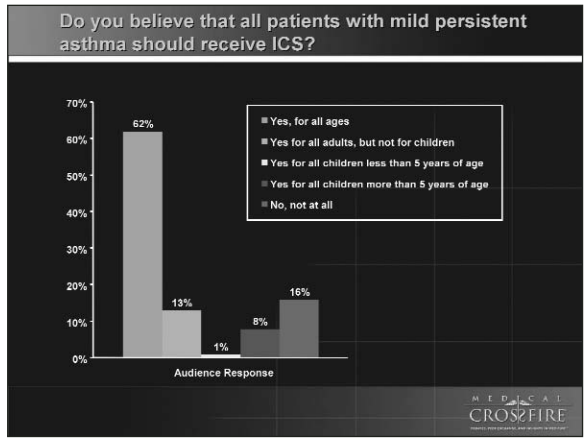

Figure 2.

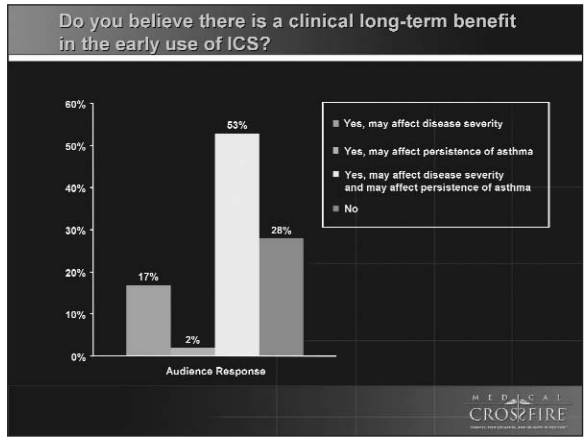

Figure 3.

Noting that the majority of the audience, 62%, responded that all patients—both adults and children, regardless of age—with mild persistent asthma should receive ICS, Dr. Szefler volunteered, "It is a very individualized decision. Remember, mild persistent asthma is defined as only a few symptoms a week. An adult or a child's parent might feel very comfortable with taking just a bronchodilator several times a week and holding off on the ICS. But, in that case, the physician would need to ask questions. Has the patient missed work or school? Have there been exacerbations? You need the whole picture to make choices."

"I am a bit surprised that so many people in the audience think that is the correct answer—and it is the correct answer, by the way," commented Dr. O'Byrne.

Dr. Salgo asked Dr. O'Byrne to clarify his point. "You mean you are surprised that word has gotten out?"

"Well, it is quite controversial, I think," answered Dr. O'Byrne, explaining that "this controversy has been fueled by a very-high-profile recent study in adults, the IMproving Asthma Control Trial [IMPACT], which looked at intermittent use versus continuous use of steroids." Although current guidelines recommend daily steroid therapy for patients with mild persistent asthma, the authors of the IMPACT trial—including Dr. Szefler, Dr. Sorkness, and Dr. Martin—found that it may be possible to instead use short, intermittent courses of inhaled or oral steroids when symptoms worsen.[12]

Dr. Salgo wondered whether there may be long-term clinical benefit—for example, in terms of disease severity or asthma persistence—to the early use of ICS. Audience members weighed in with their opinions, as shown in **Figure 3**, before Dr. Salgo turned the question over to the panelists. "Dr. Rachelefsky, what do you think? Is there a long-term clinical benefit to the early use of ICS?"

Dr. Rachelefsky cited the CAMP study,[13] in which Dr. Szefler was very involved, as providing important insight on this question as it pertains to children. "The CAMP study showed no long-term benefit from the early use of inhaled corticosteroids. There may not be long-term benefit, but there is certainly immediate benefit in the control of disease."

Dr. Salgo had a follow-up question for the panelists. "At what level of asthma severity should clinicians intervene with ICS, and with what doses?"

"I believe that an individual with any degree of persistent asthma should be on a long-term controller medication," declared Dr. Rachelefsky. "And I think we all agree that the most effective long-term controller medication is an inhaled corticosteroid. Therefore, I believe that all individuals with persistent asthma—and remember, we are not today talking about environmental control, we are not talking about other interventions, we are talking only about pharmacological intervention—should be on long-term control, with inhaled corticosteroids being my first choice."

"The answers from the audience on this question are very interesting," remarked Dr. Martin, who then shared his own response. "If the question is interpreted to mean, Is ICS a disease-modifying treatment?, then the answer is, absolutely not. Once ICS is stopped, all of the benefits are eventually lost—and that is our problem." As for short-term beneficial effects, rather than disease-modifying beneficial effects, he asserted, "Yes, there are indeed short-term beneficial effects, which are, in most cases, maintained as long as the patient stays on the inhaled steroid. But we do not have a drug that is truly disease modifying, and therefore we always need to supply continuous therapy for asthma."

Dr. Szefler entered the debate. "Dr. Rachelefsky is right that steroids do reduce morbidity. They control the disease well while the patient takes them, but once the patient stops, the benefits quickly erode in terms of controlling symptoms. We are, as Dr. Martin said, still seeking a therapy that truly modifies the disease so that patients can take a medication for a while, stop, and then not be inconvenienced by taking medications."

