JMCP

JOURNAL OF MANAGED CARE PHARMACY®

From Asthma Severity to Asthma Control: Identification of New Guidelines

Craig Jones, MD

Linda Endicott, RN, MSN

Michele B. Kaufman, BSc, PharmD, RPh

Supplement

December 2006

Vol. 12, No. 9

Continuing Education Program

JMCP

Editor-in-Chief

Frederic R. Curtiss, PhD, RPh, CEBS
(830) 935-4319, fcurtiss@amcp.org

Managing Editor

Tamara C. Faggen, (703) 323-0170
tfaggen@amcp.org

Peer Review Administrator

Jennifer A. Booker, (703) 317-0725
jmcpreview@amcp.org

Graphic Designer

Laura J. Mahoney, (703) 944-4577
lauramahoney@comcast.net

December Supplement Editor

Marilyn Stebbins, PharmD

Account Manager

Peter Palmer, (800) 486-5454, ext. 13
peter@promedgroup.net

Publisher

Judith A. Cahill, CEBS
Executive Director
Academy of Managed Care Pharmacy

This supplement to the Journal of Managed Care Pharmacy (ISSN 1083-4087) is a publication of the Academy of Managed Care Pharmacy, 100 North Pitt St., Suite 400, Alexandria, VA 22314; (703) 683-8416; (703) 683-8417 (fax).

Copyright© 2006, Academy of Managed Care Pharmacy. All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, without written permission from the Academy of Managed Care Pharmacy.

POSTMASTER: Send address changes to JMCP,
100 North Pitt St., Suite 400, Alexandria, VA 22314.

Supplement Policy Statement

Standards for Supplements to the Journal of Managed Care Pharmacy

Supplements to the *Journal of Managed Care Pharmacy* are intended to support medical education and research in areas of clinical practice, health care quality improvement, or efficient administration and delivery of health benefits. The following standards are applied to all JMCP supplements to assure quality and assist readers in evaluating potential bias and determining alternate explanations for findings and results.

1. Disclose the principal sources of funding in a manner that permits easy recognition by the reader.
2. Disclose the existence of all potential conflicts of interest among supplement contributors, including financial or personal bias.
3. Describe all drugs by generic name unless the use of the brand name is necessary to reduce the opportunity for confusion among readers.
4. Strive to report subjects of current interest to managed care pharmacists and other managed care professionals.
5. Seek and publish content that does not duplicate content in the *Journal of Managed Care Pharmacy*.
6. Subject all supplements to expert peer review.

FACULTY

Craig Jones, MD, is an assistant professor, Department of Pediatrics, Keck School of Medicine, University of Southern California, and director, Division of Allergy/Immunology and director of the Allergy/Immunology Residency Training Program, Department of Pediatrics, Los Angeles County and University of Southern California (LAC+USC) Medical Center. He is also director, in charge of the design, implementation, and management, of the Breathmobile Program, a group of 4 asthma mobile clinics that deliver ongoing care to inner-city children at their schools and at county clinics. The Breathmobile Program is a collaborative effort of the Southern California Chapter of the Asthma and Allergy Foundation of America (AAFA) and the Los Angeles County Department of Health Services (LAC DHS). This program has evolved from community outreach to more fully integrated pediatric asthma disease management for the LAC DHS.

Jones has published papers and abstracts on allergy and immunology in *Pediatric Research*, *Pediatrics in Review*, *Journal of Clinical Immunology*, *Journal of Allergy and Clinical Immunology*, *Annals of Allergy, Asthma and Immunology*, *Chest*, and *Disease Management*. He is a member of the Executive Committee and serves as a board member for Southern California AAFA, and currently serves as the chapter president; he is a past president of the Los Angeles Society of Allergy Asthma & Immunology and a past president and member of the board of directors for the California Society of Allergy Asthma & Immunology. Jones also serves as cochair of the Department of Health Services (Los Angeles County) Disease Management Committee in Pediatric Asthma. He received his undergraduate degree at the University of California at San Diego and medical degree at the University of Texas Health Science Center in San Antonio. He completed his internship and residency in pediatrics and fellowship in allergy and clinical immunology at LAC + USC Medical Center.

Linda Endicott, RN, MSN, is currently an independent consultant who has, for the past 6 years, worked as a clinical program manager in disease management and care management in both a Medicaid/Medicare managed care organization, Colorado Access, and for a nationally recognized vendor for respiratory disease management at the National Jewish Medical and Research Center, Denver, Colorado. Endicott was instrumental in the development, expansion, and quality monitoring of chronic obstructive pulmonary disease and asthma disease management programs. Prior to her career in disease management, she served as director of emergency services at leading academic and community-based health centers, during which time she served as a script consultant for—and appeared on—the show “ER.” In 1994, Endicott received a Manager of the Year award for excellence in nursing leadership and management from Rose Medical Center, Denver, Colorado. She received her bachelor of science in nursing from City College of New York/Mt. Sinai School of Nursing, cum laude, and her master of science in nursing in community health nursing and nursing education from the University of Colorado.

Michele B. Kaufman, BSc, PharmD, RPh, is the senior medical writer at Professional Resources in Management Education, Inc. and a member of PRIME's senior clinical staff. She is owner of PRN Communications Inc., a freelance medical writing/editing and clinical pharmacy/managed care consulting company in New York City and continues to hold a license as a registered pharmacist.

Kaufman has been a clinical assistant professor at St. John's University in Jamaica, New York, and clinical coordinator, drug information/internal medicine at Long Island Jewish Medical Center (LIJMC) in New Hyde Park, New York. Most recently, she served as clinical pharmacy coordinator and project leader/clinical pharmacist and geriatric case manager at HIP Health Plan of New York, New York. She serves on the editorial board of *Formulary* and is a peer reviewer and medical writer for other medical journals. Kaufman is a member of national, state, and local medical and pharmacy organizations and has published numerous articles in newsletters and journals and in online regional and national publications and forums. Kaufman received her bachelor of science degree from the University of Rhode Island (URI) College of Pharmacy, Kingston, and her doctor of pharmacy degree from the Massachusetts College of Pharmacy and Allied Health Sciences, Boston, Massachusetts. She completed a drug information fellowship at the URI Drug Information Center/Roger Williams Medical Center in Providence.

Table of Contents

From Asthma Severity to Asthma Control: Identification of New Guidelines

- S2** From Asthma Severity to Asthma Control: Identification of New Guidelines
Craig Jones, MD; Linda Endicott, RN, MSN; and Michele B. Kaufman, BSc, PharmD, RPh

- S15** Continuing Education*:
CE Submission Instructions and Posttest Worksheet

Target Audience

Managed care and other pharmacists, managed care medical directors, and consulting physicians and pharmacists

Learning Objectives

Upon completion of this program, participants will be able to

1. discuss the focus of outcomes management and models in current asthma disease management programs,
2. identify treatment options and new guidelines to improve asthma outcomes in managed care,
3. assess how changes in the proposed new asthma guidelines were identified, and
4. describe application of guidelines in asthma control and management.

This supplement was funded by an unrestricted grant from Genentech, Inc. and Novartis Pharmaceuticals Corporation.

*A total of 0.20 CEUs (2.0 contact hours) will be awarded for successful completion of this continuing education program (ACPE Program No. 255-000-06-013-H01) and 2.0 AMA PRA Category 1 credits. For faculty disclosures, please see page S13. For accreditation information, please see page S15.

The article published in this supplement represents the opinions of the authors and does not reflect the official policy or views of the Academy of Managed Care Pharmacy, the authors' institutions, Genentech, Inc., and Novartis Pharmaceuticals Corporation unless so specified. The authors have disclosed if any unlabeled use of products is mentioned in their articles. Before prescribing any medicine, clinicians should consult primary references and full prescribing information.

From Asthma Severity to Asthma Control: Identification of New Guidelines

CRAIG JONES, MD; LINDA ENDICOTT, RN, MSN; and MICHELE B. KAUFMAN, PharmD, BScPharm, RPh

ABSTRACT

BACKGROUND: Managed care pharmacists utilize clinical guidelines to assist them in identifying acceptable treatment and management of chronic diseases. For the past several months, an expert panel representing the National Asthma Education and Prevention Program (NAEPP) has discussed updated asthma guidelines, which could change future medication management of patients with asthma.

OBJECTIVE: To identify new guidelines for asthma control.

SUMMARY: Taking control of asthma is a foremost objective in managed care, as new guidelines are debated, and asthma disease management programs identify more effective models of asthma disease management. Within an effective asthma disease management program, managed care practitioners, including but not limited to physicians and pharmacists, must have a thorough understanding of the most recent clinical guidelines as well as current knowledge of the current consensus among opinion leaders regarding asthma treatment and management. This ongoing education is critical in order to allow managed care practitioners to perform their role and function within their organizations. With the advent of changing asthma practice guidelines and processes, managed care practitioners need current information to recognize and apply guidelines-based asthma control.

CONCLUSIONS: Appropriate asthma treatment requires adherence to current management guidelines. Approximately one third of asthmatics will not respond to standard asthma treatment and may even worsen while on therapy. Monitoring, close tracking, and regular evaluation of asthma patients at every health care provider visit is a strategy that can be utilized to generate improved asthma control.

