

Effects of inhaled corticosteroids on the consequences of asthma

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Asthma is a chronic inflammatory disease of the airways involving a characteristic pattern of airway infiltration with lymphocytes, eosinophils, and mast cells, subepithelial deposition of collagen, and hypertrophy and hyperplasia of smooth muscle and of goblet cells and submucosal glands. The consequences of this chronic process include episodic or persistent symptoms, bronchial hyperreactivity, attacks of bronchoconstriction that may require emergency care or hospitalization and can lead to death, impairment in quality of life, and the development of irreversible airflow obstruction. Careful pathologic studies have shown that inhaled corticosteroid therapy can reverse or suppress airway inflammation, and prospective controlled clinical trials have proven that it can also improve symptoms, reduce bronchial hyperreactivity, and reduce the frequency and severity of attacks. It is also highly likely, although it is not yet proven, that inhaled corticosteroid therapy reduces the risk of asthma fatality and prevents or retards airway wall remodeling. These beneficial effects are easily shown in patients with moderate or severe asthma. Although inhaled corticosteroid therapy also benefits patients with mild asthma, it is less certain that the costs and risks of continuous therapy are justified. For these patients, the most important issues that remain to be resolved are the nature of the risk of development of permanent airflow obstruction and the effects of early, sustained treatment on the chances of sustained remission of asthma after all therapy has been stopped. (*J Allergy Clin Immunol* 1998;102:S5-S16.)

Key words: Asthma, inflammation, irreversible obstruction, chronic airflow obstruction, remodeling, glucocorticoids, inhalation drug administration, risk-benefit assessment, remission

Asthma is a common disease, affecting as much as 8% of the population of the United States, and its prevalence appears to be increasing throughout the developed and developing worlds.¹ The consequences of the disease—symptoms that interfere with function or impair sleep; attacks that require unscheduled visits to a physician, treatment in an emergency department, or admission to a hospital; impairment of full enjoyment of life; and increased risks of premature death and of chronic airflow obstruction—are shared disproportionately. Most asthma is mild,² and a small subgroup of patients, perhaps 20% of all patients with asthma, account for as much as 80%

Abbreviations used

BHR:	Bronchial hyperresponsiveness
ESW:	Calculated overall weighted means effects size
FEF ₂₅₋₇₅ :	Forced expiratory flow after 25% to 75% of vital capacity has been expelled
FP:	Fluticasone propionate
HRCT:	High-resolution computed tomography
ICS:	Inhaled corticosteroid(s)
NAEPP:	National Asthma Education and Prevention Program
PEF:	Peak expiratory flow
pMDI:	Pressurized metered-dose inhaler
RIM:	Relative improvement in mean

of the costs of care in any given year.³ It is not entirely clear, however, what kind of patients make up the “high cost” minority. Some of them come from an even smaller subgroup, probably fewer than 5%, who are easily identified as having chronic severe disease. For them, the daily burden of asthma may be enormous, and the risk of premature death may be great: hence, even treatment that carries risks of important side effects is worthwhile as long as it is effective. But others who experience events that require costly treatments (especially emergency department visits and hospitalization) or who might even die of asthma may not have previously had symptoms or events that would have identified them as being at greater risk. This is most dramatically illustrated by retrospective studies of asthma fatalities, in which as many as 30% of those who died were considered to have had mild asthma before their final, fatal attack.^{4,5}

The facts seem to indicate that the risks of severe morbidity or death (and therefore probably also of severe attacks requiring expensive treatment) are related to the severity of disease as assessed by symptoms, pulmonary function, and medication requirements but are not zero even for patients with mild asthma.⁶ Because patients with mild disease make up such a large proportion of the population with asthma, even a low rate of a morbid event in this group means that a substantial proportion of all experiencing that event in a given year will previously have had no more than mild asthma. For patients with mild disease, then, the equation for calculating the risk-benefit ratio of treatment is quite different. The consequences perceived by those affected may be so mild that long-term treatment can be justified only if it actually improves the patient’s life in ways the patient cares about, if it reduces important

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risks that may not be visible to the patient, and if the risk of toxicity is low.

Awareness of the importance of matching the intensity and thus the potential toxicity of treatment to the intensity of disease in individual patients has long informed national and international guidelines for treatment^{7,8} and must also inform reviews of the efficacy of inhaled corticosteroid (ICS) therapy in reducing the consequences of asthma. Inhaled corticosteroids were first introduced for the treatment of patients dependent on oral corticosteroid therapy. They were found to be effective in reducing or eliminating the need for systemic corticosteroids while maintaining symptom control and lung function.⁹⁻¹² The history of their use thereafter has been one of extending their indication to populations with milder disease. The 1991 edition of the National Asthma Education and Prevention Program (NAEPP) Guidelines for the Diagnosis and Management of Asthma, for example, recommended treatment with an ICS for patients with moderate disease, whereas the 1997 revision recommends such treatment for patients with mild persistent asthma.^{7,8,13,14}

The first purpose of this review is to assess the evidence that ICS treatment diminishes or prevents the consequences of asthma. Because much of this evidence was gathered from studies of patients with moderate or severe disease, this review's second purpose is to consider the issues involved in the recommendation that ICS therapy be given to the much larger segment of the population with asthma who have mild disease.

