DAVID M. LANG, MD*
Head, Allergy and Clinical Immunology Section, Department of Pulmonary, Allergy, and Critical Care Medicine, Cleveland Clinic

The controversy over long-acting beta agonists: Examining the evidence

ABSTRACT

In the Salmeterol Multicenter Asthma Research Trial (SMART), patients receiving the long-acting beta agonist salmeterol—particularly African Americans—had a statistically significantly higher risk of fatal or potentially fatal asthma episodes. As a result, medications that contain salmeterol (Serevent, Advair) or formoterol (Foradil) carry a "black box warning." However, the benefits of these drugs continue to outweigh the risks, if they are used appropriately.

KEY POINTS

Whether the greater risk in African Americans reflects genetic predisposition, risk associated with long-acting beta agonist monotherapy, or health maintenance behaviors cannot be determined definitively at this time.

Inhaled corticosteroid monotherapy is recommended for patients with mild persistent asthma. Alternatives include monotherapy with an antileukotriene, a cromone such as inhaled cromolyn (Intal) or nedocromil (Tilade), or theophylline.

Salmeterol or formoterol should not be used as monotherapy, but rather added to inhaled corticosteroid therapy for patients with moderate or severe persistent asthma.

Inform patients about the risks and benefits of long-acting beta agonists, and document the discussion in the medical record.

Patients with asthma require regular ongoing care with periodic reexamination and follow-up.

CONCERNS THAT THREE WIDELY prescribed asthma medications are associated with an increased risk of asthma-related death led to a recommendation by the US Food and Drug Administration (FDA) on July 13, 2005, that salmeterol (Serevent), formoterol (Foradil), and the combination agent containing fluticasone propionate and salmeterol (Advair) remain on the market in the United States, but that each carry a "black box" warning.[1]

On November 18, 2005, the FDA followed this action with a public health advisory concerning long-acting beta agonists. On March 2, 2006, it approved new safety labeling for salmeterol and the fluticasone-salmeterol combination. Such labeling also applies to the recently approved budesonide-formoterol combination.

These decisions were based primarily on data from the Salmeterol Multicenter Asthma Research trial (SMART), in which patients—particularly African Americans—who received salmeterol had a statistically significant higher risk of fatal or potentially fatal asthma episodes.[2]

These actions come in a period of heightened public concern about adverse effects of drugs and the notion that some drugs do more harm than good.[3] This concern has been fueled in part by the recent imbroglio over selective cyclooxygenase 2 inhibitors.[4] In this climate, greater scrutiny of possible risks asso-

*Dr. Lang has disclosed that he has received honoraria, consulting fees, or other benefits for teaching, speaking, consulting, or conducting research for the AstraZeneca, Centocor, Critical Therapeutics, Genentech, Novartis, GlaxoSmithKline, MedPointe, Merck, Sanofi-Aventis, and Schering-Plough/Key corporations.

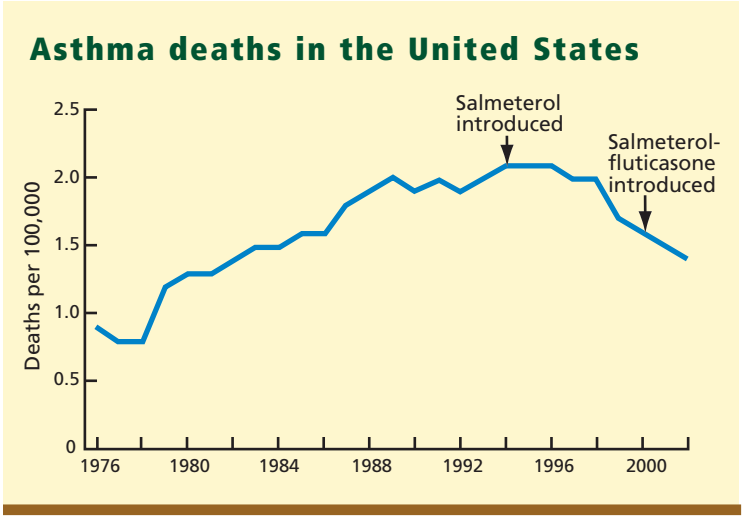

FIGURE 1

DATA FROM THE NATIONAL CENTER FOR HEALTH STATISTICS.

ciated with drug treatment can be expected.

Another element of the present situation is revealed by a Google search for any of the above three drugs combined with the term "asthma": each generates a link to a "death injury" or "side effects injury" lawyer.

This paper reviews recent trends in asthma deaths in the United States, presents the issues considered by the FDA in reaching its decision, critically examines the evidence, and offers recommendations for clinicians in managing asthma patients who are already taking or may require long-acting beta agonists.

Asthma deaths plateaued in the 1990s and have declined since 1999

ASTHMA DEATH TRENDS

In recent decades, asthma has become more prevalent, more severe, and more deadly. Between 4,000 and 4,500 people have died from asthma annually in recent years in the United States; in 2003, there were 4,099 US cases with asthma designated as the primary cause of death. This is unacceptable for a condition for which there is effective management.

Concern about beta agonists was first raised in the 1960s, when asthma death rates increased alarmingly in England, Wales, Scotland, Ireland, New Zealand, Australia, and Norway—but not in the United States or Canada.[5] This trend could not be attributed to spurious factors such as changes in diagnostic classification or death certification. It was not associated closely with a rise in asthma prevalence, but rather with an increase in case fatality. The trend was associated with use of a high-dose aerosol beta agonist, isoprenaline forte, which contained a concentration of isoprenaline several times greater than that in the standard isoprenaline inhaler used in other countries where a rise in asthma death rates was not observed.[6,7]

In the 1970s and early 1980s, a second epidemic of asthma deaths occurred in New Zealand, and again the trend was associated most closely with an increase in case fatality. The epidemiologic evidence implicated the use of inhaled fenoterol, a more potent beta agonist promoted for more severe asthma, as a major influence,[8] although this interpretation has been questioned.[9] Contributory roles for psychologic comorbidity, patterns of health care access and utilization, and socioeconomic factors have also been proposed.[9,10] When fenoterol was withdrawn from the New Zealand market, rates of asthma hospitalizations and deaths declined.[8]