KEYWORDS: Asthma, Monoclonal antibody, Asthma management, NAEPP guidelines, GINA guideline, Inhaled corticosteroids, Leukotriene receptor antagonists

J Manag Care Pharm. 2006;12(9):S2-S14

Authors

CRAIG JONES, MD, is director of allergy and immunology and an assistant professor of clinical pediatrics, Los Angeles County—University of Southern California Medical Center, Los Angeles; LINDA ENDICOTT, RN, MSN, is a consultant, Denver, Colorado; MICHELE B. KAUFMAN, PharmD, BScPharm, RPh, is a senior medical writer, PRIME, Inc., Tamarac, Florida.

AUTHOR CORRESPONDENCE: Craig Jones, MD, Director of Allergy and Immunology, Los Angeles County—USC Medical Center, 1801 E Marengo St., Room 1G1, General Labs Bldg., Los Angeles, CA 90033. Tel: (323) 226-3813; Fax: (323) 226-6049; E-mail: craigj@usc.edu

Copyright© 2006, Academy of Managed Care Pharmacy. All rights reserved.

Asthma is a chronic inflammatory airway disorder identified clinically by recurring episodes of wheezing, chest tightness, dyspnea, and coughing, particularly in the night or early morning.¹ It is characterized by airway hyperresponsiveness and inflammation. Airway obstruction can worsen when an asthmatic individual is exposed to various triggers or stimuli, which leads to airflow limitations via bronchoconstriction, mucus plugs, and increased inflammation.

Risk factors for asthma include host factors (e.g., genetic predisposition, atopy, airway hyper-responsiveness, gender, and/or race/ethnicity) as well as environmental factors that increase susceptibility for asthma development in predisposed individuals (e.g., respiratory infections, exposure to cigarette smoke, indoor/outdoor allergens, family size, occupational sensitizers, or air pollution). Asthma triggers vary from person to person and may include allergen exposure (e.g., housedust mites, animal dander, cockroaches, fungal spores, airborne pollens like grass, trees, and weeds), other environmental factors (e.g., cold air, smoke, and air pollution), strong emotional expressions (e.g., anxiety, stress, and laughter), exercise (particularly in cold air or in dry climates), medications or preservatives (e.g., aspirin, beta-blockers, nonsteroidal anti-inflammatory agents, sulfites, and benzalkonium chloride), respiratory infections, chemical irritants, occupational stimuli (e.g., flour dust for bakers; hay mold for farmers; and formaldehyde and other chemicals for plastics, rubber, and wood workers), or comorbid conditions (e.g., gastroesophageal reflux disease, rhinitis, and sinusitis).¹⁻³

A clinical history of asthma symptoms increases the likelihood that asthma is present, but other important tools should be used to make an accurate diagnosis. A physical examination may show wheezing when patients are symptomatic, and in many patients, findings consistent with allergic rhinitis and/or ocular allergies may be present.² A thorough patient assessment is essential, and it is important to consider the patient's entire clinical picture when making the diagnosis.¹⁻³ The following are critical in establishing a clear asthma diagnosis:

- Of primary significance is a history that suggests a pattern of respiratory symptoms such as recurrent episodes of chest tightness, difficulty breathing, shortness of breath, and coughing. A history may also suggest a pattern of symptoms that occur with exercise and exertion and that are improved with a bronchodilator (i.e., they are reversible). A clinical history should also evaluate whether these symptoms are related to environmental triggers, such as allergens, viral infections, and irritants.
- Objective measurements of airflow limitations, reversibility, and variability are helpful in establishing a diagnosis. Spirometry is

useful in diagnosing asthma and monitoring response to therapy. An increase in forced expiratory volume in 1 second (FEV₁) of 12% or greater or an increase in peak expiratory flow (PEF) of 15% or greater after an inhaled short-acting bronchodilator or after a trial of an inhaled corticosteroid (ICS) is diagnostic for asthma. Periodic assessments and ongoing monitoring are recommended to determine if asthma management goals are being met.^{2,3}

■ Prevalence

Asthma is a common chronic disease that causes substantial economic, social, and public health burdens on society. According to the Centers for Disease Control and Prevention, asthma prevalence has increased over the past 2 decades. The overall annual age-adjusted prevalence rate of self-reported asthma increased by 209% from 1980 to 1996. Mortality from asthma also increased during this time period.⁴ In the 2002 National Health Interview Survey (NHIS), 30.8 million people in the United States (11.1%) reported having been diagnosed with asthma by a health professional during their lifetimes (21.9 million adults and 8.9 million children).⁵

The NHIS survey estimates of current asthma prevalence included people who were diagnosed with asthma by a health professional and who still had asthma. In 2002, 20 million people (7.2% of respondents) had asthma, including 6.1 million children and 14 million adults.⁵ Approximately 60% of people with a current asthma diagnosis reported having at least 1 asthma attack in the previous year. This population may represent patients with suboptimally controlled asthma at risk for a poor outcome, such as hospitalization.

Uncontrolled asthma can interfere with daily activities, including work and school attendance. Among individuals who reported at least 1 asthma attack in the previous year (2001), children aged 5 to 17 years missed 14.7 million school days, and adults aged at least 18 years who were employed at the time of the survey missed 11.8 million work days. Health care use among this population included 13.9 million outpatient asthma visits to private physician offices and hospital outpatient departments, 1.9 million visits to emergency departments (EDs), and 484,000 hospitalizations. Among children aged 0 to 17 years, there were 196,000 hospitalizations (27 per 10,000 people), with the highest rate among children aged 0 to 4 years (59 per 10,000). In that same year, 4,261 people died from asthma. It is clear that despite the presence of well-studied, generally effective treatments for asthma, the condition remains a key public health problem in the United States.⁵

■ Managing Care

Evidence-based clinical practice guidelines for asthma have been available for 15 years. The National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program (NHLBI/NAEPP) guidelines were initially published in 1991 and

updated in 1997, with a second update on selected topics in 2002. A complete update is expected in late 2006 or early 2007. The Global Initiative for Asthma (GINA) guidelines were originally published in 1995 and have been updated several times, most recently in October 2005. The GINA guidelines are a result of collaboration between the NHLBI and the World Health Organization.^{2,3} However, despite the availability of these asthma clinical guidelines, optimal control of asthma symptoms remains an elusive goal for many patients. There are numerous reasons for this, including poor guideline compliance.

A major problem associated with the management of asthma patients is nonadherence to the medication regimens.³ Reasons for this may include (1) difficulties with inhaler devices; (2) awkward regimens (e.g., frequency, or multiple drugs); (3) side effects; (4) medication costs; (5) difficulty in obtaining medications due to insurance issues; (6) dislike of the medications; and/or (7) distant pharmacies. Some nondrug factors for nonadherence include (1) health literacy or lack of instruction; (2) fears about side effects; (3) fears or concerns that are not expressed or discussed; (4) inappropriate expectations; (5) poor supervision, training, or follow-up; (6) anger about the condition or its treatment; (7) underestimation of asthma severity; (8) cultural issues; (9) stigmatization; (10) forgetfulness or complacency; and/or (11) attitudes toward ill health.³

Some important points about adherence include the following:⁶⁻⁸

1. Adherence rates range from 5% to 50%.
2. Use patterns tend to be sporadic.
3. Nonadherence likely accounts for approximately 60% of hospitalizations.
4. Significant improvement in important outcomes may require approximately 50% adherence.

■ Costs

The costs associated with asthma are also a concern. Studies have shown that 20% of all patients with asthma account for 80% of the direct costs of treating the disease.⁹ Direct medical costs include hospital outpatient services, hospitalizations, ambulatory care visits, ED visits, physician and facility payments, and prescription medications. Indirect costs include those resulting from missed work or school days and days with restricted work activity. The estimated annual per-patient costs are \$2,584 for high-cost patients and \$140 for low-cost patients.⁹ In the United States alone in 2002, direct and indirect expenditures for all forms of asthma totaled \$14 billion, which included \$9.4 billion in direct costs and \$4.6 billion in indirect costs.¹⁰ However, despite these statistics and the wealth of information on the management of asthma, numerous studies have shown that a large portion of patients fall short of acceptable asthma treatment goals. Strategies aimed at optimizing asthma control for this subset of patients who consume the majority of resources should result in improved outcomes and decreased cost of care.

TABLE 1 Classification of Asthma Severity According to the NAEPP/NHLBI Guideline³

Severity Class	Symptoms	Nighttime Symptoms	Lung Function
Mild intermittent	Symptoms less than twice weekly symptomatic and normal PEF between exacerbations Exacerbations brief with variable intensity	Less than twice monthly	FEV ₁ or PEF >80% predicted PEF variability <20%
Mild persistent	Symptoms more than twice weekly but less than once daily Exacerbations may affect activity	More than twice a month	FEV ₁ or PEF >80% predicted PEF variability 20%–30%
Moderate persistent	Daily symptoms daily use of inhaled short-acting beta ₂ -agonist exacerbations affect activity Exacerbations more than 2 times per week and may last days	More than once weekly	FEV ₁ or PEF >60% but less than 80% predicted PEF variability >30%
Severe persistent	Continual symptoms limited physical activity Frequent exacerbations	Frequent	FEV ₁ or PEF <60% predicted PEF variability >30%

FEV₁=forced expiratory volume in 1 second; NAEPP=National Asthma Education and Prevention Program; NHLBI=National Heart, Lung, and Blood Institute; PEF=peak expiratory flow.