THE CONSEQUENCES OF ASTHMA

The idea that asthma is a chronic inflammatory disease of the airways has gained wide acceptance only within the past 15 years. The previous view of asthma, as an intermittent disease prone to unexplained spontaneous remissions and exacerbations, may account for the paucity of studies of its natural history at a time when several long-term studies of other diseases (eg, coronary artery disease and hypertension) were completed. This does not mean that the general nature of asthma's consequences, especially those that occur over the short term, are unknown. What are not well established are the determinants of risk of short-term consequences, the incidence and determinants of long-term outcome, and the relationship between the two.

Observations made in the course of clinical care and clinical research in patients with asthma have firmly established the disease's short-term consequences. The most obvious of these are recurrent chest tightness, shortness of breath, wheezing, and sputum production that interfere with activity and sleep.¹⁵ These symptoms may occur so frequently or be so severe as to significantly impair the ability to work¹⁶ and the quality of life.^{17,18} Some equally obvious consequences are experienced only by some patients with asthma; these include severe attacks requiring oral corticosteroid treatment, emergency care, or hospitalization. Finally, there is the possibility of death, a consequence known

even in antiquity.¹⁹ One sequela of asthma that is beginning to be recognized is the development of incapacitating irreversible airflow obstruction, even in the absence of exposure to tobacco smoke or fumes and dusts in the workplace.^{20,21}

In general, the risk of asthma's short-term consequences appears to be related to the severity of disease. For example, patients who have been hospitalized previously, who have airflow obstruction on baseline spirometry, and who have required treatment with systemic corticosteroids for previous attacks are significantly more likely to require hospitalization for treatment of asthma.²² A history of hospitalization in the past year or of sudden severe exacerbations indicates an increased risk of dying of asthma,²³ as does moderately severe but markedly reversible airflow obstruction and marked blood eosinophilia.²⁴ It seems likely, but it is by no means proven, that the risk of developing irreversible airflow obstruction is also related to the severity of asthma.²⁵

INTRODUCTION OF INHALED CORTICOSTEROIDS

Inhaled corticosteroids were first given to patients with severe asthma requiring treatment with an oral corticosteroid.⁹⁻¹² Subsequently, ICS therapy was used in patients for whom sympathomimetics and methylxanthines were ineffective.²⁶⁻²⁷ The results of clinical and pathologic studies of asthma in the 1980s gave impetus to the use of ICS in less severe asthma. The impelling clinical studies were those showing that in contrast to regular use of an inhaled β_2 -agonist, regular use of an ICS reduced bronchial hyperresponsiveness (BHR), an effect that was both dose- and time-dependent.^{28,29} The impelling pathologic studies were those revealing that biopsy specimens of the bronchial mucosa from patients with mild asthma showed the same, highly characteristic pattern of infiltration with lymphocytes, eosinophils, and mast cells that had previously been reported in post-mortem studies of asthma-related fatalities.³⁰⁻³² Airway inflammation was also demonstrated in allergic,³³ nonallergic,³⁴ aspirin-sensitive,³⁵ and occupational asthma.³⁶ This ongoing inflammation has been shown to be increased acutely by exposure to allergens or pollutants or by viral infection.³⁷⁻⁴⁰ All these findings have been interpreted as suggesting that prolonged application of an anti-inflammatory agent with the broad potency of a corticosteroid might act on a level fundamental to asthma's pathogenesis and would thus constitute a "disease-modifying" treatment. In contrast, regular use of inhaled β_2 -agonists is regarded as offering only symptomatic relief from transient bronchodilation.

Effects on symptoms, airway caliber, and bronchodilator use

Clinical studies of ICS agents indeed proved them to be efficacious in reducing asthma symptoms and in improving performance on tests of airway caliber and of bronchial reactivity, first with beclomethasone^{9,10,41,42} and subsequently with triamcinolone, flunisolide, budes-

onide, and fluticasone propionate (FP).⁴³⁻⁴⁹ The beneficial effects of ICS on symptoms and peak expiratory flow (PEF) have been confirmed by the analysis of collections of studies. In a systematic review of the published experience with ICS treatment of children with asthma, Calpin et al⁵⁰ (Table I) first identified all trials of ICS treatment of children with asthma published in English between January 1966 and December 1996 that were listed in the MEDLINE database. Twenty-four of the 93 studies met their criteria as randomized, double-blind, placebo-controlled studies and represented observations in 1087 children treated from 4 to 88 weeks. Because many of the studies did not report standard normal deviates or exact *P* values, a formal meta-analysis was not possible. Calpin et al⁵⁰ were able to calculate the "relative improvement in mean" (RIM), however, for the outcomes of greatest interest. Thirteen of the 15 studies that reported total symptom scores reported an improvement; the overall weighted RIM for this outcome was 50%, a halving of the severity of symptoms. Fourteen studies assessed as-needed use of inhaled β_2 -agonists, an indirect marker of symptom severity. The RIM for this outcome was a decrease of 38%. The 12 studies that assessed oral corticosteroid requirements showed a decrease of 68%. The RIM for PEF was 38 L/min, or 11% of the predicted value.