Dr. Salgo asked Dr. Szefler to address the use of ICS in children, particularly in very young children. "Does it make a difference if the child is over or under five years old?"

Focusing on his own practice strategy for children under the age of five, Dr. Szefler offered, "I have a good discussion with the parents to see which therapy they are comfortable with. If the parents are comfortable with inhaled steroids, then that would be my first choice, because inhaled steroids are proven to be effective. If the parents are not comfortable with inhaled steroids, then I might start with a leukotriene antagonist, monitor the child over time, and then make a decision to move toward inhaled steroids based on response."

Dr. Sorkness postulated that "the audience was making a distinction between children over and under five years because, clearly, the treatment in younger children has been extrapolated from studies in older children." But there are reliable data in younger children, she stated, citing the recent PEAK trial by Guilbert and associates of the Childhood Asthma Research and Education (CARE) network.[14] This report, she continued, "suggests that young children who have recurrent severe wheezing episodes and are at high risk for asthma development do very well on an inhaled steroid for the duration that it is taken. As soon as the inhaled steroid is

"We are still seeking a therapy that truly modifies the disease so that patients can take a medication for a while, stop, and then not be inconvenienced by taking medications."
—Dr. Szefler

stopped, the benefit goes away. But those children certainly benefited, and I believe this has given clinicians a greater comfort level with inhaled corticosteroid therapy, even in younger children."

Dr. Salgo inquired, "Are there some patients who simply do not respond to ICS?"

"An increasing number of studies tend to show that perhaps 25% to 30% of all asthmatics do not respond to inhaled corticosteroids,[15]" responded Dr. Martin, noting that this is "a good proportion—much higher than we had previously thought." The subsequent—and critical—question raised, he said, is, "How can we predict who is going to respond and who is not? Many studies suggest measuring sputum eosinophils or exhaled nitric oxide," continued Dr. Martin. "However, when the correlation is analyzed, it is very weak—only 0.3 or 0.4. So a good, easy measurement is still lacking." A recent study published in the *Journal of Allergy and Clinical Immunology* by the Asthma Clinical Research Network suggested that a short six-week trial of ICS could predict whether or not a patient is likely to demonstrate long-term benefit.[15] The validity of a short drug trial "is a possibility," commented Dr. Martin, "but it needs to be confirmed in longer studies and larger patient populations."

"Some of those measures may be more reliable in children than they are in adults," remarked Dr. Szefler, who added a new point. "But the different patterns of the disease have to be taken into consideration. Mild persistent disease in adults with long-standing disease may be different than emerging or evolving disease in children. In children, inflammation may play a significant role."

"What about maintenance versus rescue therapy?" queried Dr. Salgo. "Can ICS ever have a place as a rescue drug? Or are they simply maintenance drugs?"

"If the definition of a rescue therapy is an intervention to rapidly relieve bronchial constriction, then no, inhaled corticosteroids do not do that and are not useful as rescue therapy," replied Dr. O'Byrne. He did, however, point out that ICS will relieve bronchial constriction over a few hours—not over several days, as is often believed. This is the same onset of action demonstrated by the effective inhaled beta 2-agonists. Furthermore, stated Dr. O'Byrne, "there are studies with a combination of an inhaled steroid and a long-acting beta agonist—budesonide and formoterol—showing that this combination can be used as rescue therapy.[16-18] This is because formoterol is a rapid-acting bronchial dilator, so you get that benefit, while the steroid reduces the risk of exacerbation."

Dr. Rachelefsky introduced a related—albeit controversial—topic into the conversation. "One question is whether asthma morbidity can be altered in children whose asthma is triggered by upper respiratory viral illnesses by starting them on ICS at the first sign of an upper respiratory infection." Although this approach is not supported in the literature, Dr. Rachelefsky indicated that he does employ it in his own practice. "In my experience, with many children, if ICS is started at the right time, the course of that particular episode can be altered. I am curious to hear what my fellow panelists say about this subject."

Dr. Szefler clarified the issue by summarizing his colleagues' points. "As Dr. O'Byrne indicated, steroids cannot be viewed as rescue therapy to provide immediate relief. Dr. Rachelefsky, however, raised the possibility of trying to catch an evolving acute exacerbation early and step up treatment. On that point, the literature has been very controversial."

"Not being a pediatrician," stated Dr. Martin, entering the discussion, "I would ask Dr. Rachelefsky and Dr. Szefler, what do you do? Double the dose? Quadruple the dose? In adults, doubling the dose has not been shown to be effective in preventing or improving that exacerbation."

To illustrate the problem, Dr. Rachelefsky offered as a case patient a preschool child

who is not on maintenance therapy but has recurrent episodes of asthma precipitated by upper respiratory illnesses. "If the child comes home from the day care center with a runny nose, 48 hours later this child is going to have an episode of wheezing and coughing and go into exacerbation." One preventive strategy, he said, is, "at the first sign of sniffling, put the child on an inhaled corticosteroid, with nebulized budesonide or air chamber mask and an MDI." Acknowledging that this approach is not supported in the literature, Dr. Rachelefsky nonetheless asserted, "I have had anecdotal success with this strategy in a lot of children."