Guideline Use in the Management of Asthma (Current and Future)

National asthma guidelines recommend that asthma be classified and treated in accordance with a patient's baseline severity rating (while not using controller therapy). Severity in an individual can change over time, as can the frequency and severity of an individual's asthma symptoms, whether the person is on or off therapy.¹ A stepwise approach to asthma treatment exists with a goal of achieving and maintaining asthma control.^{2,3} The overall management of asthma involves 4 components: (1) monitoring response to therapy, including disease activity and disease control (symptoms and lung function); (2) controlling/avoiding asthma triggers; (3) patient and caretaker education, and (4) pharmacologic therapy. Pharmacotherapy includes the use of short-acting reliever medications for acute symptoms and the use of controller medications for long-term control of symptoms. There are also some options for difficult-to-treat, moderate-to-severe asthmatics, such as those with severe persistent asthma whose disease is poorly controlled with routine use of controller medications. These are usually patients with severe persistent asthma despite conventional pharmacotherapy. Some of the options for these patients include daily oral corticosteroids (e.g., prednisone) and oral methylxanthines (e.g., theophylline). Both of these drug classes require careful monitoring to prevent toxicities. Additional approaches to managing these patients include use of the oral leukotriene modifier zileuton; subcutaneous allergen-specific immunotherapy; and/or use of advanced therapeutics/new technologies such as subcutaneous injection of the anti-immunoglobulinE (IgE) monoclonal antibody omalizumab.² Management strategies should be individualized to meet each patient's needs.

Ongoing monitoring and periodic assessments are necessary to determine whether the goals of asthma therapy are being met. These goals include the following:

1. Preventing chronic and troublesome symptoms
2. Maintaining near-"normal" pulmonary function
3. Preventing recurrent asthma exacerbations and minimizing the need for emergency department visits or hospitalizations
4. Maintaining normal levels of activity, including exercise and other physical activity
5. Providing optimal pharmacotherapy with the least amount of adverse effects
6. Meeting patients' and families' expectations of and satisfaction with asthma care

The NAEPP guidelines classify asthma severity into 1 of 4 symptom categories, which are depicted in Table 1.³ It is recommended that severity assessment and classification be performed during the initial evaluation and before the initiation of treatment. Spirometric tests are recommended at the time of the initial assessment, after treatment is initiated until patient symptoms and PEF have stabilized, and at least every 1 to 2 years thereafter. Periodic assessments and ongoing monitoring are recommended to ascertain that therapy goals are being met. Patients should be given a written action plan based on signs and symptoms and/or PEF, and patients should be trained to recognize signs of decreasing control and appropriate actions to take. The stepwise approach for the treatment of asthma in adults and children older than 5 years is also described in the NAEPP guidelines and can be seen in Figure 1.³

Going forward to the "next generation" of asthma clinical practice guidelines, the cornerstone will likely be the monitoring and tracking of patient outcomes with a focus on asthma control. Key tenets may include routine monitoring and tracking of asthma control at each visit to the health care provider, whether that is well care or urgent care, or whether that is with a specialist or a general practitioner. During the past several months, an expert panel representing NAEPP has considered the results of recent

asthma studies to determine if changes in asthma treatment recommendations are warranted, with a goal to release updated guidelines in late 2006 or early 2007.¹¹ In an asthma disease management program in Los Angeles, one of the most important elements is to optimize control with thorough assessment at regular visit intervals.¹² Asthma patients are seen by their health care teams on a regular basis, including when they are well, in order to reinforce the patients' understanding of their daily management plans and to encourage adherence to the daily use of controller medications. Commonly and unfortunately, the health care team sees asthma patients only when they are sick. It is therefore important during the patient/family education process to reaffirm the importance of regular visit intervals (e.g., every 1-6 months as appropriate, depending on level of control).

Patient compliance with visits to the provider's office to receive ongoing assessment and asthma education may be improved by the office making simple reminder calls the day before every visit. Health care providers should provide ongoing self-management education, including control of environmental factors that exacerbate symptoms (e.g., allergens and irritants), at each visit.¹³ With change in asthma treatment and management occurring at the point of care, updated guidelines may assist providers in identifying and applying new strategies for asthma control.

Tracking Asthma Therapy

Since asthma is a variable disease, symptom control should be evaluated at each visit so the daily management plan can be modified accordingly. A systematic method of tracking control for each patient should be established and completed at each visit to document response to asthma therapy. Treatment plans can then be individualized, with the goal of optimal control.

An example of how this model of care has been successfully implemented using a population-based model is the mobile clinics in Los Angeles, California, that supplement traditional clinics by visiting schools to monitor and treat children. In each of these clinical settings, a method has been developed to identify and track poorly controlled asthma in the general population in Los Angeles. The Health Risk Assessment survey software provides a systematic way to identify poorly controlled asthma or well-controlled asthma. Risk assessment software systems may be accessed in a kiosk located in a clinic or a physician's office waiting area. These systems offer an automated survey consisting of a list of questions that the parent or asthma patient can complete while waiting to see the provider. Survey results can be used to help identify patients with suboptimally controlled asthma. Survey answer patterns are evaluated using validated scoring algorithms to help predict 3 things: (1) whether a child has asthma (yes or no); (2) if yes, whether the asthma is well controlled or poorly controlled; and (3) if poorly controlled, whether it is moderate to severe at the current time.^{14,15} A copy of the full report may be provided directly to the provider for review before the patient enters the examination room.

FIGURE 1 Stepwise Approach to Asthma Therapy in Patients >5 Years Old^{2,3}

ICS=inhaled corticosteroid; LABA=long-acting beta₂-agonist;
LTM=leukotriene modifier; SR=sustained release.

FIGURE 2 Disease Management Principles¹⁵

An individualized checklist provides a review of the education and treatment needed either to improve poorly controlled asthma or to maintain good control. The report may also be transmitted to a care manager, risk manager, or a care coordinator at the patient's health plan or managed care organization. These are simple methods to track control and help the multidisciplinary team coordinate care using uniform assessment tools.

Monitoring Asthma Control

Identifying poorly controlled asthma patients, regardless of the setting, is the first step in an effective asthma disease management program. The long-term process of achieving and maintaining asthma control is complex and requires continual focus on the following 3 areas: (1) thorough evaluation of disease activity or severity, (2) evaluation of the response to therapy, and (3) routine follow-up. This process is depicted in Figure 2.¹⁶ Implementation of the National Institutes of Health (NIH)/NAEPP guidelines for the treatment of asthma in general care settings is often difficult because thorough assessments, development of management plans, education of families, observation of patient and family

TABLE 2 Variability in FEV₁ Response¹⁷

Response	BDP-MDI (n = 12)	FP-MDI (n = 9)
Good (>15% increase)	5	3
Marginal (5%-15% increase)	2	3
Poor (<5% increase)	5	3*

*Poor response also following treatment with fluticasone propionate diskus powder inhaler.

BDP-MDI=beclomethasone dipropionate metered-dose inhaler; FEV₁=forced expiratory volume in 1 second; FP-MDI=fluticasone propionate metered-dose inhaler.

behavior, follow-up of patients at close intervals, and reinforcement are all time intensive. Through technology like the kiosk survey, simple assessment before the patient visit can be performed. Information on asthma control, recent ED visits, hospitalizations, missed school days, and the frequencies of symptoms (if any) can be collected in a time-efficient manner and can be tracked and trended over time. More time can then be spent developing management plans and educating patients. This approach at the point of care facilitates a more efficient and productive delivery of health care services.

If health care providers follow the NAEPP guidelines and classify asthma severity at baseline and initiate therapy according to each patient's severity presentation, the guidelines suggest that patients will be able to meet the goals of therapy.^{2,3} Goals of therapy are the following:

1. Minimal symptom frequency
2. Intermittent symptom frequencies of ≤ 2 days per week and ≤ 2 nights per month
3. No severe asthma flare-ups between patient visits (i.e., no ED visits, hospitalizations, or systemic steroids)
4. Lung function normal or optimal for patient
5. No asthma-related activity or exercise limitations

It is anticipated that the next version of the NAEPP guidelines will go a step further to address the need to track asthma control in patients. The current guidelines suggest that, over time, asthma is a highly variable condition. Symptoms wax and wane. At times, a patient may be at a low level, with intermittent or mild disease, while at other times, the symptom presentation may be more moderate to severe. The current NAEPP and GINA guidelines suggest that if appropriate therapy is started for a particular patient's symptom frequency at the time of the evaluation, adherence is good, and the health care team has provided the appropriate education for the patient to be well controlled. Studies have provided evidence on what happens when asthma patients are treated according to these clinical practice guidelines. This evidence also provides a rationale for the need to identify and track asthma control.^{14,15}

Clinical Evidence

Inhaled Corticosteroids: Adults (>18 Years)