Effects on quality of life

It might be argued that some of the outcomes shown to be affected favorably such as PEF, FEV₁, and frequency of as-needed use of an inhaled β_2 -agonist are of greater interest to physicians and scientists than they are to patients. What matters to patients can be reasonably presumed to be their "quality of life," the sum of their abilities to function physically, socially, and emotionally in their day-to-day lives.⁵¹ Such quality-of-life measurements reflect the intangible costs of asthma and, in addition, can be a predictor of compliance.⁵² Patients who believe that a treatment is improving their quality of life are presumably more likely to comply with the treatment.

Specific instruments have been developed and validated to assess the quality of life in patients with asthma.^{17,18,53} These instruments have not been available long enough for many studies to complete an analysis of the effects of different asthma treatments on quality of life, but their use in a controlled study of 342 patients with moderately severe asthma has shown that regular use of FP improved patient assessments of their physical function, vitality, mental health, and general health perception.⁵⁴ At least some of these subjective improvements might have been functions of the improvement in the quality of sleep brought about by FP treatment. Noonan et al⁵⁵ have also shown that FP reduces oral prednisone requirements while improving asthma control and several quality-of-life variables.

Effects on costs

The first mission of medicine is to relieve suffering and to reverse or prevent the loss of life or function, but the

uninterrupted rise in health care expenditures has focused attention on the costs of care even in developed countries. Rutten et al⁵² have calculated the costs and benefits of the addition of an ICS to an inhaled β_2 -agonist in their study of 274 adults with moderately severe obstructive airway disease. Treatment with the combination of an ICS and an inhaled β_2 -agonist led to significant improvements in FEV₁, PC₂₀, and symptom-free days compared with treatment with an inhaled β_2 -agonist alone but also led to an increase in cost. This increase was estimated at \$572 per patient-year, \$375 more than treatment with an inhaled β_2 -agonist alone (\$156 per patient-year) and was partly offset by reductions in other health care costs in the group treated with combined therapy. However, the net difference was still \$201 per patient-year, a difference that enabled the calculation that the cost for each symptom-free day gained was about \$5.00. These calculations are highly sensitive to the disease severity of the group studied and the effectiveness of the ICS in preventing costly events, such as unscheduled clinic visits, emergency treatment, or hospitalization. An early question is therefore whether ICS agents are effective in the treatment of patients with asthma who contribute most to the costs of asthma, those with severe disease.

Effects on risks of hospitalization and death from asthma

The demonstrations of efficacy of ICS therapy in reducing symptoms and β_2 -agonist use and in improving performance on tests of airflow obstruction suggest that they should also be effective in preventing the most costly consequence of asthma, hospitalization, and the most dreaded, death. The risks of these consequences increase with the severity of asthma,^{22,56} and therefore the groups of patients most at risk have long been targeted for ICS treatment in asthma treatment guidelines.^{7,8} That an outcome should be confidently expected does not make it so, of course, and it is a further assumption that treatment with corticosteroids will prevent or reverse exacerbations induced by their most common cause, viral upper respiratory tract infection.^{57,58} Treatment with oral prednisone does not appear to alter the course or severity of cold symptoms in healthy adults,⁵⁹ but it does appear to reduce the likelihood of precipitation of an asthma exacerbation. Prompt initiation of oral corticosteroid treatment on the appearance of symptoms of a "cold" has been shown to reduce the frequency of hospitalization in children with asthma.⁶⁰

Two studies have taken epidemiologic approaches to analyzing the effects of ICS treatment on hospitalization rates. The first simply analyzed gross trends in prevalence, hospitalization rates, and medication use among Swedish children.⁶¹ Over a 15-year period, the prevalence of asthma doubled and the proportion of children with severe asthma remained constant, but the numbers of hospitalizations and of days spent in a hospital for treatment of asthma decreased. The investigators attribute this remarkable disparity to the rise in the use of ICS treatment over the same period. Bolstering this con-

TABLE I. Effectiveness of ICS on the clinical consequences of mild asthma in children

	Symptoms			Medication use		PEF	
	Total symptoms RIM (%)	Cough RIM (%)	Wheeze RIM (%)	β_2 -Agonist RIM (%)	Oral steroid RIM (%)	AM (L/min)	Predicted RIM (%)
Weighted mean	50	24	36	37	68	38	11
95% CI	(49,51)	(23,25)	(35,37)	(36,38)	(66,70)	(34.3,41.7)	(9.5,12.5)