In contrast, asthma death rates rose more gradually during the 1970s and 1980s in many countries (including the United States) that did not experience the 1960s epidemic. As asthma deaths increased, so did rates of hospitalization and emergency department visits.[11] It is tempting to attribute the rise in asthma deaths to the undeniable increase in asthma prevalence that also occurred.[12–14] However, studies using similar methodology indicate no remarkable disparity in prevalence of asthma in children in New Zealand, Australia, and Canada, despite hospitalization and death rates from asthma that are several times higher.[15–17]

Asthma mortality rates in the United States are highest in African Americans living in poorer areas of large cities.[11,18,19] Race, ethnicity, and poverty appear to contribute independently to this greater risk.[20]

In the United States, the asthma death rate rose to a plateau in the mid-1990s, and since 1999 has decreased (FIGURE 1).[21] It has also decreased in New Zealand,[6] Australia,[22] England and Wales,[23] and Israel.[24]

As shown in FIGURE 1, the asthma mortality rate in the United States in 1997 and 1998,

2.0 per 100,000, was lower than in 1994–1996, ie, 2.1 per 100,000. In 1999, a transition occurred from the ninth version of the International Classification of Diseases (ICD-9), in which asthma carried the code 493, to ICD-10, in which asthma is coded J45 and J46. For this reason, the decline to 1.7 per 100,000 observed in 1999 was initially questioned as spurious; however, further declines in 2000, 2001, and 2002 indicate that annual rates of asthma deaths in the United States in the initial years of the 21st century are declining,[25] and that the trend is real.

In countries where asthma death rates have stopped increasing, prescriptions for inhaled corticosteroids have increased,[5,21–24] implying that more frequent use of inhaled corticosteroids by patients with potentially fatal asthma accounts for this new trend. This explanation has been supported by a number of studies.[26,27] However, the results of SMART[2] have refocused attention on beta agonists and the possibility that regular use of long-acting beta agonists plays a role in some fatal and near-fatal asthma episodes.

EVIDENCE THAT LONG-ACTING BETA AGONISTS ARE BENEFICIAL

In clinical trials,[28–33] patients who received long-acting beta agonists in combination with inhaled corticosteroids had fewer symptoms (including nocturnal awakening), improved lung function, better health-related quality of life, less use of "rescue" medications, and lower rates of exacerbations and severe exacerbations than did patients who received inhaled corticosteroid monotherapy at the same or higher doses.[28–33]

Walters et al,[34] in a Cochrane review, analyzed 85 randomized controlled trials that lasted at least 2 weeks and that compared long-acting beta agonists with placebo in chronic asthma. Of the 85 studies, 56 had parallel group designs and 29 had crossover designs. Salmeterol was used in 60 studies and formoterol in 25. The treatment period was 2 to 4 weeks in 32 studies and 12 to 52 weeks in 53 studies. Inhaled corticosteroids were used concurrently in 34 studies, 21 studies did not permit their use, and 35 permitted either inhaled corticosteroids or the cromones nedocromil (Tilade) or cromolyn (Intal). Long-acting beta agonists had statistically significant advantages compared with placebo in morning peak expiratory flow rate, evening peak expiratory flow rate, asthma symptoms, use of rescue medication, and quality of life. The risk of asthma exacerbation was significantly lower in adults using long-acting beta agonists in combination with inhaled corticosteroids.

Several other meta-analyses also found significantly lower exacerbation rates with the combination of an inhaled corticosteroid and a long-acting beta agonist compared with inhaled corticosteroid monotherapy.[35–37] A prospective economic analysis found combination therapy to be more cost-effective than inhaled corticosteroid monotherapy in higher doses in managing moderate-to-severe persistent asthma.[38] Neither cohort studies[39–41] nor case-control studies[42–44] have found evidence linking long-acting beta agonist exposure to a risk of fatal or near-fatal asthma.

Combination therapy in moderate persistent asthma

In the Oxis and Pulmicort Turbuhaler in the Management of Asthma (**OPTIMA**) trial,[30] 1,272 patients with moderate persistent asthma took the inhaled corticosteroid budesonide (Pulmicort) in a low dose (100 μg twice a day) for 4 weeks to demonstrate that this did not control their asthma optimally—by definition, they had moderate persistent asthma. They then were randomized to one of four treatment groups: budesonide monotherapy at either 100 or 200 μg twice a day or the combination of budesonide 100 or 200 μg twice a day plus formoterol 4.5 μg twice a day.

Asthma death rates are highest in African Americans living in poor areas of large cities

A statistically significant benefit was observed in patients randomized to the combination of inhaled corticosteroid and long-acting beta agonist. Moreover, those taking a lower dose of budesonide (100 μg twice a day) combined with formoterol had superior outcomes (including a lower rate of severe exacerbations, and a higher morning peak expiratory flow rate) compared with those randomized to a doubling of the inhaled corticosteroid dose, ie, budesonide 200 μg twice a day (**FIGURE 2**).

The number needed to treat with low-dose

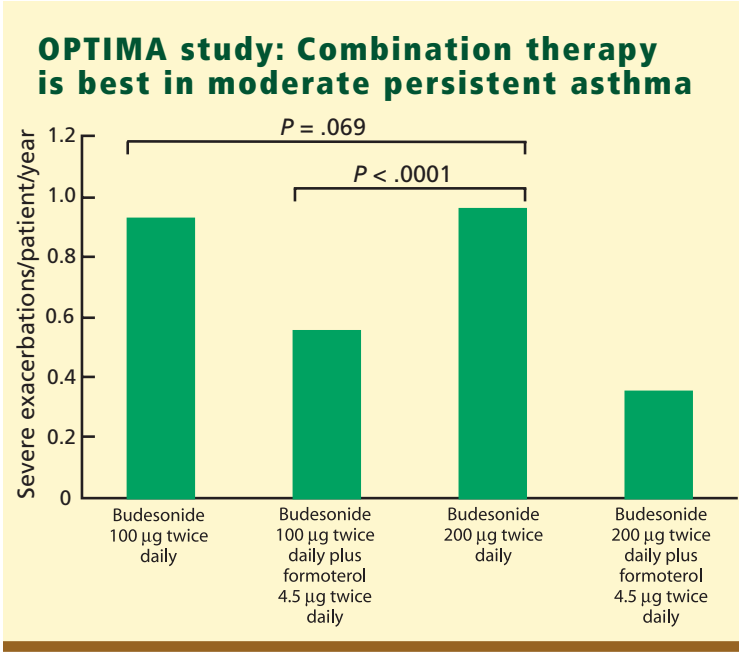

FIGURE 2. Rates of the primary outcome in the Oxis and Pulmicort Turbuhaler in the Management of Asthma (OPTIMA) trial in the subgroup with moderate persistent asthma.