"And is this a practice to be taken at the first sign of a sniffle?" objected Dr. Sorkness.

Dr. Rachelefsky adhered to his recommendation, arguing, "Once the patient starts wheezing, it is too late for these drugs to work because they are not rescue drugs—they take time to become effective."

Adverse Effects of ICS

"Perhaps, out in the real world among practitioners and patients, there is a gap between the perception of a therapy and the reality of a therapy's results," suggested Dr. Salgo, who then moved on to a parallel question. "Likewise, is there a gap between the perception of unwanted adverse effects of ICS and their actual impact?"

"Absolutely," affirmed Dr. Sorkness, noting that the misperceptions about adverse effects of ICS extend to physicians, pharmacists, and patients themselves. The local adverse effects of ICS include oral candidiasis and dysphonia.[4] At higher doses, ICS may produce systemic adverse effects associated with cortisol suppression, including growth retardation, glucose intolerance, and an increased risk for osteoporosis and fracture.[19] The occurrence of adverse events is linked to several factors, including the pharmacological profile of the specific drug, delivery device, drug dosage, and characteristics of the individual patient.[20]

"Interestingly," continued Dr. Sorkness, "some surveys have suggested that physicians are overly concerned about adverse effects of inhaled corticosteroids that rarely occur. When physicians are asked how often they have seen these adverse effects in their practices, their experience is actually very little." She suggested that this misplaced concern is indicative of "steroid phobia" that "translates to a reticence of prescribing."

"What about new and emerging ICS—the so-called 'soft' ICS?" inquired Dr. Salgo. Soft steroids were designed to be delivered close to the site of their therapeutic action, thus reducing systemic exposure and the likelihood of unwanted adverse effects.[21] They therefore have the potential for a higher therapeutic ratio, with high efficacy and improved safety and tolerability.[4] "What do the new-generation ICS offer in terms of safety?"

Dr. Sorkness proposed that the difference lies in systemic versus local adverse effects. "Physicians observe and patients report that local adverse effects—whether they be the mouth effects of candidiasis, or dysphonia, or other problems—really affect patients. The new inhaled steroids may significantly change that scenario. By giving a prodrug, in which an esterase cleaves it directly in the lung, many of the local adverse effects are bypassed. Clearly, the new-generation steroids may change what we have to offer our patients."

"Is there a gap between the perception of unwanted adverse effects of ICS and their actual impact?"
—Dr. Salgo

ICS Dosing and Delivery

Dr. Salgo directed his next question to the audience members; the responses are tallied in **Figure 4**. "When considering an ICS therapy, is the drug or the device more important? Or are they equally important? The results show that 79% of the ***Medical Crossfire*** audience says that both are equally important for effectiveness. Panelists, are they equally important in your view?"

"Absolutely," affirmed Dr. Sorkness. "They are a package." She expressed the opinion that "I do not believe it is wise to separate these products to strictly look at the drug itself."

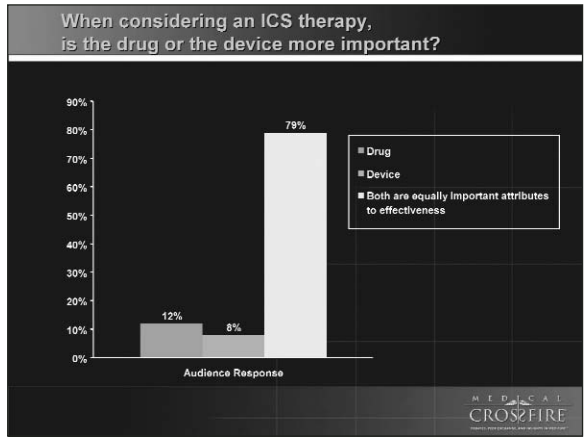

Figure 4.

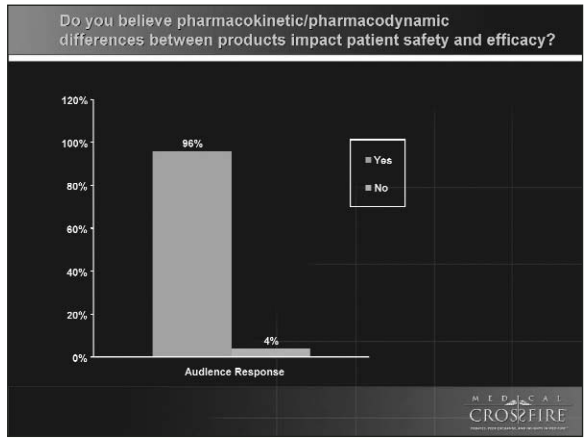

Figure 5.

"Let's take a look at new and emerging agents," requested Dr. Salgo. "What do they offer in terms of dosing and delivery?"