Data from Calpin et al. *J Allergy Clin Immunol* 1997;100:455.
AM, Absolute improvement in mean PEF.

clusion is the fact that the hospitalization rate decreased least in children under the age of 5 years, to whom Swedish physicians seemed less inclined, relative to older children, to prescribe ICS treatment.⁶¹

The second, more persuasive epidemiologic study analyzed retrospectively a cohort of nearly 17,000 patients with asthma enrolled in a health maintenance organization in Massachusetts.⁶² All of the patients studied had a prescription payment provision in their health insurance. Thus all prescriptions for asthma medications were probably captured. β_2 -Agonists were the most prescribed medication (to 86% of patients with asthma); ICS therapy was next (prescribed to 40% of patients with asthma). The rate of hospitalization among those who filled more than 8 prescriptions for β_2 -agonists was 4-fold higher than in those who were not dispensed β_2 -agonists. By comparison, filling of prescriptions for an ICS reduced the risk of hospitalization by 50% overall and by 70% in those dispensed more than 8 β_2 -agonists per year. The increase in the relative risk of hospitalization with greater use of inhaled β_2 -agonists probably indicates that greater use of β_2 -agonists is a marker of increasing severity of disease. This makes the decrease in relative risk of hospitalization with greater use of ICS all the more impressive, for greater prescription of inhaled corticosteroids themselves is probably also a marker of disease severity.

Epidemiologic studies can only establish associations between a treatment and an outcome. A recent clinical study of classical design has shown that the association between use of an ICS and reduction in the risk of hospitalization is causal in nature.⁶³ This study, conducted as a multicenter, prospective, blinded study of 852 patients with mild-to-moderate asthma, compared exacerbation rates and symptom control in groups treated with 1 of 4 combinations of budesonide and formoterol, a long-acting β_2 -agonist. In this study a 4-fold increase in budesonide caused a sharp reduction in the rates of both mild and severe exacerbations; the combination of high-dose budesonide and formoterol reduced exacerbations even further. This study also showed that improvement in symptom control was greatest with the combination of the high-dose ICS and the long-acting β_2 -agonist.

Death is so rare an event in patients with asthma that conducting a classical, prospective study able to demonstrate an effect of ICS treatment on the mortality rate would require enrollment of so large a number of subjects as to be unfeasible. The weight of indirect evidence

nonetheless suggests strongly that ICS use does protect against this most dreaded outcome. Retrospective studies of patients who died of asthma have revealed several characteristics that indicate a heightened risk for death (eg, 1 or more hospitalizations or emergency department visits for treatment of asthma,^{23,64} highly variable peak flow,^{65,66} or severe BHR^{67,68}). All these features of asthma have been shown to be altered favorably by ICS treatment.

A follow-up study of 45 survivors of near-fatal asthma attacks has confirmed that aggressive use of ICS can dramatically improve some of these high-risk markers (eg, severe BHR).⁶⁹ Indirect though it may be, the evidence that ICS therapy reduces the risk of death from asthma is strong. Indeed, it is difficult to conceive of an ethical review board approving the use of a placebo in any future controlled trial of therapy in the small but important subgroup of patients with asthma who have survived 1 potentially fatal attack and who have such a high risk of dying of a subsequent attack.⁷⁰

Effects in severe asthma

The majority of studies of regular ICS therapy have examined patients with at least moderately severe asthma. The consistency of the finding of clinical benefit in so many studies establishes their clinical efficacy in this population. These findings also invite speculation that ICS must also be effective in patients with asthma with disease at the extremes of the spectrum (ie, the small proportion with severe disease on one end and the vast proportion with mild disease on the other).

The key questions about ICS treatment for these 2 groups are quite different. For those with severe disease, the question has to do with dose dependence: If a standard dose of an ICS reduces symptoms and improves results of tests of airway caliber, will larger doses reduce them even further? For those with mild disease, only occasionally bothered by symptoms of airflow obstruction that can usually be relieved promptly by treatment with an inhaled β_2 -agonist, the question is whether a reduction in this small signal can be demonstrated from regular treatment with any long-term-control medication. Furthermore, if such a benefit can be demonstrated, is it worth the cost of therapy and even a very low or minimal risk of toxicity?