DATA FROM O'BYRNE PM, BARNES PJ, RODRIGUEZ-ROISIN, ET AL. LOW DOSE INHALED BUDESONIDE AND FORMOTEROL IN MILD PERSISTENT ASTHMA: THE OPTIMA RANDOMIZED TRIAL. AM J RESPIR CRIT CARE MED 2001; 164:1392–1397.

Number needed to treat with combined therapy vs corticosteroid monotherapy to prevent 1 exacerbation in 1 year in moderate asthma: 5.2

budesonide plus formoterol compared with low-dose budesonide monotherapy to prevent one exacerbation over 1 year was 5.2; compared with high-dose budesonide monotherapy it was 7.6. In other words, 5.2 (or 7.6) asthma patients would need to be treated with a low-dose inhaled corticosteroid combined with a long-acting beta agonist, instead of low-dose (or higher dose) inhaled corticosteroid monotherapy, to prevent one severe exacerbation over 1 year. These calculations support the contention that these statistically significant differences are clinically meaningful.

On the basis of such evidence, the most recent guidelines from the National Asthma Education and Prevention Program (NAEPP) recommend low-dose inhaled corticosteroids combined with long-acting beta agonists as the preferred treatment for patients with moderate persistent asthma.[45]

Combination therapy in severe persistent asthma

Combination therapy is also superior to corticosteroid monotherapy at higher doses for patients with severe persistent asthma.

Jenkins et al[46] found the combination of fluticasone propionate (Flovent) 250 µg plus salmeterol 50 µg twice a day was superior to budesonide 800 µg twice a day. Other studies had similar results.[28,29,33]

The NAEPP guidelines also recommend inhaled corticosteroids in combination with long-acting beta agonists as the preferred treatment option for severe persistent asthma.[45]

Inhaled corticosteroid monotherapy for mild persistent asthma

In a separate arm of the OPTIMA trial,[30] 698 patients with mild persistent asthma were randomized to receive placebo, low-dose inhaled corticosteroid monotherapy (budesonide 100 µg twice a day), or the combination of budesonide 100 µg twice a day and formoterol 4.5 µg twice a day. Both active-treatment groups had significantly lower exacerbation rates over 12 months compared with the placebo group (FIGURE 3), with no significant difference between the treatments.

Based on such evidence, the most recent update of the NAEPP guidelines recommends low-dose inhaled corticosteroid monotherapy for mild persistent asthma[45]; there is no established benefit in adding a long-acting beta agonist to a low-dose inhaled steroid for treatment of mild persistent asthma.

EVIDENCE IMPLYING RISK WITH LONG-ACTING BETA AGONISTS

Serevent Nationwide Surveillance trial

After salmeterol was approved in the United Kingdom, the Serevent Nationwide Surveillance (SNS) trial[47] enrolled 25,180 asthma patients, who were randomized in a two-to-one ratio to receive either salmeterol 50 µg twice a day or albuterol (Proventil) 200 µg four times a day added to their current asthma therapy for 16 weeks. More than two thirds (69%) of the patients took inhaled corticosteroids concurrently.

Twelve of the 16,787 patients in the salmeterol group died of asthma or other respiratory causes, compared with 2 of 8,393 patients in the albuterol group; the difference was not statistically significant (relative risk [RR] = 3.0, P = .105).

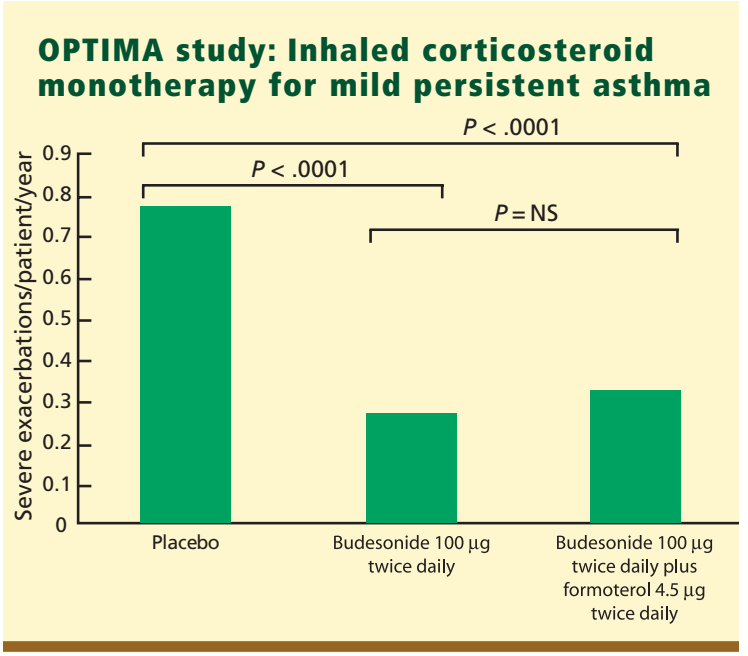

FIGURE 3. Primary outcome data for the OPTIMA study subgroup with mild persistent asthma.

DATA FROM O'BYRNE PM, BARNES PJ, RODRIGUEZ-ROISIN, ET AL. LOW DOSE INHALED BUDESONIDE AND FORMOTEROL IN MILD PERSISTENT ASTHMA. THE OPTIMA RANDOMIZED TRIAL. AM J RESPIR CRIT CARE MED 2001; 164:1392–1397.

SMART patients were seen only once, at study entry

In interpreting this finding, one should note that more patients in the albuterol group withdrew from the study for asthma-related reasons (3.8% vs 2.9%, RR = 0.77*P* = .0002). This is important, as patients who may have had more severe disease and would have been at higher risk of untoward outcomes were removed from the albuterol arm of the study at a proportionally greater rate.

SMART

In view of the concerns raised by the SNS trial, SMART[2] was designed and carried out in the United States as an observational study with sufficient power (with a projected 60,000 patients) to determine whether regular use of long-acting beta agonists increases the risk of potentially fatal asthmatic events. SMART was launched in 1996. Patients were randomized in a double-blind fashion to receive either salmeterol 42 µg twice a day or placebo in addition to their usual asthma therapy for 28 weeks.

The rate of the primary outcome (respiratory-related deaths or life-threatening experiences) was not significantly greater with salmeterol than with placebo (RR = 1.40, 95% confidence interval [CI] 0.91–2.14). However, in 2003, the trial was halted early because of difficulty enrolling the targeted number of 60,000 patients and because of an interim analysis that revealed significantly higher rates of secondary outcomes in African Americans.