In an NIH/NHLBI-sponsored pilot study,¹⁷ Szeffler et al. compared the relative beneficial and systemic effects of 2 different ICSs in a dose-response relationship in a 24-week, parallel, open-label, multicenter trial in patients with mild-to-moderate persistent asthma using serial dosing (low to moderate to high) of ICSs. Thirty adult subjects were randomized to receive either beclomethasone dipropionate (BDP) in a metered-dose inhaler (MDI) with a spacer (OptiChamber, Respironics), or fluticasone propionate (FP) MDI with a spacer for 24 weeks. The goal was to determine which ICS dose provided the most beneficial response without introducing risk. There were 15 patients randomized to each treatment group. Doses were selected to result in comparable overnight plasma cortisol concentration suppression. The serial dosing for BDP-MDI was 168, 672, and 1,344 mcg/day using the Vancril chlorofluorocarbon (CFC) 84-mcg/actuation (Schering). The serial dosing for FP-MDI was 88, 352, and 704 mcg/day using the Flovent CFC 44-mcg/actuation (GlaxoSmithKline). Each study dose was administered for 6 weeks. To assess maximal response, FP dry-powder inhaler (DPI, Flovent Diskhaler) 2,000 mcg/day was then administered to all patients for 21 days. Inflammatory markers and airway function were measured at baseline (before treatment initiation), after each of the 3 ICS-MDI study doses was administered for 6 weeks, and, finally, after week 3 of the FP-DPI dosing. Tests included spirometry, methacholine challenge, asthma control assessment, exhaled nitrous oxide (eNO, which is a noninvasive marker for airway inflammation), exercise testing, and induced sputum values. Overnight plasma cortisol levels were measured at these same times, except they were not measured after week 3 of the FP-DPI dosing. The primary outcome variable for assessing comparative effectiveness was FEV₁. The secondary outcomes were methacholine PC₂₀, (a provocative concentration of methacholine that reduces the FEV₁ by 20% from baseline; this test is used to determine airway reactivity²), exercise-induced fall in FEV₁, eNO, and sputum eosinophils.

There were no significant differences between the 2 study groups at baseline. Overnight plasma cortisol was suppressed in a dose-dependent manner. The FEV₁ maximally increased (n = 13), and the near-maximal methacholine PC₂₀ change (n = 7) occurred at the medium dose (672 mcg) for BDP-MDI. The FEV₁ maximally increased (n = 12), and the near-maximal methacholine PC₂₀ change (n = 7) occurred at the low dose (88 mcg) for FP-MDI. In neither of the treatment groups did the FEV₁ or the maximum PC₂₀ increase following the 2,000-mcg/day dosing of FP-DPI. In the exercise challenge, BDP-MDI (n = 9) maximal inhibition of the absolute fall in FEV₁ and of the area-under-the-curve (AUC) from baseline also occurred following medium-strength dosing. The number of FP-MDI-treated patients completing the exercise challenge was too small to assess. However, the data identified maximum inhibition of the absolute fall in FEV₁ (n = 6) and of the AUC decline (n = 5) occurring at the high dose and only slightly

higher than with medium dosing of FP-MDI. Sputum eosinophils were maximally reduced following high dosing with BDP-MDI ($n = 5$) and following medium dosing with FP-MDI ($n = 6$). Comparison of this effect was difficult due to baseline differences in sputum eosinophils, which tended to be higher for BDP-MDI. Patient variability in FEV₁ response can be seen in Table 2 and Figure 3.

A variable response to ICSs was observed in this study but could not be attributed to poor medication adherence, as this was closely monitored. Good patient response was also associated with a high eNO level (median, 17.6 vs. 11.1 part per billion), higher median maximal bronchodilator reversibility (25.2% vs. 8.8%), and a lower median FEV₁/FVC (forced vital capacity) ratio (0.63 vs. 0.73) before treatment, than with poor-response patients. Excellent improvement in PC₂₀ versus poor improvement was found to be associated with high sputum eosinophil levels (3.4% vs. 0.1%) and older age at onset of asthma (20-29 years vs. <10 years).

This study showed significant variability in patient response to ICSs. Most patients with moderate persistent asthma gleaned response from low-to-medium doses of ICSs. High-dose therapy with ICSs did not improve efficacy, but it did result in an increase in systemic effects, particularly suppression of overnight cortisol production. About one third of patients had a poor response to treatment as measured by methacholine PC₂₀ and FEV₁. The authors note that a larger patient population needs to be studied in order to identify a more identifiable dose-response relationship in efficacy measures of ICSs. Additionally, further studies are needed to characterize and identify so-called “poor responders” so that alternative treatment strategies can be identified.

Inhaled Corticosteroids, Leukotriene Modifiers: Adults (>15 Years)

In a similar but larger study, Malmstrom et al. compared the clinical benefit of either an ICS (beclomethasone) or an oral leukotriene receptor antagonist (LTRA, montelukast) in patients aged 15 to 85 years with chronic mild-to-moderate asthma and an FEV₁ 50% to 85% of predicted value.¹⁸ This was a 12-week, multicenter, international, randomized, double-blind, double-dummy, placebo-controlled, parallel-group study. These patients were nonsmokers, had asthma for at least 1 year before entry in the study, had an average beta-agonist use of at least 1 puff daily, had a daytime asthma score of at least 64 (of a possible 336), and had an increase of at least 15% in absolute FEV₁ after inhaled beta-agonist use on at least 2 of 3 visits during period 1 of the study. The study consisted of a 2-week, single-blind, placebo run-in period (period 1) followed by a 12-week, double-blind treatment period (period 2) and a 3-week, double-blind placebo washout period (period 3). Of 2,253 patients who were screened, 895 eligible patients were randomized to 1 of 3 treatment groups in a ratio of 3:2:2, to receive (1) montelukast 10 mg once daily in the evening; (2) inhaled BDP, 200 mcg twice daily; or (3) placebo. To assess

FIGURE 3 Variability in FEV₁ Response for the 3 Study Doses of Beclomethasone MDI and Fluticasone MDI, Followed by Doses of Fluticasone Propionate Diskus¹⁶

BDP=beclomethasone dipropionate; DPI=dry-powder inhaler; FEV₁=forced expiratory volume in 1 second; FP=fluticasone propionate; MDI=metered-dose inhaler.

withdrawal from therapy, during period 3, a subset of patients originally receiving active treatment ($n = 40$) were switched to placebo in a blinded fashion. The patients originally assigned to receive placebo continued to receive it. Placebo and montelukast 10 mg tablets were identical, as were BDP (100 mcg/puff) and placebo inhalers. The short-acting beta-agonist, albuterol, 100 mcg/puff, was allowed if needed. If asthma worsened and required additional treatment, oral corticosteroids were administered according to protocol. If 2 worsening asthma episodes occurred, patients were discontinued from the study. The primary endpoints were daytime asthma symptom score and FEV₁. Secondary endpoints were PEF rates in the morning and evening, as-needed beta-agonist use, nocturnal awakenings, asthma-specific quality of life (QOL), and worsening asthma episodes.

Spirometry training and assessment were done according to the American Thoracic Society guidelines. Spirometry was completed at baseline (before the start of the study) and at each visit after inhaled beta-agonist therapy, theophylline therapy, or antihistamine therapy had been withheld for at least 6, 24, or 48 hours, respectively. Answers to specific questions on a diary card regarding daily asthma symptoms, nocturnal awakenings, and morning and evening PEF rates were specifically queried, as was daily use of as-needed salmeterol. Three assessments of PEF rates were requested in the morning and evening before study medication dosing, and the best of the 3 measurements was recorded. Other endpoints were evaluated and included (1) peripheral blood eosinophil counts, (2) global patient and physician evaluation scores (7-point scale: 6 means “very much worse” and 0 means “very much better”), and (3) evaluation of asthma QOL. Asthma outcome endpoints that were evaluated included (1) asthma attacks (worsening defined as requiring oral corticosteroids, a physician’s office visit, an ED visit, or a hospitalization);

FIGURE 4 Comparison of Montelukast and Beclomethasone in Patients with Chronic Asthma¹⁷

FEV₁ = forced expiratory volume in 1 second.

(2) percentage of days with exacerbations of asthma; and (3) percentage of asthma-control days (ACDs). Patient compliance was evaluated. For each efficacy endpoint, only patients who had baseline measurements and at least 1 measurement after randomization were included.

The percentage of patients who discontinued the study during periods 2 and 3 was significantly greater in the placebo group (18.3%) than in the BDP group (9.6%) or the montelukast group (10.6%). Reasons for discontinuation included protocol deviations, withdrawal of consent, pregnancy, and loss to follow-up. Additionally, 11 placebo-treated patients (4%), 8 montelukast-treated patients (2%), and 5 BDP-treated patients (2%) discontinued treatment due to clinical adverse effects; a worsening of their asthma was the most common of these effects (8 placebo-treated patients, 4 montelukast-treated patients, and 1 BDP-treated patient). Other adverse effects associated with treatment discontinuation included menstrual disorder, eyelid edema, and pharyngeal discomfort (placebo group); epididymitis, urticaria, vasovagal reaction, and trauma (montelukast group); and rash, dyspepsia, neoplasm, and asthenia or fatigue (BDP group). Mean compliance ($\pm$ SD) with inhaled study medication in period 2 was $89.6\% \pm 36.3\%$ in the placebo group, $87.6\% \pm 30.9\%$ in the montelukast group, and $88.6\% \pm 34.8\%$ in the BDP group. Mean compliance with oral medication in this same period was $99.6\% \pm 2.6\%$ in the placebo group, $99.8\% \pm 0.9\%$ in the montelukast group, and $99.3\% \pm 3.4\%$ in the BDP group.