"We will continue to see more, better inhaled steroids that try to exploit pharmacokinetic and pharmacodynamic attributes," speculated Dr. Sorkness. Such an approach will allow better drugs, better delivery systems, and better receptor binding, she added. "Ciclesonide, for example, is a prodrug delivered directly to the lung. This attribute not only prevents oral adverse effects, it also increases protein binding, which decreases some of the systemic adverse effects." In addition, she continued, a recent shift to hydrofluoroalkane (HFA) propellants "provides, in general, the better attribute of particle sizes that allow better distribution in the parts of the lung that count. We are going to continue to see improvement in agents and delivery systems as time goes on."

"Most of the inhaled steroids currently available at low to medium doses are equally effective and equally safe," premised Dr. Szefler, who nonetheless ventured one concern. "It is bothersome that they generally show a growth effect early in the course of treatment. Until a steroid comes along without that growth effect, even at low doses, there will not be an advance in that area." High doses, however, "are where the inhaled steroids differentiate themselves," he continued. "And if we move toward pushing control, we may in some situations want to use high doses; new preparations will then be very important in terms of assuring delivery and being safe.[22]"

"Advances will be seen in the delivery of the drug," Dr. Martin chimed in. "They will become more and more patient-friendly."

Picking up on this point, Dr. Sorkness added, "Relevant to the issue of control and adherence, the built-in dose counters in many of the delivery systems offer a huge advantage. Patients will know when their inhalers are running out, and that is a good thing."

"One new inhaled steroid that has recently become available—ciclesonide—has some of the attributes that we have been

talking about," pointed out Dr. O'Byrne. "It is highly protein bound. It appears to have less systemic bioavailability than some of the others. Clearly, the incidence of topical adverse effects such as candidiasis and thrush—which are a problem in adults, though less so in children—is much lower. It remains to be seen whether this steroid has a strong clinical advantage, but it certainly has an advantage based on the pharmacology."

Treatment Selection

Choosing the Right Therapy

To frame the panel's discussion of treatment selection, Dr. Salgo first sought the perspective of the audience by again inviting participation in the audience response system. "The first question I have for our audience is, Do you believe pharmacokinetic and pharmacodynamic differences among products have an impact on patient safety and efficacy?" The tallied results demonstrated that an overwhelming majority of audience members, as shown in **Figure 5**, believe that there are differences in patient safety and efficacy that are dependent on the pharmacokinetic and pharmacodynamic profiles of the products. Expressing surprise with this near-unanimous opinion, Dr. Salgo turned to the panelists for reaction. "Dr. Sorkness, are you surprised that everybody is on the same page?"

"I am not surprised," averred Dr. Sorkness, "There is evidence in the marketplace among second-generation inhaled steroids that those differences translate into safety and efficacy. I believe this will continue to hold true with a third generation of inhaled steroids."

Speculating that the minority of respondents who doubted the impact of pharmacokinetic and pharmacodynamic differences "are probably thinking in terms of the low to medium doses, which are more generally used," Dr. Szefler agreed that at these doses "there is probably little room for very much difference. But, as I said before, the high doses really differentiate the products. In particular, high-dose, high-potency steroids carry a greater risk for systemic effects and long-term adverse effects."

Dr. Salgo turned to the audience again, this time to poll their opinion on the user-friendliness of various devices, including metered-dose inhalers, breath-actuated dry powders, and spacers or measured-dose devices. The answers are reviewed in **Figure 6**.

The ***Medical Crossfire*** panelists shared their own perspectives on this question, starting with Dr. Sorkness. "The issue is age dependency," she proposed. "The reality is—at least in adults, and likely in children over the age of five—that the new breath-actuated dry powders are very easy to use; patients like them a lot. These products are not practical for use in children younger than five, and that is why there is a greater use of metered-dose inhalers and spacers for that younger set."

Dr. Szefler emphasized the importance of patient preference. "Which device is easiest to use may depend on the patient. Certainly, the dry-powder devices are easy to use, but not all patients use them the right way. The metered-dose inhaler requires some coordination. The nebulizer was not mentioned, but it may be the easiest to administer in children."

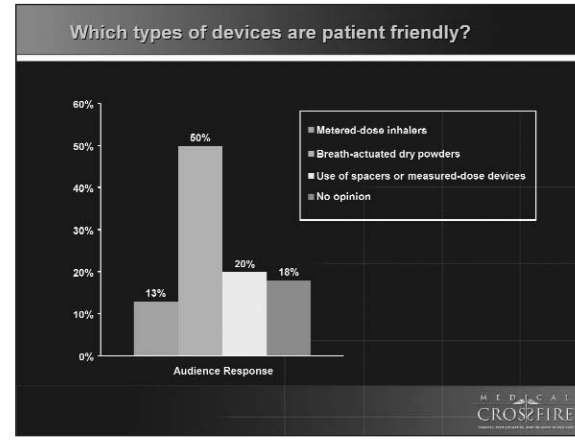

Figure 6.

"Technique is everything. Some patients with arthritis, for example, really cannot coordinate metered-dose inhalers. Clinicians need to choose the device that will work best for the patient."

—Dr. Szefler

"In the past," offered Dr. Martin, "metered-dose inhalers were very difficult to use; the coordination had to be almost perfect. But now there are more user-friendly metered-dose inhalers such as HFA-propelled beclomethasone."