Compared with the placebo group, the salmeterol group had significantly higher rates of:

- Respiratory-related deaths (RR 2.16, 95% CI 1.06–4.41)
- Asthma-related deaths (RR 4.37, 95% CI 1.25–15.34)
- Combined asthma-related deaths or life-threatening experiences (RR 1.71, 95% CI 1.01–2.89).

There were 13 asthma-related deaths and 37 combined asthma-related deaths or life-threatening experiences in the salmeterol group, compared with 3 and 22, respectively, in the placebo group. Of the 16 asthma deaths in the study, 13 (81%) occurred in the initial phase of SMART, when patients were recruited via print, radio, and television advertising; afterward, subjects were recruited directly by investigators.

These differences in outcomes occurred mainly in African Americans. African Americans who were not taking inhaled corticosteroids before randomization and who received salmeterol had higher rates of combined respiratory-related deaths or life-threatening experiences (RR 5.61, 95% CI 1.25–25.26, number needed to harm 162.8) and combined asthma-related deaths or life-threatening experiences (RR 10.46, 95% CI 1.34–81.58, number needed to harm 162.3).

Medication exposures were not tracked during the study, and allocation to inhaled corticosteroids combined with salmeterol was not randomized, so the effect of concomitant inhaled corticosteroid use cannot be determined from these data. No significant difference was noted between the placebo and salmeterol groups in asthma-related withdrawals.

Possible explanations for these findings

There are several potential explanations for the greater rate of untoward outcomes with salmeterol in SMART.

Genetic polymorphisms. An asthma subgroup homozygous for the Arg/Arg 16 geno-

type of the beta-2 adrenergic receptor may be predisposed to adverse events with regular use of long-acting beta agonists.

Genetic polymorphisms of the beta-2 adrenergic receptor influence the clinical response.[48] A number of studies have focused on amino acid 16, which may be either arginine (Arg) or glycine. With regular use of short-acting beta agonists, people with the Arg/Arg 16 genotype are predisposed to adverse effects,[48,49] including a reduction in the morning peak expiratory flow rate and an increased rate of exacerbations, which improve after regular use of short-acting beta agonists is stopped. Racial variation in the distribution of genetic polymorphisms, such as the gene encoding the beta-2 adrenergic receptor, places African Americans at greater risk for asthma exacerbation when they take short-acting beta agonists regularly.

It is unclear whether this risk also applies to long-acting beta agonists. Wechsler et al[50] reported that the morning peak expiratory flow rate declined in Arg/Arg 16 patients receiving salmeterol monotherapy, providing support for this contention. However, in an earlier study by Taylor et al[51] that used a three-way placebo-controlled crossover design, Arg/Arg 16 patients experienced declines in morning peak expiratory flow rate while randomized to regular short-acting beta agonists, but not with regular salmeterol. A significant increase in exacerbations was observed in the albuterol arm of the study, but not with regular use of salmeterol.

Both studies[50,51] were retrospective. Large prospective population studies are required to resolve this matter and are currently under way.

The notion that pharmacogenetics explains the findings observed in SMART rests on evidence that the Arg/Arg 16 genotype is more prevalent in African Americans than in whites, but the disparity does not appear to be sufficient to make this a tenable interpretation. Patients in SMART did not undergo genotyping, but we can make the following speculative estimates. Arg/Arg 16 is found in one sixth of whites and up to one fifth of African Americans.[49] Therefore, of the 4,685 African Americans enrolled in SMART, 937 would be expected to have the Arg/Arg 16 genotype; of the 18,642 whites, a corresponding 3,107 would have the Arg/Arg 16—about 3.3 times as many. One would expect significant morbidity and mortality among whites as well if this were the sole explanation for untoward outcomes from regular long-acting beta agonist use, yet this was not observed in SMART.

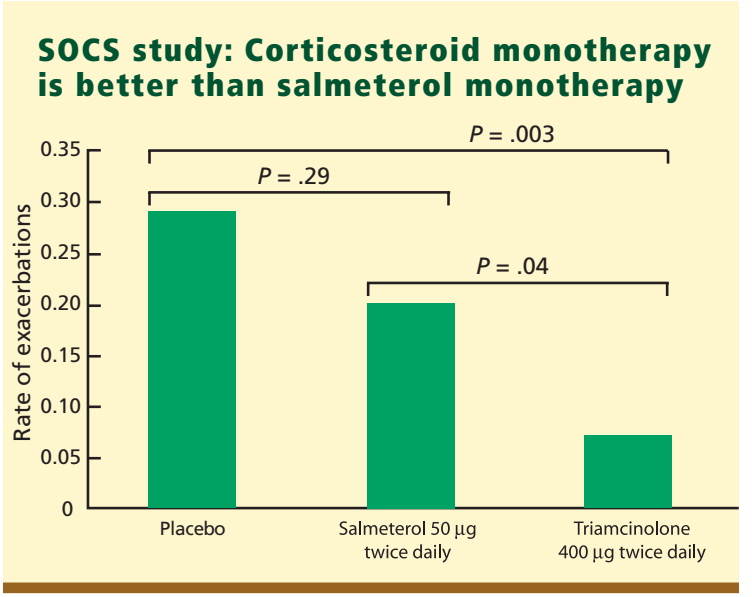

FIGURE 4. Rate of asthma exacerbation during 16 weeks of treatment.

DATA FROM LAZARUS S, BOUSHEY HA, FAHY JV, ET AL. LONG-ACTING β_2AGONIST MONOTHERAPY VS CONTINUED THERAPY WITH INHALED CORTICOSTEROIDS IN PATIENTS WITH PERSISTENT ASTHMA. A RANDOMIZED CONTROLLED TRIAL. JAMA 2001; 285:2583–2593.

Arg/Arg 16 is found in approximately 1 in 6 whites and 1 in 5 African Americans

'Masking' of inflammation. Long-acting beta agonist monotherapy may mask inflammation and thereby heighten the risk of fatal and near-fatal events.

The OPTIMA trial[30] was not designed to assess the role of long-acting beta agonist monotherapy.