Both montelukast and BDP treatment, compared with placebo, significantly improved FEV₁, daytime symptom scores, and the secondary endpoints ($P < 0.001$). The average percentage change from baseline in FEV₁ was 13.1%, 7.4%, and 0.7% for BDP, montelukast, and placebo, respectively ($P < 0.001$ for each active treatment vs. placebo; $P < 0.010$ for BDP vs. montelukast). The daily symptom score average change from baseline was -0.62 for

BDP, -0.41 for montelukast, and -0.17 for placebo ($P < 0.001$ for each active treatment vs. placebo; $P < 0.010$ for BDP vs. montelukast). The same statistical significance was noted when comparing PEF rates, QOL, reduced nocturnal awakenings, reduced asthma attacks, increased number of ACDs, and decreased number of asthma exacerbation days. Overall, BDP had a larger mean clinical benefit than montelukast. The differences between montelukast and BDP were 5.8% for FEV₁, -0.21 for daytime symptom scores, -0.67 for puffs/day of beta-agonist use, 15.3 L/min for morning PEF, 11.2 L/min for evening PEF, and -0.70 for nocturnal awakenings. However, montelukast had a faster onset of action and a greater initial response than BDP. Seven to 10 days after therapy initiation, the BDP effect bypassed that of montelukast. Physician global assessments were similar to the patient global assessments. Patients felt better after 12 weeks of treatment: 94.2% for BDP, 89.1% for montelukast, and 73.4% for placebo ($P < 0.001$ for each active treatment vs. placebo). Similar decreases in peripheral blood eosinophil counts ($P < 0.050$ vs. placebo) were also noted. Patients treated with placebo, montelukast, and BDP had asthma exacerbations on 26.1%, 15.2%, and 9.7% of days, respectively. The percentage of days with asthma exacerbations was decreased by 63% with BDP vs. placebo ($P < 0.050$), and 42% with montelukast vs. placebo ($P < 0.050$). The percentage of patients with at least 1 asthma attack during treatment was 27.3% for placebo, 15.6% for montelukast, and 10.1% for BDP. Discontinuation of both medications caused slow but definite decreases in effect. After drug discontinuation, patients showed no rebound worsening of asthma. Worsening asthma, headache, and upper respiratory tract infection (URI) were the most commonly reported adverse effects during treatment.

Medication doses used in this study mimic initial clinical dosing for asthmatic patients. In this study of mild-to-moderate asthmatics (treated with montelukast or inhaled BDP, some patients had little or no improvement (~30%), some patients got worse (~30%), and others had larger improvements (~40%). The distribution of treatment responses for FEV₁ can be seen in Figure 4. This study showed a similar distribution of response to that conducted by Szefer et al. These studies showed that by using currently available asthma therapies in clinically approved doses, some patients would have an adequate response while others would not, and it is difficult to predict nonresponders. Malmstrom et al. recommended that future asthma studies generate response distributions in different patient groups (e.g., different demographic groups, severity groups) to better understand how these populations respond to differing asthma therapies. Additionally, long-term effects of inhaled BDP and montelukast were unable to be identified due to the short course of treatment in this study. They did, however, show that both inhaled BDP and montelukast each protected patients against worsening of asthma episodes.

In addition, Israel et al. sought to determine whether an ICS compared with the LTRA, montelukast, would provide equivalent

effects determined by ACDs.¹⁹ This was a randomized, multicenter, double-blind, placebo-controlled, parallel-group study of asthmatics (n = 782) defined as having (1) an FEV₁ percent predicted value between 50% and 85% at rest, and at least a 15% increase in FEV₁ after albuterol administration; (2) a weekly average beta-agonist use of >2 puffs/day; and (3) an age span between 15 and 85 years. Additionally, patients had to have had at least a 1-year history of clinical asthma symptoms and be nonsmokers. Patients were randomized in a 3:3:1 ratio to receive either montelukast 10 mg daily, inhaled BDP 200 mcg twice daily, or placebo treatment for 6 weeks in a double-dummy manner. Week 1 was a prestudy screening period, followed by a 2-week, single-blind, placebo baseline period, followed by a 6-week treatment period. Clinic visits were scheduled at the end of the prestudy week 1, at the end of the week 2 single-blind, placebo baseline period, and every 3 weeks during double-blind therapy. The primary study objective was to compare the effects of the 2 active treatments, as evaluated by ACDs. Secondary endpoints included (1) change from baseline in FEV₁, (2) beta-agonist use, (3) asthma attacks, (4) asthma flares, (5) sustained asthma control, (6) rescue corticosteroid use, and (7) adverse effects. Daily diary cards with information regarding asthma attacks (yes or no), nighttime awakening, and albuterol use (number of puffs per day) were completed throughout the single- and double-blind treatment periods. All patients with a baseline evaluation and at least 1 postrandomization measurement were included in the analysis. There were 782 patients who entered the double-blind period: 332 received BDP-ICS, 339 received montelukast, and 111 received placebo. There were 752 patients who completed the 6-week, double-blind study.

The percentage of ACDs for the active treatment groups was almost identical (97.7% overlap in the distribution), with montelukast being at least equal to inhaled BDP. Both were greater than placebo when frequency of asthma attacks, asthma flare-ups, and rescue oral corticosteroid use were compared. Inhaled BDP had a greater effect than montelukast at improving FEV₁, and both active treatments were better than placebo at improving FEV₁. The difference between the 2 active treatments (montelukast vs. inhaled BDP) from placebo in the percentage of days of asthma control was significant (14.6% [P < 0.001] and 14.4% [P < 0.001], respectively). The effect of both active treatments on ACDs gradually increased with time. The effects of montelukast and inhaled BDP on airway function and asthma control can be seen in Figure 5. Both active treatments, compared with placebo, reduced average beta-agonist use (P < 0.001 for each comparison), and both did not differ from each other in this effect. The percentage of patients receiving active treatments with at least 1 episode of sustained asthma control was not significantly different (P = 0.324), and both active treatments were significantly superior to placebo for this endpoint. The mean percentages of sustained asthma control were 33.4% (montelukast), 32.1% (inhaled BDP), and 19.3% (placebo). The percentage of overlap between the active treatments for ACDs was 100% (95% confidence

FIGURE 5 Effects of Montelukast and Beclomethasone on Airway Function and Asthma Control¹⁸

Frequency distributions of days of asthma control (expressed as percentage of days during the 6-week treatment period) for montelukast and beclomethasone. The overlap between montelukast and beclomethasone in the patient response distributions for days of asthma control was 97.7% (95% confidence interval, 89.0-100.0).

FIGURE 6 Frequency Distributions of Change From Baseline FEV₁ for Beclomethasone and Montelukast¹⁸

FEV₁ = forced expiratory volume in 1 second.

interval, 91.2%-100%). The active treatments were generally well tolerated. The most frequently reported adverse effects in >5% of patients were URIs, headache, sinusitis, and asthma, and did not differ between the active treatment groups. Laboratory test abnormalities were similar among the treatment groups.

In this study, although the extent of clinical control achieved was not the primary purpose of the study, both montelukast and inhaled BDP treatment did not achieve a high level of asthma control.¹⁹ Neither treatment group differed in measures of clinical effectiveness, including reduction in beta-agonist use or the need for oral corticosteroids, and they did not differ in the extent of sustained asthma relief. It was therefore surprising that these authors identified that both montelukast and inhaled BDP differed in their effects on airway function, as can be seen in Figure 6.

FIGURE 7 Response Profiles to Fluticasone and Montelukast in Mild-to-Moderate Persistent Childhood Asthma¹⁹

As noted, the change from baseline in FEV₁ for montelukast and inhaled BDP showed the same distribution as the 2 studies previously reviewed.^{17,18} Additionally, since fixed dosing for a finite period of time is not ideal treatment in the clinical setting, other therapeutic interventions are required to achieve full asthma control. Higher doses of ICSs can be used, but as noted by Szeffler et al. in the previously reviewed study, a flat dose-response relationship can occur with inhaled BDP if used at doses higher than those used in this study.¹⁷ The authors note that this study demonstrates similar response rates for montelukast and inhaled BDP when evaluating broad and clinically relevant measures of asthma control in chronic asthmatics, which supports the use of montelukast as initial therapy as an alternative to ICSs. In patients who are not controlled with either montelukast or an ICS, the combination of both agents may provide additional control when symptoms are not controlled with either agent alone. Asthmatics treated with ICSs, compared with leukotriene modifiers, might yield effects on FEV₁ that are disproportionate to clinical effects achieved. Therefore, when evaluating treatment response, practitioners may need to place greater importance on clinical indices than on measurements of airway quality.