It is only recently that clear evidence of dose dependency for the clinical benefits of ICS has been established. The first studies found no additional benefit from 2- and 4-fold increases in the dose of inhaled beclometha-

sone.^{9,10,71} Later, more promising studies of high-dose ICS therapy focused on asthma so severe as to require long-term oral corticosteroid treatment. Smith and Hodson^{72,73} found a great reduction in requirements for oral prednisone and in frequency of hospitalization when an inhaler delivering high-dose beclomethasone (250 µg/puff) was substituted for a standard inhaler (50 µg/puff). Although encouraging, their findings may have been overly optimistic because their study was uncontrolled.⁷² Indeed, in a later, well-controlled study of high-dose inhaled beclomethasone in patients with asthma receiving long-term oral corticosteroid treatment, 30% of the group treated with *placebo* were weaned from oral steroid therapy.⁷⁴ A significantly larger proportion of those treated with high-dose beclomethasone dipropionate were weaned from oral therapy, but the impressive response in the placebo group made the absence of a standard-dose treatment arm seem an important deficiency in the study. The importance of this flaw in the study's design was emphasized by the findings of Hummel et al,⁷⁵ who were unable to demonstrate that daily inhalation of 1500 µg of beclomethasone was any more effective than inhalation of 300 µg in weaning patients with severe asthma from oral prednisone.

Other early studies that attempted to establish a clear link between dose and response were inconsistent, with some studies showing a relationship,^{72,73,76,77} and others not.^{9,10,78} The success of a study of dose dependency for triamcinolone's effects on FEV₁⁷⁹ is attributable to its use of a very low dose, 200 µg per day (1 puff twice a day), rather than to clear evidence of additional improvement as the dose was increased up to 1600 µg/day. This "leveling-off" effect on FEV₁ may not be true for all clinically important endpoints.

Pedersen et al⁸⁰ examined another endpoint, exercise-induced bronchospasm, and showed that a low dose of inhaled budesonide administered to children with moderately severe asthma reduced symptoms and raised PEF as effectively as higher doses but that the low dose was significantly less effective in inhibiting exercise-induced bronchospasm. Other investigators have suggested that the agent selected and the population studied are also important determinants of whether a dose-response relationship can be shown. Using moderate-to-high doses of the highly potent ICS FP, Noonan et al⁵⁵ were able to show dose dependency for weaning severely ill patients with asthma from oral corticosteroids. By studying FP doses ranging from 100 to 800 µg daily in large numbers of patients with at least moderately severe asthma, an international study group was further able to show dose-dependent increases in PEF, FEV₁, and symptom-free days, as well as a dose-dependent reduction in frequency of asthma exacerbations.⁸¹ Another multicenter study, this one examining the effects of 168 µg and 336 µg of beclomethasone and of 88 µg and 220 µg of FP taken twice daily by 790 patients with asthma, showed dose dependency for the improvement in FEV₁ in those with moderate, as well as in those with severe, airflow obstruction; the higher dose of FP produced the greatest improvement.⁸²

Effects in mild asthma

The dramatic efficacy of ICS in altering the consequences of moderate and severe asthma led naturally to an interest in their efficacy for mild asthma. Mild asthma differs from severe asthma in the degree, but not in the nature, of the disturbances of markers of inflammation in the airways.⁸³ The severity of asthma has been correlated with several inflammatory indices such as epithelial denudation,⁸⁴ eosinophil number and activation,⁸⁵⁻⁸⁷ T-cell activation,³⁴ and cytokine expression⁸⁸; hence, one would expect long-term use of an anti-inflammatory agent, such as an ICS, to be effective. Inhaled corticosteroids have indeed been shown to reverse many of these indices of inflammation.⁸⁹⁻⁹¹

Demonstrating clinical efficacy in patients with mild asthma can be challenging, however, for in patients with only mild disturbances in function, the maximal possible change (ie, to normal function) is small. Detection of a small signal in a clinical trial requires enrollment of a large number of subjects. This is likely to be especially true for the endpoints patients most care about, such as symptoms and quality of life, as opposed to measurements of morning PEF or BHR to methacholine.

The findings of 2 well-designed, long-term studies in adults with mild asthma, one by Juniper et al⁹² in Canada and the other by Haahtela et al⁹³ in Finland, had such impact on clinical practice that they are worth reviewing in some detail. The study by Juniper et al⁹² differed from most previous studies of ICS in that it focused on patients with mild asthma, who were not at that time regarded as candidates for long-term ICS treatment. Thirty-two were treated for a full year with either placebo or budesonide, 400 µg/d (taken in 2 doses). Budesonide had significantly greater effects on symptom severity (as inferred from subject diary entries), on as-needed use of inhaled albuterol, on FEV₁, BHR to methacholine, and the frequency of exacerbations requiring an "open" course of treatment with inhaled budesonide or oral prednisone.⁹² The improvements in the various endpoints seemed to reach a plateau at 6 months; by the end of the year, the PC₂₀ to methacholine had improved dramatically in the budesonide group, rising into the normal range in 5 of the 16 subjects.

The study by Haahtela et al⁹³ compared the effects of 2 years' treatment with a high dose of inhaled budesonide (1200 µg/d) and with placebo in 103 adults with newly diagnosed asthma. Again, the patients treated with ICS did significantly better, as judged by the increase in morning PEF (32.8 vs 4.8 L/sec), in PC₁₅ for methacholine (+1.6 vs +0.5 doubling concentrations), symptom scores, and as-needed treatments with an inhaled β₂-agonist. The difference in the frequency of exacerbations requiring prednisone favored budesonide treatment, but the significance of this difference was not stated.