The Salmeterol or Corticosteroids (SOCS) study did examine this issue.[52] In a 6-week open-label run-in phase, 422 patients received an inhaled corticosteroid in a low dose, ie, triamcinolone (Azmacort) 400 µg twice a day. After the run-in, 164 patients with well-controlled asthma entered the main study. Although NAEPP guidelines[53] recommend classifying asthma severity before starting treatment, as these 164 achieved good control on a low dose of inhaled corticosteroid, they may be regarded as fulfilling the criteria for mild persistent asthma.

These patients were randomized to

TABLE 1

receive placebo, triamcinolone continued at the same dose, or salmeterol 42 µg twice a day. At 16 weeks, the rate of exacerbations was significantly lower with triamcinolone than with either placebo ($P = .003$) or salmeterol ($P = .04$) (FIGURE 4). No statistically significant difference in the asthma exacerbation rate was noted between the placebo and salmeterol groups ($P = .29$).

Regular, ongoing care is essential for good asthma control

The number needed to treat for triamcinolone compared with placebo was 4.5, while the number needed to harm for salmeterol compared with triamcinolone was 7.7.

Interestingly, there was no statistically significant difference in morning peak expiratory flow rate, either within groups or among the placebo, salmeterol, or triamcinolone groups, although a trend for a decline in the peak expiratory flow rate was observed in the placebo group and a trend for an increase in this flow rate was observed in the salmeterol and triamcinolone groups. Asthma symptoms worsened with placebo but did not change significantly in the active-treatment groups. A statistically significant increase in sputum eosinophils was observed in the placebo ($P < .03$) and salmeterol ($P < .04$) groups, but not with triamcinolone.

These findings imply that monotherapy with a long-acting beta agonist may improve symptoms and lung function while masking unchecked airway inflammation. Such patients are vulnerable and are at higher risk of serious asthmatic exacerbations. These data concerning salmeterol monotherapy are important to bear in mind when combined with another element of SMART, described below.

Regular follow-up is essential

The design of SMART called for patients to be seen once at entry, when they received a 7-month supply of study drug. They were subsequently contacted every 4 weeks by telephone, without periodic objective assessments or measurements of lung function. Most of the asthma deaths were in patients recruited early in the study (1996–1998) via advertising, who may have been less likely to pursue regular care with a health care provider.

Of 26,355 subjects enrolled in SMART, 1 in 6 were African American. Previous studies[54,55] found African Americans to be less likely to receive continuous, ongoing medical care, the sine qua non for optimal control of asthma, and also more likely to obtain asthma care episodically in an emergency department. Compared with whites, young African Americans receiving Medicaid[56] and nonindigent African American adults participating in a managed care organization[57] were more likely to require emergency department management of asthma and were less likely to pursue regular outpatient care. Compared with the white patients in SMART,[2] African Americans had worse lung function, higher rates of health service utilization (emergency department visits and hospitalizations in the previous year), and lower rates of inhaled corticosteroid use at baseline (TABLE 1).

It is clear that African Americans in SMART were at greater risk of untoward outcomes even before they entered the study, based upon greater asthma severity and poorer asthma control. Their lower rate of inhaled corticosteroid use would also predispose more of them to the risk of long-acting beta agonist monotherapy noted above.

WHAT ABOUT FORMOTEROL?

In a meta-analysis, Mann et al[58] found that more patients who had received formoterol in a high dose (24 μg twice a day) had serious asthma exacerbations than did patients who received placebo, prompting concern.[59] However, a more recent study found no increase in serious asthma exacerbations with this higher dose of formoterol than with lower formoterol doses or placebo.[60] The 24-μg dose twice a day is not approved by the FDA. No studies similar to SNS or SMART have been performed with formoterol.

NEW META-ANALYSIS

A recent meta-analysis of randomized double-blind studies in which long-acting beta agonist therapy was compared with placebo found significantly higher rates of death from asthma and hospitalization for asthma exacerbations with salmeterol or formoterol than with placebo.[61] The odds ratio for hospitalization with long-acting beta agonists was 2.6 (95% CI 1.6–4.3) for both adults and children.

This report did not offer any new data but rather was an analysis of selected papers previously published or accessed at the FDA Web site.

Of 33,826 patients in the studies analyzed, 26,355 (78%) were in SMART.[2] In the mortality meta-analysis, SMART accounted for 80% of the effect size, and the explanation for the association of long-acting beta agonists with asthma mortality found in the meta-analysis can be considered in the context of the comments above regarding SMART and its methodological shortcomings.

However, a higher hospitalization rate was also observed in association with long-acting beta agonist therapy compared with placebo (odds ratio = 2.6, 95% CI 1.6–4.3), with lower rates for salmeterol and formoterol, as well as for adults and children. In view of this finding, it is important to note that these analyses did not include numerous studies[29–32] in which asthma care outcomes for the combination of lower-dose inhaled corticosteroids and long-acting beta agonists were compared with inhaled corticosteroids given at a higher dose. The overall use of concomitant inhaled corticosteroids in the studies analyzed in the meta-analyses was only 54% and 53%, respectively, in patients in the long-acting beta agonist and placebo groups.

No adjustment was made in the analyses for disease severity, comorbid conditions, or the race or ethnicity of subjects. In many of the studies, adherence was not consistently monitored.

The study that had the largest effect size (26%) for risk of hospitalization enrolled children ages 5 to 12, with a mean forced expiratory volume in 1 second (FEV_1) of 71% of predicted.[62] In this multinational, multicenter study, participants were randomized to receive placebo or formoterol 12 or 24 μg twice a day for 12 months. As noted above, the latter dose is not approved by the FDA. Approximately one third of these children were taking either cromolyn or nedocromil as their "controller." Among children with more severe asthma, as reflected in poor reversibility of FEV_1 and mean FEV_1 less than 70% of predicted, there were proportionally more withdrawals from the placebo group because of nonserious asthma flares. As in SNS,[47] those with more severe disease and at greater risk for untoward outcomes were removed from the placebo group at a proportionally greater rate.

SMART should not discourage us from prescribing long-acting beta agonists for moderate or severe asthma

It is unclear if the higher risk of asthma hospitalization in association with long-acting beta agonist exposure found in the meta-analysis[61] can be generalized to common clinical situations encountered by practitioners. Clinicians are typically faced with a choice of prescribing a long-acting beta agonist combined with an inhaled corticosteroid, or alternatives such as higher-dose inhaled corticosteroid monotherapy or an inhaled corticosteroid combined with another controller (eg, antileukotriene or theophylline), not long-acting beta agonist monotherapy.