This distribution of asthma response has been observed in the pediatric population as well. Zeiger et al. studied the intraindividual and interindividual response profiles and predictors of response to ICSs and an LTRA in school-age children.²⁰ This was a multicenter, double-masked, 2-sequence, 16-week crossover trial in children aged 6 to 17 years with mild-to-moderate persistent asthma using only "as needed" bronchodilators. The patients (n = 144) were randomized to receive an ICS, fluticasone propionate (100 mcg/inhalation, twice daily) or montelukast (5 to 10 mg nightly, age dependent). A 5- to 10-day run-in period after enrollment characterized each patient's asthmatic features while off controller therapy. During each 8-week treatment period each patient received an active drug and a matching placebo for the alter-

native drug. The first 4 weeks of the second treatment period were felt to be an adequate washout period for the first drug, and the second 4 weeks of each treatment period were therefore used to compare outcomes between the 2 active treatments. Clinical, pulmonary, and inflammatory responses were evaluated.

Outcomes were evaluated from daily patient diaries. The principal secondary outcome, ACD, was defined as a day with no daytime or nighttime asthma symptoms, no rescue albuterol use for asthma symptoms, a PEF <80% of personal best, no asthma health care use, and no asthma-related absences from work or school. The PEF was evaluated upon awakening and before bedtime. The following outcomes were determined at randomization and each 4-week treatment evaluation as part of the Asthma Control Questionnaire (ACQ): symptoms, albuterol use, and FEV₁. The ACQ is scored on a 7-point scale (0 = good control, 6 = poor control). Additionally, eNO, FEV₁/FVC, and FEV₁ were determined, as was resistance of the respiratory system at 5 Hz (R5) and area of reactance (AX). These last 2 tests are potential indicators of small-airway function. To help characterize each patient's phenotype, some of the following procedures (but not all) were performed prior to randomization: asthma history, allergen skin tests, total blood eosinophil count, serum IgE measurement, spirometry, methacholine P20, and eNO measurement. Only patients who completed both treatment periods were included in the analyses.

Of the 144 patients initially randomized, only 127 (88.2%) completed both treatment periods. Improvements in most clinical outcomes (ACDs, ACQ, albuterol use), pulmonary responses (FEV₁/FVC, PEF variability, morning PEF, and measures of impedance), and inflammatory biomarkers (eNO) significantly improved more with ICSs than montelukast treatment. The eNO test was a predictor of ACDs ($P = 0.011$) and a response indicator in selecting the difference in ACD response between ICS and montelukast ($P = 0.003$). The ACDs both significantly increased for ICS (2.8 days/week) and montelukast (2.1 days/week), $P < 0.001$. The change in ACDs per week from baseline can be seen in Figure 7. In the ICS-treated patients, 59% improved ≥ 2 days/week compared with 47% for montelukast-treated patients, and 13% of ICS patients improved 1 to <2 days/week compared with 12% of montelukast-treated patients. When individual responses were compared, 29.3% of ICS-treated patients had ≥ 1 ACD per week during treatment compared with 12.2% of montelukast-treated patients. Compared with baseline scores, both treatments showed significant improvements in ACQ scores, but better control was achieved with ICSs ($P = 0.001$). Albuterol use decreased significantly with both treatments, but a greater decrease was observed with ICS treatment. The ICS therapy had significant improvements in prebronchodilator FEV₁/FVC, PEF variability, morning PEF, R5, and AX, in addition to a 6.8% FEV₁ mean improvement. Montelukast treatment led to significant improvements from baseline in morning PEF, and a 1.9% increase in FEV₁. Comparing prebronchodilator effects of

ICS and montelukast, the former had greater effects in FEV₁/FVC ($P < 0.001$), PEF variability ($P = 0.003$), and AX ($P = 0.001$). A greater decrease in eNO was noted following ICS treatment ($P = 0.003$), but both drugs decreased eNO. At the baseline measurement, higher eNO levels ($P = 0.036$), more positive aeroallergen skin test responses ($P = 0.008$), greater albuterol use ($P = 0.029$), and fewer ACDs predicted more ACDs following ICSs. During ICS treatment, eNO decreases were associated with positive clinical responses.

This study resulted in more positive clinical, pulmonary, and inflammatory responses in mild-to-moderate persistent asthma in children treated with ICSs compared with montelukast, supporting the first-line use of ICSs. As a predictor of patient response, eNO might help to identify individual children not receiving asthma controllers who would achieve a greater improvement in ACDs with an ICS compared with an LTRA. Like the previously evaluated studies, there was a similar proportion of patients with no change in ACDs from baseline following treatment with either an ICS or an LTRA.

Inhaled Corticosteroids, Nedocromil: Children (5-12 Years)

Finally, the Childhood Asthma Management Program (CAMP) Research Group of NHLBI conducted a study that evaluated 2 active treatments, or placebo, on the long-term treatment of mild-to-moderate asthma.²¹ Children ($n = 1,041$) aged 5 through 12 years were randomized to receive 200 mcg budesonide ($n = 311$), 8 mg nedocromil ($n = 312$), or placebo ($n = 418$) twice daily in a placebo-controlled manner. The objective of the study was to evaluate whether the long-term, continuous treatment (for 4-6 years) with either an ICS (budesonide) or an inhaled noncorticosteroid drug (nedocromil) produced an improvement in lung growth and whether it was safe as compared with only symptomatic treatment (e.g., albuterol and prednisone, if needed). All patients used albuterol for symptoms. The primary outcome was lung growth, assessed by the change in FEV₁ after bronchodilator administration, and the secondary outcomes were the degree of airway responsiveness, physical growth, psychological development, and morbidity.

Spirometry was performed twice yearly and a methacholine challenge was performed yearly. The children (or their parents or guardians) completed a daily diary card that recorded nighttime awakenings due to asthma, morning and evening peak flow measurements, use of study medication, use of albuterol for symptoms and for prevention of exercise-induced bronchospasm, prednisone use, school absences due to asthma, visits to a physician's office or hospital due to asthma, and severity of symptoms. Patient's height and weight were recorded at each follow-up visit; total bone mineral density of the spine from L1 to L4 and the Tanner stage of sexual development were assessed annually. Bone age (skeletal maturation) was assessed during the last 8 months of follow-up and used to estimate projected final height. Additionally, 4 neurocognitive tests were administered, 1 at baseline and then again 3 years later; 8 psychosocial questionnaires (including the Children's Depression Inventory) were

FIGURE 8 Comparison of Budesonide and Nedocromil in Asthmatic Children²⁰

FEV₁ = forced expiratory volume in 1 second; PC = methacholine provocative concentration.

completed at baseline and at each follow-up visit. Skin testing for a core of allergens was performed at baseline and 4 years later. Anterior and posterior eye lens images were obtained during the last 8 months of follow-up, to be observed for posterior subcapsular cataracts.

The 3 study groups were similar at baseline except there were more boys in the nedocromil group. The follow-up duration was also similar in all groups, with a mean of 4.3 years. There was no significant difference in the primary outcome or the change in FEV₁ after bronchodilator administration between the treatment groups and placebo. Compared with the placebo-treated patients, the budesonide-treated patients had a significantly smaller decline in the FEV₁/FVC before bronchodilator administration (0.2% vs. 1.8%). Budesonide-treated patients also had lower airway responsiveness to methacholine ($P < 0.001$ vs. placebo), fewer hospitalizations (43% lower rate compared with placebo, and 2.5 vs. 4.4/100 person-years), fewer urgent care visits (45% lower rate, 12 vs. 22/100 person-years; $P < 0.001$), a greater reduction in albuterol use for asthma symptoms, fewer prednisone courses (43% lower rate of use, $P < 0.001$), and a smaller percentage of days on which additional asthma medications were needed. The FEV₁ PC₂₀ response to methacholine in children treated with budesonide and nedocromil can be seen in Figure 8. Budesonide treatment improved the FEV₁ after bronchodilator administration by 103.2% of the predicted value to a mean of 106.8% within 2 months, but this value diminished to 103.8% by the end of the treatment period. Nedocromil-treated patients versus placebo-treated patients had significantly reduced urgent care visits (27% fewer visits, 16 vs. 22/100 person-years; $P = 0.020$, and 16% fewer prednisone courses ($P = 0.010$). The mean height increase that was mostly evident during the first year of treatment was 1.1 cm less in the budesonide group compared with the placebo group (22.7 vs. 23.8, $P = 0.005$). The height

FIGURE 9 A New Way to Predict the Response to Inhaled Corticosteroids in Asthma¹²⁰ **FIGURE 10** A New Way to Predict the Response to Inhaled Corticosteroids in Asthma II^{20,21}

Geometric mean value of PC₂₀ at various time points over the 4-year follow-up, stratified by treatment group assignment and H33Q genotype. The mean PC₂₀ of individuals on corticosteroids who also possessed a copy of the 33Q variant improved significantly by the end of the first year of the study and continued to improve substantially with time and corticosteroid usage. The mean PC₂₀ value at 4 years is within the range normally ascribed to individuals without the diagnosis of asthma.

PC = methacholine provocative concentration.

difference was similar between the placebo group and the nedocromil group. One nedocromil-treated patient died; she had been receiving supplemental treatment, including ICSs, for several months before her death. One placebo-treated patient required intubation for an asthma exacerbation.