The difficulties in showing an effect on the severity of symptomatology in patients whose lives are only slightly affected by their symptoms was demonstrated by another study of regular treatment with a standard dose of inhaled budesonide (400 µg/d) in patients with newly diagnosed asthma.⁹⁴ The 75 adults who took part in this

randomized, placebo-controlled study had asthma diagnosed only in the preceding year, but they did not all have mild asthma (ie, they were described as having "mild-to-moderate asthma"). Their mean baseline value for FEV₁ was only slightly reduced (91% of predicted value), but some had baseline values as low as 63% of predicted value. Thus not all the subjects studied would be considered to have "mild" disease by the current NAEPP guidelines for the management of asthma.^{7,8} Even so, the significant improvements in both morning PEF and PC₂₀ (histamine) noted with budesonide treatment were not accompanied by significant reduction in asthma symptoms or in β_2 -agonist use. As the authors noted, a possible explanation for the incomplete response in the symptom scores was that the scores were generally low, and some patients did not have any symptoms at all during the run-in period.

Given the great volume of literature on ICS treatment of asthma, it is surprising that the number of well-designed, controlled studies of patients with *mild* asthma should be so few. In their review of 129 articles retrieved by a medical database search of English language literature dealing with asthma and ICS since 1976, Hatoum et al⁹⁵ found only 5 studies that met their inclusion criteria for rigor in trial design and for enrollment of patients with mild asthma only (defined as an exacerbation of cough and wheezing of no greater frequency than once or twice a week, few clinical symptoms between exacerbations, limited symptoms of nocturnal asthma, minimal evidence of airway obstruction on spirometry, and rapid response to bronchodilator therapy). The one outcome measure common to the studies was PEF, so only this measure was used in a meta-analysis of the pooled findings. The calculated overall weighted mean effects size (ESW) was 0.59 (CI, 0.32-0.84), indicating a medium, rather than a large effect, but the effect was consistent across the studies and was quite robust. Hatoum et al⁹⁵ concluded from their meta-analysis that ICS are beneficial in mild chronic asthma. They acknowledge that their calculations may have underestimated the magnitude of the effect because the control group in 2 of the studies they analyzed was treated with cromolyn rather than placebo. Regrettably, they do not comment on the effects of ICS treatment on other outcomes (eg, symptoms) that are of greater concern to patients than PEF values. Four of the studies they analyzed did provide data on symptom severity, however, and all showed that ICS treatment reduced symptoms significantly from the pretreatment, run-in period.⁹⁶⁻⁹⁹ Three studies showed reductions that were significantly greater with ICS than with cromoglycate.⁹⁷⁻⁹⁹ The fact that ICS agents are effective as a treatment for mild asthma does not, of course, necessarily mean that all patients with a diagnosis of asthma should use an ICS. As Drazen and Israel¹⁰⁰ commented in their editorial on an article by Haahtela et al (see ref.117), a major question is whether the benefit is worth the risk. In the current era, we must also ask whether it is worth the cost. In patients with mild asthma, symptoms only occasionally interfere with function and are promptly reversed by inhalation of a β_2 -ago-

nist. The risk of severe attacks requiring emergency treatment or hospitalization is very low. It is legitimate to ask whether the improvements in these modest burdens of disease are worth even the minimal risks of potentially serious toxicities and the modest cost associated with long-term use of a low dose of an ICS.

For ICS and mild asthma, the equation relating benefit to risk and to cost is sensitive to new evidence on potential toxicities, such as the impairment of growth in children¹⁰¹⁻¹⁰³ or the occurrence of glaucoma¹⁰⁴ and cataracts in adults¹⁰⁵ and to new evidence on potential benefits. Accumulating evidence of one potential benefit, slowing or preventing the development of irreversible airway narrowing, strongly shaped the recommendations of the 1997 version of the NAEPP asthma guidelines.^{7,8} Another potential benefit—that early, sustained use of ICS treatment would improve the chances of prolonged, sustained remission—seems less likely but has not been ruled out.

Effects on development of irreversible airflow obstruction

Emphasis on reversibility of airflow obstruction as a defining feature of asthma may have contributed to a delay in recognition of its potential for leading to irreversible airflow obstruction. For decades, asthma was considered a completely reversible obstructive airway disease, but many patients had evidence of some residual airway obstruction. This irreversible component is more prominent in patients with severe disease and even persists after an aggressive course of anti-inflammatory treatment. A detailed discussion of this feature of asthma's natural history is beyond the scope of this review (see article in this issue by Barbee and Murphy), but several studies of asthma in older adults gave rise to the idea that asthma can lead to irreversible airflow obstruction^{20,21,106}; several studies of the rate of decline in tests of airway caliber in large numbers of patients with asthma have given it credibility.¹⁰⁷⁻¹⁰⁹

The process responsible for the permanent narrowing of the airway lumen is a chronic, irreversible thickening of the walls of the airways described as "airway wall remodeling." Thickening of the airway wall has been demonstrated by pathologic studies and by radiographic studies with the use of high-resolution computed tomography.¹¹⁰ The pathologic changes responsible include infiltration of the airway wall by inflammatory cells, edema, hyperplasia of epithelial goblet cells and of mucus-secreting glands, subepithelial collagen deposition, subepithelial accumulation of myofibroblasts, and thickening of the medial smooth muscle layers.¹¹¹⁻¹¹³ These pathologic changes are presumed to result from repeated or chronic release of the cytokines, proteases, and other chemical mediators of inflammation.