Previous meta-analyses showed that the combination of an inhaled corticosteroid at a low dose plus a long-acting beta agonist is associated with superior outcomes compared with higher-dose inhaled corticosteroid monotherapy.[35–37] These data have led to the recommendation in the most recent update of the NAEPP for combination therapy with inhaled corticosteroids and long-acting beta agonists for patients with moderate persistent

NOTES FOR A PATIENT RECORD

Documentation for initiating or continuing long-acting beta agonists

Risks, benefits, and alternatives to treatment with a long-acting beta agonist were discussed and understood.

The patient was informed that the FDA recently issued a black box warning regarding use of long-acting beta agonists for management of asthma. This warning was based on results of SMART (*Chest* 2006; 129:15–26), which found a statistically significant increase in episodes of fatal and near-fatal asthma in patients randomized to salmeterol compared with placebo, primarily affecting African Americans. Whether this reflects a genetic predisposition, risk associated with long-acting beta agonist monotherapy, or health maintenance behaviors cannot be determined definitively at this time.

The patient was told that currently there is an honest difference of opinion regarding the role of long-acting beta agonists for asthma, and that based on interpretation of the evidence in the medical literature, it is my judgment that the potential for benefit with use of inhaled corticosteroids combined with long-acting beta agonists in his/her case exceeds the potential for risk.

The patient was told about alternatives to inhaled corticosteroids combined with long-acting beta agonists, including but not limited to higher-dose inhaled corticosteroids, or inhaled corticosteroids at lower dose in combination with another "controller" (antileukotrienes, theophylline, nedocromil, or cromolyn); however, compared with these alternatives, the evidence indicates that outcomes are superior with the combination of inhaled corticosteroids and long-acting beta agonists.

Also discussed were two important messages from SMART and previous studies, ie, that long-acting beta agonists should only be taken in combination with inhaled corticosteroids, and that regular follow-up is essential to achieve the goals of asthma management.

Expressing full understanding of these issues, the patient agreed to take/continue regular inhaled corticosteroids and long-acting beta agonists for asthma.

Physicians may wish to document their reasons for prescribing these drugs and their discussions with patients

asthma and severe persistent asthma (level A evidence).[45]

Salpeter et al[61] assert that the asthma death rate has increased in the United States in the past decade and state that "salmeterol may be responsible for approximately 4,000 of the 5,000 asthma-related deaths that occur in the United States each year." As illustrated in FIGURE 1, annual asthma death rates plateaued in the 1990s and have declined since 1999. Salmeterol entered the US market in 1994, while the salmeterol-fluticasone propionate combination was introduced in 2000. Readers are encouraged to carefully examine the line graph in FIGURE 1 and to decide for themselves whether there has been an upsurge or a decline in asthma death rates in the past decade and the likely impact of the introduction of salmeterol and the salmeterol-fluticasone combination on asthma mortality trends in the United States.

WHAT SHOULD WE TELL PATIENTS?

The magnitude of exposure to long-acting beta agonists is substantial. In July 2005, the *New York Times* reported that 17.2 million prescriptions had been dispensed for Advair in the previous 12 months[63]; this is an underestimate of long-acting beta agonist exposure, as it does not include Serevent and Foradil. Based on the level of exposure in the US population, even a minor risk of adverse effects with regular use of long-acting beta agonists would have considerable impact from a population standpoint. For this reason, additional studies are warranted to achieve a clearer understanding of the implications of the SMART data.

In light of the FDA actions, the decision to prescribe or continue to prescribe long-acting beta agonists should be based on a determination of risks and benefits made by each asthma patient in partnership with his or her physician.

So what should asthma care providers tell their patients regarding long-acting beta agonists, based on what we know now?

Asthma care providers may wish to document in their patients' medical records that long-acting beta agonist treatment is being started or continued, based on this being favorable from a risk-benefit standpoint (see NOTES FOR A PATIENT RECORD, on this page). We are required to adhere to the "reasonable patient standard," under which we must inform our

patients of the nature of their condition and its treatment, including alternative treatments, and no treatment. This is particularly important for medications that carry a black box warning.[1]

Mild persistent asthma

For patients with mild persistent asthma, evidence has not convincingly shown superior outcomes with combined inhaled corticosteroids and long-acting beta agonists compared with inhaled corticosteroid monotherapy. As these therapeutic options are equally efficacious, patients with mild persistent asthma should receive inhaled corticosteroid monotherapy. This evidence-based management recommendation is also mentioned in the black box warning issued by the FDA for the salmeterol-fluticasone combination, which encourages prescribing the combination for patients whose asthma is not adequately controlled "with other asthma-controller medications (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment" with two maintenance therapies (Advair package insert, GlaxoSmithKline, Research Triangle, NC).

As an alternative, monotherapy with an antileukotriene, a cromone (inhaled cromolyn or nedocromil), or theophylline may be considered. Long-acting beta agonist monotherapy is not appropriate.

In mild persistent asthma, corticosteroid monotherapy is as good as combined therapy

Moderate or severe persistent asthma

For patients with moderate or severe persistent asthma, evidence indicates that combination therapy with an inhaled corticosteroid plus a long-acting beta agonist is associated with superior outcomes compared with inhaled corticosteroids at the same or higher dose.[35–37,45]

Randomized, double-blind studies have shown this combination to be more effective than the combination of an inhaled corticosteroid and a leukotriene modifier for patients whose asthma is not optimally controlled on low-dose or moderate-dose inhaled corticosteroid monotherapy.[64,65] The combination of an inhaled corticosteroid and a leukotriene modifier was associated with equivalent asthma control compared with the combination of an inhaled corticosteroid and a long-acting beta agonist in a study that entailed a "noninferiority" analysis.[66]

A recent Cochrane review found that when asthma control is not achieved with low-dose or moderate-dose inhaled corticosteroid monotherapy, adding a long-acting beta agonist is superior to adding an antileukotriene drug for reducing exacerbations over time, improving lung function, and reducing symptoms and as-needed use of short-acting beta agonists.[67] Additional studies are needed to clarify the questions raised by SMART; however, current evidence for management of moderate or severe persistent asthma indicates that the benefits of combined inhaled corticosteroids and long-acting beta agonist therapy outweigh the risks.

An important point: the absolute magnitude of the increased risk of untoward outcomes with a long-acting beta agonist according to SMART was very small[2] and is exceeded by the likelihood of benefit that will accrue by adding these drugs to inhaled corticosteroids, as reflected by the number needed to treat and the number needed to harm calculations for the data presented above.