Better asthma control was achieved in the budesonide treatment group as indicated by significantly fewer asthma symptoms ($P = 0.005$), less albuterol use ($P < 0.001$), and more episode-free days ($P = 0.010$). Changes in morning peak flow and the number of nighttime awakenings per month were similar in all groups. Compliance with treatment was similar between the budesonide group and the placebo group (73.7% vs. 76.2%, respectively), but was lower in the nedocromil group (70.2%). When comparisons

were made over the entire follow-up time, the budesonide group significantly differed from the placebo group in all respiratory (spirometric) measures ($P < 0.001$), whereas the nedocromil group did not significantly differ from the placebo group in any measure. Changes in growth velocity and bone density in the active treatment groups were similar to placebo at the end of the study. The only psychosocial measure that was different from placebo was a greater improvement in the total score of the Children's Depression Inventory in the budesonide group, indicating less depression compared with placebo (a decline of 3.2 vs. 2.2; $P = 0.010$). One child in the budesonide group was classified as having a questionable posterior subcapsular cataract.

This study found that neither treatment with nedocromil nor budesonide improved lung function, as measured by the percentage of the predicted value for FEV₁ after bronchodilator administration, which was unexpected. The widely accepted, clinically useful, highly reproducible and predictive measure of lung function, FEV₁, was used because it correlates well with disease progression, health care use, and asthma severity, while accurately describing the natural history of childhood asthma. As a result of normal lung growth, the FEV₁/FVC before bronchodilator administration declined over time in all 3 groups. There was also a lack of long-term improvement in the active treatment groups compared with placebo. The findings of improved airway responsiveness and health outcomes in this study favored budesonide but were not statistically significant, similar to results of short-term studies, including the one previously reviewed. After discontinuation of the study medication, no differences were observed among the 3 groups in lung function or growth from baseline to the final measurement, except for FEV₁/FVC before bronchodilator administration. Continuous daily treatment with inhaled budesonide led to better asthma control than symptomatic treatment or nedocromil treatment in mild-to-moderate asthmatic children, with side effects limited to small but transient growth velocity reductions. This study revealed the importance of long-term, controlled trials in the treatment of asthmatics.

The CAMP study followed patient response over an average of 4 to 5 years of therapy in ideal conditions with follow-up.²¹ On average, the ICS-treated patient's airway reactivity improved. Tantisira et al. mapped out the 4-year change in airway responsiveness of ICS-treated patients in the CAMP study, as measured by PC change, and found a normal distribution.²² Using the same CAMP study data, which looked "good," Tantisira et al. demonstrated that some patients have a good outcome, some a poor outcome, and some a worse response outcome, the same bell curve as previously described. This deception of averages can be seen in Figure 9.²² This response suggests that other factors aside from treatment type contributed to this response. Therefore, it becomes increasingly more important to track asthma control and response to therapy, because there are patients who either in the short term or the long term and, even under ideal conditions, do not adequately respond.

Tantisira et al. also evaluated and revealed that there was a certain gene involved in immune regulation.²² Of all the CAMP patients studied, 701 were successfully genotyped at H33Q and had data for the outcomes of interest. Only genotypic information from whites was analyzed, due to concerns over possible population stratification. Approximately 30% of these patients had been randomized to the ICS treatment group. Baseline gender, age, ethnic distributions, FEV₁, and PC₂₀ were similar between steroid and nedocromil groups. Use of ICSs over time was associated with significant improvements in FEV₁ and PC₂₀. There were no significant differences between children randomized to placebo or nedocromil. This study basically demonstrated that patients on ICSs with coding for the H33Q variant allele gene will have a dramatic therapeutic response (PC₂₀ reactivity) over 4 to 5 years, as depicted in Figure 10. If a patient has any other form of this gene (e.g., H33H), the response will be limited to zero, suggesting a biological basis for asthma treatment response, which needs to be considered along with social issues, compliance issues, and behavioral issues.

Summary of Clinical Trial Experience

1. Asthma control can be achieved and maintained by many patients.
2. Response to all classes of controller medication is variable, and approximately one third of patients will not respond to a particular class and may even worsen while on conventional pharmacotherapy.
3. Pharmacogenetics may help to predict asthma response patterns; however, until that time comes, it is not known who will respond to therapy and who will not, requiring close tracking of patient responses.
4. It is important to carefully track the response to therapy at each patient visit.
5. Currently, there is no clear, universal objective measure of asthma control because clinical control of asthma is a construct of both subjective and objective measures. A subjective measure is needed that could include measures for daytime symptoms, nighttime symptoms, albuterol use, ED visits, hospitalizations, and missed days from work or school. This thorough asthma assessment is needed at every visit. Lung function is included, but it is not enough.

Conclusions

Asthma should be appropriately diagnosed and treated according to current clinical practice guidelines.^{2,3} Most asthmatics achieve and maintain asthma control on conventional pharmacotherapy; however, response to controller medications is variable. Approximately one third of asthmatics will not respond to standard asthma treatment and may even worsen while on the therapy. Other options to manage these patients (e.g., those with severe persistent asthma despite conventional pharmacotherapy) may include subcutaneous omalizumab, subcutaneous allergen-

specific immunotherapy, oral theophylline, oral zileuton, and/or oral daily corticosteroids. In the future, pharmacogenetics may also help to predict asthma response patterns. Therefore, close tracking of patient responses is necessary to determine who will and who will not respond to standard therapies. Monitoring and reevaluating each patient's response and outcomes should occur continually with follow-up every 1-6 months, or once control occurs, depending on disease severity. Adherence to treatment (and avoidance of triggers) can be enhanced with education at regular intervals and phone call reminders of office visits. A health risk assessment should be performed and may be obtained in a technological manner, either as part of a disease management program or a stand-alone program in a provider's office.

A clear universal objective measure of asthma control is needed. A universal subjective measure is also needed. New asthma guidelines are expected in less than a year and will likely focus on asthma control. Monitoring, tracking, and evaluating an individual patient's asthma outcomes, at each and every patient visit, have been shown to improve asthma control; therefore, strategies to accomplish these goals must be identified and implemented to generate best practices at the point of care delivery.

DISCLOSURES

Funding for this research was provided by Genentech, Inc. and Novartis Pharmaceuticals Corporation. Author Craig Jones discloses that he receives grant/research support from Genentech and Merck, is a member of the speaker's bureau for Genentech, Novartis, Merck, sanofi-aventis, and Critical Therapeutics, and is a consultant for sanofi-aventis, Genentech, Novartis, Merck, and Critical Therapeutics. He has received an honorarium from PRIME for participation in this supplement. Author Linda Endicott discloses that she received an honorarium from PRIME for participation in this supplement. Author Michele B. Kaufman, is senior medical writer at PRIME; she discloses no other potential bias or conflicts of interest relating to this article. Jones served as principal author of the study. Study concept and design were contributed by Endicott and Kaufman. Data collection and interpretation and writing of the manuscript and its revision were the work of all authors.

REFERENCES

1. Kelly HM, Sorkness CA. Asthma. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 5th ed. New York, NY: McGraw-Hill; 2002:475-510.
2. Global Initiative for Asthma. Global strategy for asthma management and prevention. NHLBI/WHO workshop report, March 1993. Revised 2002. Bethesda, MD: National Institutes of Health, National Heart, Lung, and Blood Institute. Publication no.: 02-3659.
3. National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program. Expert panel report 2: guidelines for the diagnosis and management of asthma. Bethesda, MD: U.S. Department of Health and Human Services; 1997. NIH publication no.: 97-4051.
4. Surveillance for asthma—United States, 1980-1999. *MMWR Morb Mortal Wkly Rep*. 2002;51(SS01):1-13.
5. Health E-Stats page. National Center for Health Statistics Web site. Asthma prevalence, health care use and mortality, 2002. Available at: <http://www.cdc.gov/nchs/products/pubs/pubd/hestats/asthma/asthma.htm>. Accessed July 27, 2006.
6. Suissa S, Ernst P, Kezouh A. Regular use of inhaled corticosteroids and the long term prevention of hospitalization for asthma. *Thorax*. 2002;57(10):880-84.