"Bioavailability is a big issue," added Dr. Sorkness. "The first-pass metabolism of these drugs certainly is important. Anything that decreases oral bioavailability will likely affect the safety. How much of that is device-dependent versus pharmacologic drug-dependent—well, that remains to be seen. One of the reality checks is this: if you are able to teach a patient how to use a device well, then it probably does not make much difference what the delivery system is."

Dr. Szefler agreed, declaring, "Technique is everything. Some patients with arthritis, for example, really cannot coordinate metered-dose inhalers. Clinicians need to choose the device that will work best for the patient."

"What value does pharmacokinetics and pharmacodynamics have for specific types of patients?" inquired Dr. Salgo.

"I'm glad you asked about specific populations versus the general population, because when we talk about our patients as a whole then we are really missing a part of the equation," commented Dr. Martin before addressing Dr. Salgo's question. "One aspect of pharmacokinetics and pharmacodynamics that can make a difference is particle size. A certain percentage of our asthmatic patients have marked inflammation in the very distal airways, and in these patients a small-particle-size inhaled steroid delivered appropriately could be beneficial, whereas in other patients it may not matter whatsoever."

"And what about pharmacokinetics and pharmacodynamics in children?" pursued Dr. Salgo. "Would you select a certain agent for a child based on pharmacokinetics or pharmacodynamics, for one reason or another?"

Dr. Szefler responded, "There are certain things that need to be considered because some drugs are very readily bioavailable through oral absorption. Almost all are

drugs available systemically if they are administered to the lung. So it does become very important to make advances where there will be drugs that are metabolized in the lung and not systemically available. There is still some room for improvement."

Considerations in the Decision-Making Process

"What features do various groups respond to in their decision-making process?" queried Dr. Salgo, who listed patients, physicians, and third-party payers among those having input in treatment selection.

Dr. Rachelefsky suggested that the motivations of primary-care physicians and asthma specialists differ when it comes to making decisions about product selection. "The primary-care physician wants to make patients better without having to spend a lot of time teaching the patient how to use various devices; they want satisfied customers," he explained. On the other hand, he continued, "The asthma specialist wants a product that is effective and safe at the same time. The issue of adverse effects is more important to the asthma specialist."

As for the patient, the priority is "to get better and not be made worse by the treatment," offered Dr. Rachelefsky. "Patients also do not want to be inconvenienced by the treatment, so a once-a-day product is much better for them than a twice-a-day product. Patients also prefer a device that is easy to use, and they do not want to experience adverse effects." The influence of third-party payers, he continued, "has become very important in the United States because which treatment patients can have depends on the formularies their payers allow and the amount of their copayment. So if three people in one family have asthma and the family has a $200-a-month copayment, that will influence what the clinician can prescribe."

To summarize, Dr. Rachelefsky laid out the bottom line, as he sees it. "A product that is easy for the patient to take and the doctor to prescribe and that makes the patient better —that is what we want to achieve."

"Dr. Martin, can you take me down the decision tree?" requested Dr. Salgo. "How do you select a product for a given patient, taking into account the clinical evidence and the patient's phenotype and genotype?"

"This is a very important question, and we really do not have answers for it," lamented Dr. Martin. In asthma, the use of phenotypes to predict success of certain medications in specific patients is not well developed, he said, while genotypes may become important in the future. "But at the present time, what are helpful guidelines for the patient? I would say ease of use and cost of the medication, which we usually do not take into account, but there are significant differences between medications."

In children, reviewed Dr. Szefler, "Current data seem to show that allergic airway inflammation responds best to inhaled steroids. Once we are pointed in that direction, in terms of choosing the inhaled steroid, it is very device-dependent and individualized for the patient, depending on which device they can handle or which device they prefer. Cost and formularies are also important."

Addressing a query from Dr. Salgo about using new ICS as monotherapy, Dr. Szefler hypothesized, "In terms of monotherapy, I believe the inhaled steroids will remain for the next several years—perhaps five to 10 years—the cornerstone of asthma therapy. What we are hungry for now is an immunomodulator that will actually shut off the disease. Until we have one, we will have to be satisfied with the medications that adequately control the disease."

"The evidence is quite compelling that for many—perhaps even most—patients, inhaled steroids should be monotherapy," asserted Dr. O'Byrne, who called ICS monotherapy "the right initial approach for many patients, particularly those in primary-care practice, where the level of severity is less than what is seen in asthma specialty

practice." For his part, offered Dr. O'Byrne, he is curious as to whether the availability of inhaled steroids that are extremely safe at very high doses will give monotherapy more credence over adding additional therapies at lower doses.

Dr. Salgo pursued this point further. "When do you use high doses of ICS, and when do you use ICS as part of a combination treatment strategy?"

"Quite honestly," ventured Dr. Sorkness, "I think we should be somewhat content with the inhaled steroids we have now and will have in the future. The vast majority of individuals with persistent asthma can be safely controlled with low doses, which means we have an effective therapy that is actually quite safe." And although she, too, would love to have an immunomodulator, conceded Dr. Sorkness, "it is not here. Right now, we ought to maximize treatment and be comfortable convincing patients to take this medication and control their disease."