The SMART data should not discourage prescribing long-acting beta agonists to patients with moderate or severe persistent asthma, or from continuing them in patients who are doing well. Rather, they should reinforce the message that asthma is a condition for which periodic reexamination and follow-up is required for the goals of management to be achieved.

REFERENCES

1. **Aaronson D.** The "black box" warning and allergy drugs. J Allergy Clin Immunol 2006; 117:40–44.
2. **Nelson H, Weiss S, Bleecker E, Yancey S, Dorinsky P.** The Salmeterol Multicenter Asthma Research Trial. Chest 2006; 129:15–26.
3. **Critser G.** Generation Rx: How Prescription Drugs Are Altering American Lives, Minds, and Bodies. Boston MA, Houghton-Mifflin, 2005
4. **Topol E.** Arthritis medicines and cardiovascular events—"house of coxibs." JAMA 2005; 293:366–368.
5. **Beasley CRW, Pearce NE, Crane J.** Worldwide trends in asthma mortality during the twentieth century. In: Lenfant C, Sheffer A, editors. Fatal Asthma. Lung Biology in Health and Disease Series. New York: Marcel Dekker, 1998:13–30.
6. **Stolley PD, Schinnar R.** Association between asthma mortality and isoproterenol aerosols: a review. Prev Med 1978; 7:319–338.
7. **Crane J, Pearce N, Flatt A, et al.** Prescribed fenoterol and death from

asthma in New Zealand 1981–83: case-control study. Lancet 1989; 1:917–922.
8. **Beasley R, Pearce N, Crane J, Burgess C.** β-agonists: what is the evidence that their use increases the risk of asthma morbidity and mortality? J Allergy Clin Immunol 1999; 103:S18–30.
9. **McFadden ER, Warren EL.** Observations on asthma mortality. Ann Intern Med 1997; 127:142–147.
10. **Garrett J, Kolbe J, Richards G, Whitlock T, Rea H.** Major reduction in asthma morbidity and continued reduction in asthma mortality in New Zealand; what lessons have been learned? Thorax 1995; 50:303–311.
11. **Mannino DM, Homa DM, Pertkowski CA, et al.** Surveillance for asthma—United States, 1960–1995. MMWR 1998; 47:1–27.
12. **Peat JK, van den Berg RH, Green WF, Mellis CM, Leeder SR, Woolcock AJ.** Changing prevalence of asthma in Australian children. BMJ 1994; 308:1591–1596.
13. **Haahtela T, Lindholm H, Bjorksten F, Koskenvuo K, Laitinen LA.** Prevalence of asthma in Finnish young men. BMJ 1990; 301:266–268.
14. **Ninan TK, Russell G.** Respiratory symptoms and atopy in Aberdeen schoolchildren: evidence from two surveys 25 years apart. BMJ 1992; 304:873–875.
15. **Asher MI, Pattemore PK, Harrison AC, Mitchell EA, Rea HH, Stewart AW.** International comparison of the prevalence of bronchial hyperresponsiveness and asthma symptoms. Am Rev Respir Dis 1988; 138:524–529.
16. **Sears MR, Jones DT, Holdaway MD.** Prevalence of bronchial reactivity to inhaled methacholine in New Zealand children. Thorax 1986; 41:283–291.
17. **Fitzgerald JM, Sears MR, Roberts RS.** Symptoms of asthma and airway hyperresponsiveness to methacholine in a population of Canadian schoolchildren. Am Rev Respir Dis 1988; 138:285.
18. **Lang DM, Polansky M.** Patterns of asthma mortality in Philadelphia: 1969–1991. N Engl J Med 1994; 331:1542–1547.
19. **Carr W, Zeitel L, Weiss K.** Variations in asthma hospitalizations and deaths in New York City. Am J Public Health 1992; 82:59–65.
20. **Grant EN, Lyttle CS, Weiss KB.** The relation of socioeconomic factors and racial/ethnic differences in US asthma mortality. Am J Public Health 2000; 90:1923–1925.
21. **Lang DM.** 2001: The asthma odyssey. Ann Allergy Asthma Immunol 2001; 87:91–95.
22. **Wilson JW, Jenkins CR.** Asthma mortality: where is it going? Med J Aust 1996; 164:391–393.
23. **Campbell MJ, Cogman GR, Holgate ST, Johnston SL.** Age specific trends in asthma mortality in England and Wales, 1983–95: results of an observational study. Br Med J 1997; 314:1439–1441.
24. **Goldman M, Rachmiel M, Gendler I, Katz Y.** Decrease in asthma mortality rate in Israel from 1991–1995: is it related to increased use of inhaled corticosteroids? J Allergy Clin Immunol 2000; 105:71–74.
25. Data obtained from www.cdc.gov. Accessed October 16, 2006.
26. **Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B.** Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med 2000; 343:332–336.
27. **Ernst P, Spitzer WO, Suissa S, et al.** Risk of fatal and near-fatal asthma in relation to inhaled corticosteroid use. JAMA 1992; 268:3462–3464.
28. **O'Byrne P.** Pharmacologic interventions to reduce the risk of asthma exacerbations. Proc Am Thorac Soc 2004; 1:105–108.
29. **Pauwells RA, Lofdahl C, Postma DS, O'Byrne P, Barnes PJ, Ullman A.** Effect of inhaled formoterol and budesonide on exacerbations of asthma. N Engl J Med 1997; 337:1405–1411.
30. **O'Byrne P, Barnes P, Rodriguez-Roisin R, et al.** Low dose inhaled budesonide and formoterol in mild persistent asthma. The OPTIMA Randomized Trial. Am J Respir Crit Care Med 2001; 164:1392–1397.
31. **Greening AP, Ind PW, Northfield M, Shaw G.** Added salmeterol versus higher dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Lancet 1994; 344:219–224.
32. **Woolcock A, Lundback B, Ringdal N, Jacques LA.** Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. Am J Respir Crit Care Med 1996; 153:1481–1488.
33. **Bateman ED, Boushey HA, Bousquet J, et al.** Can guideline defined asthma control be achieved? The Gaining Optimal Asthma Control study. Am J Respir Crit Care Med 2004; 170:836–844.
34. **Walters EH, Walters JAE, Gibson MDP.** Long-acting beta2-agonists for stable chronic asthma. Cochrane Database Syst Rev 2003, Issue 3. Art. No. CD001385. DOI: 10.1002/14651858.CD001385.
35. **Shrewsbury S, Pyke S, Britton M.** Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). BMJ 2000; 320:1368–1373.
36. **Masoli M, Weatherall M, Holt S, Beasley R.** Moderate dose inhaled corticosteroids plus salmeterol versus higher doses of inhaled corticosteroid in symptomatic asthma. Thorax 2005; 60:730–734.
37. **Sin DD, Man J, Sharpe H, Gan WQ, Man SFP.** Pharmacological management to reduce exacerbations in adults with asthma. A systematic review and meta-analysis. JAMA 2004; 292:367–376.
38. **Lundback B, Jenkins C, Price MJ, Thwaites RM.** Cost-effectiveness of salmeterol/fluticasone propionate combination product 50/250 microgram twice daily and budesonide 800 microgram twice daily in the treatment of adults and adolescents with asthma. Respir Med 2000; 94:724–732.
39. **Mann RD, Kubota K, Pearce G, Wilton L.** Salmeterol: a study by prescription event monitoring in a UK cohort of 15,407 patients. J Clin Epidemiol 1996; 49:247–250.
40. **Lanes S, Lanza L, Wentworth C.** Risk of emergency care, hospitalization, and ICU stays for acute asthma among recipients of salmeterol. Am J Respir Crit Care Med 1998; 158:857–861.
41. **Meier CR, Jick H.** Drug use and pulmonary death rates in increasing symptomatic asthma patients in the UK. Thorax 1997; 52:612–617.
42. **Williams C, Crossland L, Finnerty J, et al.** A case control study of salmeterol and near fatal attacks of asthma. Thorax 1998; 53:7–13.
43. **Lanes S, Garcia Rodriguez LA, Herta C.** Respiratory medications and risk of asthma death. Thorax 2002; 57:683–686.
44. **Anderson HR, Ayres JG, Sturdy PM, et al.** Bronchodilator treatment and deaths from asthma: case control study. Br Med J 2005; 330:117–124.
45. Expert Panel Report: Guidelines for the diagnosis and management of asthma. Update on Selected Topics—2002. J Allergy Clin Immunol 2002; 110:S141–S207.
46. **Jenkins C, Woolcock AJ, Saarelainin P, Lundback B, James MH.** Salmeterol/fluticasone propionate combination therapy 50/250 micrograms twice daily is more effective than budesonide 800 micrograms twice daily in treating moderate to severe asthma. Respir Med 2000; 94:715–723.
47. **Castle W, Fuller R, Hall J, Palmer J.** Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. BMJ 1993; 306:1034–1037.
48. **Johnson M.** Molecular mechanisms of β2-adrenergic receptor function, response, and regulation. J Allergy Clin Immunol 2006; 117:18–24.
49. **Wechsler M, Israel E.** How pharmacogenetics will play a role in the management of asthma. Am J Respir Crit Care Med 2005; 172:12–18.
50. **Wechsler M, Lehman E, Lazarus S, et al.** β-adrenergic receptor polymorphisms and response to salmeterol. Am J Respir Crit Care Med 2006; 173:519–526.
51. **Taylor DR, Drazen JM, Herbison GP, Yandava CN, Hancox RJ, Town GI.** Asthma exacerbations during long term beta agonist use: influence of beta 2 adrenoceptor polymorphism. Thorax 2000; 55:762–767.
52. **Lazarus SC, Boushey HA, Fahy J, et al.** Long-acting β_2-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma. A randomized controlled trial. JAMA 2001; 285:2583–2593.
53. Expert Panel Report 2: Guidelines for the diagnosis and management of asthma. US Department of Health and Human Services. Publication No. 97-4052; 1997.
54. **Mak H, Johnston P, Abbey H, Talamo RC.** Prevalence of asthma and health service utilization of asthmatic children in an inner city. J Allergy Clin Immunol 1982; 70:367–372.