7. Bender B, Milgrom H, Apter A. Adherence intervention research: what have we learned and what do we do next? *J Allergy Clin Immunol*. 2003;112(3):489-94.
8. Williams LK, Pladevall M, Xi H, et al. Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. *J Allergy Clin Immunol*. 2004;114(6):1288-93.
9. Smith DH, Malone DC, Lawson KA, Okamoto LJ, Battista C, Saunders WB. A national estimate of the economic costs of asthma. *Am J Respir Crit Care Med*. 1997;156(3 pt 2):787-93.
10. National Heart, Lung, and Blood Institute. Morbidity and mortality: May 2002 chart book on cardiovascular, lung, and blood diseases. Available at: http://www.nhlbi.nih.gov/resources/docs/02_chtbk.pdf. Accessed July 27, 2006.
11. National Heart, Lung, and Blood Institute. NHLBI study suggests symptom-driven therapy may be sufficient for some adults with mild persistent asthma. Available at: <http://www.nhlbi.nih.gov/new/press/05-04-13.htm>. Accessed November 24, 2006.
12. Jones CA, Clement LT, Hanley-Lopez J, et al. The Breathmobile Program: structure, implementation and evaluation of a large scale, urban, pediatric disease management program. *Dis Manag*. 2005;8(4):205-22.
13. National Asthma Education and Prevention Program (NAEPP): Expert panel report: guidelines for the diagnosis and management of asthma. Update on selected topics 2002. Available at: <http://www.nhlbi.nih.gov/guidelines/asthma/asthmafullrpt.pdf#search=%22naepp%202002%20guidelines%22>. Accessed September 15, 2006.
14. Jones CA, Morphey T, Clement LT, et al. A school-based case identification process for identifying inner city children with asthma: the Breathmobile Program. *Chest*. 2004;125(3):924-34.
15. Kachru R, Jones CA, Morphey T, et al. Clinical validation for the extension of the breathmobile case identification survey to identify children with uncontrolled asthma in an urban lower socioeconomic environment: the Breathmobile Program. *Ann Allergy Asthma Immunol*. In press.
16. Jones CA. From asthma severity to asthma control: application of new guidelines. Presented at: Case Management Society of America; June 2006; Dallas, TX.
17. Szeffler SJ, Martin RJ, King TS, et al. Significant variability in response to inhaled corticosteroids for persistent asthma. *J Allergy Clin Immunol*. 2002;109(3):410-18.
18. Malmstrom K, Rodriguez-Gomez G, Guerra J, et al., for the Montelukast/Beclomethasone Study Group. Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma: a randomized, controlled trial. *Ann Intern Med*. 1999;130(6):487-95.
19. Israel E, Chervinsky PS, Friedman B, et al. Effects of montelukast and beclomethasone on airway function asthma control. *J Allergy Clin Immunol*. 2002;110(6):847-54.
20. Zeiger RS, Szeffler SJ, Phillips BR, et al. Response profiles to fluticasone and montelukast in mild-to-moderate persistent childhood asthma. *J Allergy Clin Immunol*. 2006;117(1):45-52.
21. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med*. 2000;343(15):1054-63.
22. Tantisira KG, Hwang ES, Raby BA, et al. TBX21: a functional variant predicts improvement in asthma with the use of inhaled corticosteroids. *Proc Natl Acad Sci USA*. 2004;101(52):18099-19001.

From Asthma Severity to Asthma Control: Identification of New Guidelines

Professional Resources in Management Education, Inc. (PRIME) is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmaceutical education. A total of 0.20 CEUs (2.0 contact hours) will be awarded and a continuing education statement will be sent to pharmacists for successful completion of this continuing education program, which is defined as receiving a minimum score of 70% on the posttest and completion of the Program Evaluation form. ACPE Universal Program No. 255-000-06-013-H01. (Release date: December 1, 2006; Expiration date: December 31, 2007)

Professional Resources in Management Education, Inc. (PRIME) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. This activity has been planned and implemented in accordance with the Essential Areas and Policies of ACCME through sponsorship of PRIME. PRIME designates this educational activity for a maximum of 2.0 AMA PRA Category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent on the activity.

Continuing Education for this program is processed solely through the AMCP.org Online Learning Center site at www.amcp.org (Learning Center/Online CE). No mailed forms will be accepted.

The posttest worksheet (below) is provided to assist you in marking your answers prior to entering the online CE center for submission; these pages cannot be submitted for CE credits.

In order to receive CE credit for this program, you must complete the following forms online:

1. Posttest form for this program, "From Asthma Severity to Asthma Control: Identification of New Guidelines," on the AMCP.org Online Learning Center site—to receive CE credit, you must receive a score of at least 70%. You will have 2 opportunities to pass the posttest.
2. Program Evaluation form

Upon successful completion of this program, you will automatically receive your CE statement. Your CE credits will be automatically archived and tracked for you on the AMCP.org Online Learning Center site. All information is kept confidential.

Note: There will be a \$10 processing fee for nonmembers. (See payment instructions on site.)

Posttest Worksheet: From Asthma Severity to Control: Identification of New Guidelines

1. Asthma is a chronic inflammatory disorder characterized by all of the following *except*
 - a. nighttime coughing.
 - b. early-morning dyspnea.
 - c. chest tightness.
 - d. apnea.
2. Managing asthma involves the following concepts:
 - a. Routine monitoring of symptoms and lung function
 - b. Control and/or avoidance of asthma triggers
 - c. Patient education
 - d. All of the above
3. The gold standard for the diagnosis of asthma is the methacholine challenge.
 - a. True
 - b. False
4. All of the following are critical in establishing a clear diagnosis of asthma *except*
 - a. exclusion of alternative diagnoses.
 - b. measurement of airflow limitation.
 - c. demonstration of the reversibility of airflow obstruction.
 - d. careful family history.

5. For a patient with moderate to severe asthma on guideline-recommended therapies who is continuing to experience asthma exacerbations, which of the following is the most appropriate therapeutic option?
 - a. Empiric trial of antibiotics
 - b. Pulmonary rehabilitation
 - c. Anti-IgE therapies
 - d. Hospital admission for further evaluation
6. All of the following are components of direct asthma costs *except*
 - a. expenditures resulting from physician visits.
 - b. expenditures resulting from prescription drugs.
 - c. expenditures resulting from lost work days.
 - d. expenditures resulting from hospitalization.
7. Which of the following is *not* a recognized asthma trigger?
 - a. Animal dander
 - b. Mycoplasma pneumoniae infection
 - c. Gastroesophageal reflux
 - d. Strong emotional expressions
8. Which of the following is *not* a component of effective asthma management according to the current NAEPP asthma guidelines?
 - a. Objective assessment of asthma severity
 - b. Partnership between patient, family, and health care providers
 - c. Removal of economic barriers to care through patient assistance programs
 - d. Avoiding or eliminating asthma triggers
9. Which of the following categories of drugs is the most effective therapy for long-term asthma control?
 - a. Leukotriene modifiers
 - b. Long-acting β_2 -agonists
 - c. Short-acting β_2 -agonists
 - d. Inhaled corticosteroids
10. Which of the following therapies is an alternative to inhaled corticosteroids as monotherapy for long-term asthma control according to NAEPP?
 - a. Ipratropium bromide
 - b. Omalizumab
 - c. Montelukast
 - d. Salmeterol
11. Which of the following are goals of long-term management of asthma, according to GINA?
 - a. Minimal or no requirement for "as needed" or short-acting β_2 -agonists
 - b. Absence of necessity for ICU care
 - c. Circadian variation of PEF of <40% throughout the day
 - d. 50% decrease in asthma exacerbations
12. Patients should receive routine asthma care from their primary care physician and should only be seen by their asthma specialist when they are experiencing an exacerbation.
 - a. True
 - b. False
13. Which of the following hormonal measures is typically assessed in research studies involving inhaled corticosteroids?
 - a. Thyrotropin-stimulating hormone levels
 - b. Androstenedione levels
 - c. Plasma cortisol levels
 - d. Urinary vanillylmandelic acid excretion
14. Which of the following can be used to predict asthma response patterns?
 - a. Ethnicity
 - b. Age at onset of asthma symptoms
 - c. Pharmacogenetics
 - d. Initial response to bronchodilator therapy
15. Which of the following is *not* a currently accepted standard severity classification for asthma patients?
 - a. Mild intermittent
 - b. Moderate persistent
 - c. Severe intermittent
 - d. Moderate persistent

Evaluation Questions (not scored)

1. Which of the following changes do you believe your organization could successfully implement, with or without national guidelines changes, to improve management for your patients/members with asthma?
 - a. Eliminate the distinction between the moderate and severe categories of asthma, as this only increases the complexity of disease management
 - b. Standardize medication management guidelines for patient groups (moderate and severe asthma) for generalists
 - c. Initiate a collaborative pharmacist-case manager model that will improve strategies for patient adherence
 - d. Review the asthma clinical practice guidelines in my organization and determine if they are current; if not, update them
2. Which of the following interventions can most readily be implemented in your patient/member population to achieve reduction in overall asthma burden?
 - a. Control of infections
 - b. Use of omalizumab
 - c. Use of theophylline
 - d. Avoidance of allergens
3. Which approach could pharmacy case managers in your organization initiate to improve asthma treatment and management outcomes?
 - a. Include the cost of comorbidities in the organization's treatment costs in order to better ascertain the impact of asthma and thereby raise awareness
 - b. Initiate patient follow-up-calls after any event/exacerbation to provide information on the newest treatment guidelines
 - c. Provide treating physicians with information on strategies for asthma control
 - d. Place reminder calls to patients to conduct well-visits with their practitioners.
4. What is your first choice of learning method for CME?
 - a. Local dinner meeting
 - b. Symposium at national meeting
 - c. Online program
 - d. Webconference
 - e. Printed material or CD-ROM
 - f. Lunch program at work
5. What is your second choice of learning method for CME?
 - a. Local dinner meeting
 - b. Symposium at national meeting
 - c. Online program
 - d. Webconference
 - e. Printed material or CD-ROM

To complete this activity, go to www.amcp.org (Learning Center/Online CE), where you will access the posttest and evaluation form.

JMCP

JOURNAL OF MANAGED CARE PHARMACY®

Supplement