Dr. Martin agreed with his colleague's perspective on current therapy, remarking, "Monotherapy for mild persistent asthma—and even for moderate persistent asthma, as long as it is controlled—is where we are for the foreseeable future. Combination therapy, particularly with long-acting beta agonists, is the next step." Providing a best-practice tip, he advised, "I would emphasize that we cannot just prescribe an inhaled steroid—or any therapy, for that matter—without a defined treatment period and an evaluation of whether or not it is working. If it works, excellent. If not, intervene with additional therapies or change the therapy."

"And combination therapy—is it ever warranted as first-line treatment?" inquired Dr. Salgo.

"For most patients, the answer is no," replied Dr. O'Byrne, adding that current research is focusing on identifying patients who might benefit from combination therapy as first-line treatment. Among the patient groups being suggested as potential beneficiaries are those with longer durations of asthma, those with airflow obstruction, and those with frequent exacerbations. "But these are patients who generally are managed in more specialty practices," he pointed out, "and therefore most patients who present in primary care will and should be treated with ICS as monotherapy."

Agreeing with his colleague's comments, Dr. Szefler sought an opportunity to address the issue of exacerbations. "Asthma control is relatively easy to gauge and easy to manage. But exacerbations are still a mystery. How do we anticipate them? How do we use treatments to effectively attenuate them? Can we achieve early intervention in children?" The literature, he reviewed, "shows that early intervention, at best, attenuates an exacerbation but does not really reduce frequency of significant exacerbations."

Dr. Sorkness asserted that there are some patients who benefit from combination therapy as a first-line treatment. "There are enough studies to suggest that, in patients who present with moderate to severe disease and who have a lot of exacerbations, a combination product may be needed as a first treatment in order to gain control; then the clinician can back off the combination." The key to asthma treatment, she concluded, "is matching the patient to the right approach."

Final Thoughts

"In this ***Medical Crossfire***, we have reached agreement on the efficacy and the value of inhaled steroids," observed Dr. O'Byrne in offering his take-away message from the discussion. "What we have been debating are the fine points of their use. The major issue that remains is, how do we get physicians to use steroids more than they are currently? That is really our challenge for the next few years."

Dr. Szefler and Dr. Sorkness focused their final thoughts on areas of asthma care in which best practices remain to be fully elu-

cidated. "One area that is a bit confusing," offered Dr. Szefler, "is determining when it is appropriate to stop therapy. Often, especially with children, we deal with patients who decide to stop therapy—for example, for summer vacation—and then have an exacerbation. We do not have good guidance in terms of when to stop the therapy once we have started it." For her part, Dr. Sorkness lamented the lack of reliable data on matching drugs to patients. "We have some global sense of the right kinds of drugs for our patients with asthma, but one size does not fit all. We need to do more to appreciate phenotypic and genotypic characteristics that will allow us to maximize treatment and get the best control in that individual patient."

Picking up on the theme of individualized treatment, Dr. Rachelefsky supported his colleagues' emphasis on including the patient in the process. "What I liked about this ***Medical Crossfire*** is that we all agreed that the patient is important to the decision-making process. Treatment is not just numbers and drugs. Include the patient in the mix." Dr. Rachelefsky left the audience with one additional point. "Remember, asthma is not a fixed disease; it is a variable disease. Every time you see the patient, you need to think about varying the therapy depending on the control needed at that particular time."

Dr. Martin closed this ***Medical Crossfire*** with an exhortation to fellow practitioners. "The latest catch phrase—*personalized medicine*—really applies to asthma patients. Studies and data are very helpful in understanding trends in the overall patient population. But for our individual patients, we have to listen to that patient, find out what works and what does not, and move forward from there." ■

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Notes

Issues in the Management of Persistent Asthma

Looking Forward at Inhaled Corticosteroid Therapy

CME Test

1. Which of the following statements best describes the ideal role of LABA in asthma care?

a. first-line monotherapy
b. second-line monotherapy
c. adjunct to ICS therapy
d. adjunct to leukotriene therapy

2. What should be the first step in the patient whose asthma is not well controlled on ICS?

a. confirm that the patient is adherent and compliant
b. switch to a different ICS
c. increase the dose of ICS
d. add an adjunctive therapy

3. According to the GINA guidelines, control—the new goal for asthma therapy—is achieved when

a. symptoms and exacerbations are resolved.
b. symptoms and exacerbations are occasional.
c. symptoms and exacerbations are rare.
d. symptoms are occasional and exacerbations are rare.

4. Which patients with mild persistent asthma should receive ICS?

a. all adults
b. all adults and all children
c. all adults and all children aged more than two years
d. all adults and all children aged more than five years

5. Which of the following statements about the evidence base for ICS therapy in young children (less than five years) is accurate?

a. Young children should not receive ICS because data in children are unavailable.
b. Young children should not receive ICS because data are available only in children aged more than five.
c. Young children should receive ICS, based on the extrapolation of data in children aged more than five.
d. Young children should receive ICS, based on data specific to this age group.