55. **Coultas DB, Gong H, Grad R, et al.** Respiratory diseases in minorities in the United States. Am J Respir Crit Care Med 1994; 149:S93–S131.
56. **Lozano P, Connell FA, Koepsell TD.** Use of health services by African-American children with asthma on Medicaid. JAMA 1995; 274:469–473.
57. **Zoratti EM, Havstad S, Rodriguez J, Robens-Paradise Y, Lafata JE, McCarthy BD.** Health care service use by African-Americans and Caucasians with asthma in a managed care setting. Am J Respir Crit Care Med 1998; 158:371–377.
58. **Mann M, Chowdhury B, Sullivan E, et al.** Serious asthma exacerbations in asthmatics treated with high-dose formoterol. Chest 2003; 124:70–74.
59. **Martinez FD.** Safety of long-acting beta-agonists—an urgent need to clear the air. N Engl J Med 2005; 353:2637–2639.
60. **Wolfe J, LaForce C, Friedman B, et al.** Formoterol 24 μg bid, and serious asthma exacerbations. Chest 2006; 129:27–38.
61. **Salpeter SR, Buckley NS, Ormiston TM, Salpeter EE.** Meta-analysis: effect of long-acting β-agonists on severe asthma exacerbations and asthma-related deaths. Ann Intern Med 2006; 144:904–912.
62. **Bensch G, Berger W, Blokhin GM, et al.** One-year efficacy and safety of inhaled formoterol dry powder in children with persistent asthma. Ann Allergy Asthma Immunol 2002; 89:180–190.
63. **Grady D.** Experts to consider withdrawal of asthma drugs. New York Times, 7/13/05.
64. **Nelson H, Busse W, Kerwin E, et al.** Fluticasone propionate/salmeterol combination provides more effective asthma control than low-dose inhaled corticosteroid plus montelukast. J Allergy Clin Immunol 2000; 106:1088–1095.
65. **Busse W, Nelson H, Wolfe J, Kalberg C, Yancey SW, Rickard KA.** Comparison of inhaled salmeterol and oral zafirlukast in patients with asthma. J Allergy Clin Immunol 1999; 103:1075–1080.
66. **Bjermer L, Bisgaard H, Bousquet J, et al.** Montelukast and fluticasone compared with salmeterol and fluticasone in protecting against asthma exacerbation in adults: one year, double blind, randomized, comparative trial. BMJ 2003; 327:891.
67. **Ram FS, Cates CJ, Ducharme FM.** Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. Cochrane Database Syst Rev 2005; CD003137.

ADDRESS: *David M. Lang, MD, Allergy and Clinical Immunology Section, Department of Pulmonary, Allergy, and Critical Care Medicine, C22, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail langd@ccf.org.*