Appreciation of the anti-inflammatory actions of corticosteroids invited speculation that their long-term use might prevent airway wall remodeling. This idea received support from studies showing reductions in basement membrane thickness after treatment with beclomethasone, 1000 μ g/d,¹¹⁴ or FP, 500 μ g/d.¹¹⁵

These advances in the understanding of asthma—recognition that asthma can lead to irreversible airflow obstruction and recognition that asthma is associated with apparently irreversible pathologic changes in the airway wall—laid the groundwork for attributing great importance to apparently persistent differences in FEV₁ in patients receiving long-term treatment with placebo or an ICS. Two large clinical studies, 1 in children and 1 in adults, have thus had great impact. First, Agertoft and Pedersen¹¹⁶ compared the annual changes in FEV₁ and in FEF₂₅₋₇₅ in 216 children with mild-to-moderate asthma treated with budesonide for 3 to 6 years with the changes in 62 similar children whose parents declined corticosteroid treatment. In the children not treated with budesonide, the annual decrease in FEV₁ was 1% to 3% of predicted value; in contrast, FEV₁ improved significantly, by 3.9% of predicted value per year, in the budesonide-treated group. Furthermore, the children who started ICS therapy later than 5 years after the onset of asthma achieved significantly lower FEV₁ values (as a percent of predicted value) than children who started the treatment within 2 years of disease onset.

Similar findings have come from studies of adults with asthma.^{93,117,118} The first report by Haahtela et al⁹³ of the beneficial effects of budesonide treatment on PEF, β_2 -agonist use, and BHR in adults with recently diagnosed asthma has already been described (see above). Budesonide also seemed to affect the rate of change in FEV₁ over the 2 years of treatment: it rose 0.13 L in the budesonide group and did not change in the group receiving terbutaline ($P < .05$). Expressed as a trend, FEV₁ fell significantly in the terbutaline group at a rate of 0.200 L per year.⁹³ A follow-up study examined the changes brought about by high-dose budesonide (1200 μ g/d) in 38 subjects who had previously been treated only with terbutaline.¹¹⁷ FEV₁ and BHR improved, but the improvements were only half as great as those seen in the subjects who began receiving budesonide at the outset of the study. This difference in the degree of response persisted. Even after 1 year of treatment, the improvements in FEV₁ and BHR were only half as great as those in patients to whom budesonide had been given for the 2 previous years.

A similar study of the improvements in FEV₁ and BHR in patients treated with ICS from disease outset, or with ICS for 6 months after 2.5 years of prior treatment with bronchodilators alone, likewise showed smaller improvements in patients for whom treatment with corticosteroids was delayed.¹¹⁹ The degree of improvement in BHR was significantly less in the delayed versus initial ICS treatment group; the improvement in FEV₁ (8.5% vs 13.8%, respectively) was also less in the delayed versus initial ICS treatment group, though not to a statistically significant degree.

In a study of quite different design, the duration of asthma symptoms before initiation of treatment with inhaled budesonide also correlated negatively with the maximal FEV₁ and PEF achieved after 1 year of inhaled budesonide therapy.¹¹⁸ The greatest proportionate difference was between the improvements in those who began receiving budesonide within 6 months of the appearance

of symptoms and those who began receiving it 6 to 12 months later. These results support the idea that delaying initiation of treatment with an ICS, even for 6 months, reduces the degree of optimal airway function that can be achieved with corticosteroid therapy.

The coincidence of epidemiologic studies suggesting that asthma can progress to severe chronic obstructive lung disease, of pathologic studies suggesting that asthma is associated with fibrotic remodeling of the airway wall (even in patients with mild persistent asthma⁸³), and of clinical studies showing losses in the best function achieved with ICS if such therapy is delayed makes a case for early institution of ICS treatment. It has led some to emphasize the importance of identifying young adults with asthma so that treatment can be started “to prevent the evolution of respiratory impairment.”¹²⁰ These study data were also an important contributor to the decision of the NAEPP to recommend expanding the indication for “chronic controller therapy,” as with an ICS, from patients with moderate or severe asthma in the 1991 guidelines,^{13,14} to treatment of patients with mild persistent asthma in the 1997 revision.^{7,8}

The guidelines were prepared by an authoritative group of experts, but even those experts (including the author of this review) will acknowledge that the guidelines could not always be “evidence based.” The logic that all patients with mild persistent asthma should be treated with a long-term controller therapy (eg, ICS) bears scrutiny. Mild persistent asthma is quite mild. It is defined as asthma causing symptoms on 2 or more occasions per week or interrupting sleep 2 or more times per month or asthma that is associated with greater than 20% variability of PEF or exacerbations that interfere with activity. FEV₁ may be normal but cannot be less than 80% of predicted value.