6. What percentage of asthmatic patients do not respond to ICS?

a. 10% to 15%
b. 15% to 20%
c. 20% to 25%
d. 25% to 30%

7. In which group of patients are the breath-actuated dry powders least effective?

a. patients with mild asthma
b. patients with moderate to severe asthma
c. patients older than five years
d. patients younger than five years

8. Which treatment is likely to be the cornerstone of asthma therapy over the next five to 10 years?

a. LABA monotherapy
b. ICS monotherapy
c. ICS combination therapy
d. immunomodulators

9. Is ICS combination therapy ever warranted as first-line treatment?

a. No.
b. Yes, in adults, but never in children.
c. Yes, in certain specific patient populations.
d. The clinical data are unclear on this question.

10. What pharmacokinetic/pharmacodynamic parameters would be beneficial in new ICS?

a. prodrugs that minimize systemic adverse effects
b. improved propellants, such as hydrofluoroalkanes, providing better lung distribution of active drug
c. greater protein binding, which may reduce systemic effects
d. all of the above

Programmed by

American Academy of Allergy Asthma & Immunology

Issues in the Management of Persistent Asthma

Looking Forward at Inhaled Corticosteroid Therapy

Registration Form

In order to obtain *AMA PRA category 1 credits™*, participants are required to:

1. Read the learning objectives, review the activity, and complete the self-assessment test.
2. Complete this registration form, record your test answers in the box below, and complete the activity evaluation form.
3. Send the activity registration and evaluation forms to:
   American Academy of Allergy, Asthma and Immunology, Attn: Education Coordinator
   via mail: 555 E. Wells Street, Suite 1100, Milwaukee, WI 53202 or **via fax:** (414) 272-6070

Self-Assessment Test

Circle the best answer for each question on the CME test.

1.	A	B	C	D	**6.**	A	B	C	D
2.	A	B	C	D	**7.**	A	B	C	D
3.	A	B	C	D	**8.**	A	B	C	D
4.	A	B	C	D	**9.**	A	B	C	D
5.	A	B	C	D	**10.**	A	B	C	D

(Please print clearly.)

First Name _____ MI _____ Last Name _____

Degree _____ Affiliation _____

Specialty _____ Last 4 digits of SS# _____
(For credit reporting purposes only)

Day Phone _____ Evening Phone _____

Fax _____ E-Mail _____

Preferred Mailing Address: ❍ Home ❍ Business

_____

_____

City _____ State _____ Zip _____

I attest that I have completed the "Issues in the Management of Persistent Asthma: Looking Forward at Inhaled Corticosteroid Therapy" activity as designed.

Physicians

I claim____ *AMA PRA Category 1 Credit(s)™* for participating in this activity (1 credit for each hour of participation, not to exceed one 1.5 credits).

Nurses

I claim____ CE Contact Hours for participating in this activity (not to exceed 1.8 CE Contact Hours).

_____

Signature Date

A continuing education credit letter will be mailed to you within 3 to 4 weeks.

Credit for this activity is available until May 31, 2009.
American Academy of Allergy, Asthma and Immunology
Attn: Education Coordinator
555 E. Wells Street, Suite 1100, Milwaukee, WI 53202

Issues in the Management of Persistent Asthma

Looking Forward at Inhaled Corticosteroid Therapy

Activity Evaluation Form

Please note: CE credit letters and long-term credit retention information will only be issued upon receipt of this completed evaluation form. The planning and execution of useful and educationally sound continuing education activities are guided in large part by input from participants. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few moments to complete this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants. Thank you for your cooperation!

Program Objectives

Having completed this activity, are you better able to:

	Strongly Agree				Strongly Disagree
State the current role of ICS in the treatment of persistent asthma.	5	4	3	2	1
List the limitations of current ICS therapies and the potential advantages of new and emerging ICS therapies.	5	4	3	2	1
Appraise whether differences in pharmacodynamics and pharmacokinetics confer safety and efficacy advantages for inhaled corticosteroids.	5	4	3	2	1
State the relative benefits and drawbacks to current inhaled corticosteroid drug and delivery technology and describe the future of ICS technology.	5	4	3	2	1
Evaluate inhaled corticosteroid therapy options based on evidence as well as clinical practice parameters (best usage, number needed to treat, etc.).	5	4	3	2	1

Overall Evaluation

	Strongly Agree				Strongly Disagree
The information presented increased my awareness/understanding of the subject.	5	4	3	2	1
The information presented will influence how I practice.	5	4	3	2	1
The information presented will help me improve patient care.	5	4	3	2	1
The faculty demonstrated current knowledge of the subject.	5	4	3	2	1
The activity was educationally sound and scientifically balanced.	5	4	3	2	1
The activity avoided commercial bias or influence.	5	4	3	2	1
Overall, the activity met my expectations.	5	4	3	2	1
I would recommend this activity to my colleagues.	5	4	3	2	1

Based on information presented in the program, I will (check one):

❒ Do nothing, as the content was not convincing

❒ Seek additional information on this topic

❒ Do nothing. Barriers at my institution prevent me from changing my practice.

❒ Change my practice

❒ Do nothing, as current practice reflects program's recommendations

If you anticipate changing one or more aspects of your practice as a result of your participation in this activity, please provide us with a brief description of how you plan to do so.

Please provide any additional comments pertaining to this activity (positives and negatives) and suggestions for improvement.

Please list any topics that you would like to be addressed in future educational activities.

CME Test Answer Key

1. c. Pointing out that the United States is one of the few countries that allow LABA to be used as monotherapy, Dr. O'Byrne posited, "I do not think anybody would debate that LABA, when used as the only therapy for asthma, do pose risk, [however,] the combination of inhaled steroids and LABA improve every important outcome, exacerbations, and, particularly, severe exacerbations, in every properly conducted clinical trial." The other panelists—and the ***Medical Crossfire*** live audience—agreed with their colleague that LABA are an acceptable alternative to higher doses of ICS.
Locator: The Role of Available and Emerging Inhaled Corticosteroids/Optimizing ICS: Adjunctive Therapy or Higher Doses?

2. a. Dr. Szefler asserted, to agreement from his colleagues, that compliance and adherence would be his first concern in the patient whose asthma was not well controlled on ICS. "I would confirm that the patient had filled the prescription and was taking the ICS the right way" before adjusting the therapeutic regimen, stated Dr. Szefler.
Locator: The Role of Available and Emerging Inhaled Corticosteroids/Optimizing ICS: Adjunctive Therapy or Higher Doses?

3. d. According to the GINA guidelines, asthma control is defined as the control of the clinical manifestations of asthma, including symptoms, sleep disturbances, limitations of daily activity, impairment of lung function, and use of rescue medication. Asthma is said to be controlled when recurrences of symptoms are occasional and severe exacerbations are rare.
Locator: The Role of Available and Emerging Inhaled Corticosteroids/Reaching the New Goal: Asthma Control

4. b. When this question was posed to the ***Medical Crossfire*** live audience, 62% responded that all patients with mild persistent asthma—both adults and children, regardless of age—should receive ICS. "I am a bit surprised that so many people in the audience think that is the correct answer—and it is the correct answer, by the way," commented Dr. O'Byrne, noting that current guidelines recommend daily steroid therapy for all patients with mild persistent asthma.
Locator: The Role of Available and Emerging Inhaled Corticosteroids/Therapeutic Strategies in ICS Treatment

5. d. Although the use of ICS therapy in young children has been supported by the extrapolation of data in older children, Dr. Sorkness pointed out that there are reliable data supporting ICS therapy in children younger than five. As a whole, she said, these data "suggest that young children, especially those who have recurrent severe wheezing episodes and are at high risk for asthma development, do very well on an inhaled steroid for the duration that it is taken."
Locator: The Role of Available and Emerging Inhaled Corticosteroids/Therapeutic Strategies in ICS Treatment

6. d. "An increasing number of studies tend to show that perhaps 25% to 30% of all asthmatics do not respond to inhaled corticosteroids," observed Dr. Martin, noting that this is "a good proportion—much higher than we had previously thought."
Locator: The Role of Available and Emerging Inhaled Corticosteroids/Therapeutic Strategies in ICS Treatment

7. d. Most patients find the new breath-actuated powders to be very easy to use. However, cautioned Dr. Sorkness, "These products are not practical for use in children younger than five, and that is why there is a greater use of metered-dose inhalers and spacers for that younger set."
Locator: Treatment Selection/Choosing the Right Therapy

8. b. Dr. Szefler posited, "In terms of monotherapy, I believe the inhaled steroids will remain for the next several years—perhaps five or 10 years—the cornerstone of asthma therapy. What we are hungry for now is an immunomodulator that will actually shut off the disease. Until we have one, we will have to be satisfied with the medications that adequately control the disease." Dr. O'Byrne, Dr. Sorkness, and Dr. Martin expressed agreement that ICS monotherapy is the right initial approach for most patients.
Locator: Treatment Selection/Considerations in the Decision-Making Process

9. c. Dr. Sorkness asserted that there are some patients who benefit from combination therapy as a first-line treatment. "There are enough studies to suggest that, in patients who present with moderate to severe disease and who have a lot of exacerbations, a combination product may be needed as a first treatment in order to gain control; then the clinician can back off the combination."
Locator: Treatment Selection/Considerations in the Decision-Making Process

10. d. Dr. Sorkness stated, "We will continue to see more, better inhaled steroids that try to exploit pharmacokinetic and pharmacodynamic attributes," speculated Dr. Sorkness. Such an approach will allow better drugs, better delivery systems, and better receptor binding, she added. "Ciclesonide, for example, is a prodrug delivered directly to the lung. This attribute not only prevents oral adverse effects, it also increases protein binding, which decreases some of the systemic adverse effects." In addition, she continued, a recent shift to hydrofluoroalkane propellants "provides, in general, the better attribute of particle sizes that allow better distribution in the parts of the lung that count. We are going to continue to see improvement in agents and delivery systems as time goes on."
Locator: The Role of Available and Emerging Inhaled Corticosteroids/ICS Dosing and Delivery