The economic consequences alone of treating all patients with mild persistent asthma may be great. If one third of the estimated 15 million Americans with asthma have mild persistent asthma, formerly treated with inhaled β_2 -agonists on an as-needed basis alone, the additional costs of one corticosteroid inhaler per month (estimated at \$30 per month) for these patients would add \$1.8 billion to medication expenditures. It can only be conjectured at present whether this cost would be offset by savings from fewer hospitalizations, emergency department visits, and additional prescriptions for β_2 -agonists inhalers, and for the indirect costs of interference with attendance at work or school. Most of the evidence of efficacy of ICS on these outcomes is provided by studies that included patients with moderate asthma. The outcomes most persuasively shown by studies of patients with mild asthma are in endpoints such as FEV₁, PEF, BHR, and symptom severity.

Induction of remission of asthma

Asthma is correctly regarded as a chronic illness, but childhood asthma sometimes appears to enter spontaneously prolonged clinical remissions during the years of adolescence.¹²¹⁻¹²³ Spontaneous remissions may also occur in

TABLE II. Summary results of studies on the effect of withdrawing ICS in asthma

Study	Treatment duration	Steroid dose ($\mu\text{g}/\text{d}$)	Asthma severity	Time to relapse	Early intervention	Back to baseline?
Gibson et al ¹³¹	>1 mo	200-1500	Mild/moderate	<1 mo	No	—
Chervinsky et al ¹³²	>1 mo	400-800	Mild/moderate	≤ 1 mo	No	—
Kraan et al ²⁸	2 mo	400	Moderate	2 mo	No	Yes
Vathenen et al ¹²⁹	6 wk	800	Moderate	1 wk	No	Yes
Bel et al ¹²⁸	1 mo	800	Moderate/severe	2 wk	No	Yes
Magnussen et al ¹³⁰	6 mo	2000	Severe	6 wk	No	Yes
Waalkens et al ¹³⁵	2.5 y	600	Moderate/severe	6 mo (20% no)*	No	No
Juniper et al ¹²⁶	1 y	400	Mild	≥ 3 mo (30% no)*	Yes	No
Haahtela et al ¹¹⁷	2 y	1200	Mild/moderate	NR (33% no)*	Yes	No

NR, Not reported.

*Percentage of subjects without relapse over the period of observation.

adults with asthma. When a change in the responses to the question "Have you ever had asthma?" from "yes" at the first interview to "no" at a second interview 6 years later was used as an indication of remission of the disease, a surprising 60% of the subjects identified in a population survey as having asthma in 1972 were considered to be in remission in 1978.¹⁰⁷ In a similar longitudinal study of a general population sample, Bronnimann and Burrows¹²⁴ found a 22% remission rate in 136 patients with asthma surveyed twice over a 9-year interval. The rate of remission was highest in adolescents and fell off sharply in adults over age 30 years. In fact, adults between the ages of 30 and 60 years with active asthma symptoms had only a 10% chance of symptom remission over a 9-year period. Using a more rigorous definition of asthma remission—the absence of pulmonary symptoms, normal BHR, and an FEV₁ greater than 90% of predicted value—Panhuysen et al¹²⁵ found that 11% of adult patients with asthma, referred for treatment to a regional asthma clinic between 1962 and 1970, had experienced remission of the disease when studied again 25 years later. The features at the initial visit that correlated with remission at follow-up were younger age, less severe airflow obstruction, and a shorter period between the onset of asthma symptoms and active, specialized treatment of the disease.

The knowledge that asthma may enter remission, coupled with the belief that the anti-inflammatory action of ICS is a "disease-modifying" treatment, led to the hope that early, sustained use of ICS would increase the chances of sustained remission of the disease after ICS withdrawal. This hope was nurtured in a report by Juniper et al¹²⁶ on the maintenance of improvements in airway responsiveness and clinical asthma when budesonide was reduced or discontinued. The study was, in part, a follow-up of the same group's previous study of 32 adults with mild asthma treated with placebo or with budesonide, 400 $\mu\text{g}/\text{d}$, for 1 year, in which budesonide improved BHR into the normal range in 5 of the 16 subjects.⁹² It was a full 3 months before symptoms and reductions in FEV₁ returned in those subjects whose dose of budesonide was reduced or eliminated. Of the 8 subjects who had had mild asthma at entry and who had

taken budesonide for 1 year, clear deterioration was evident in only 3 subjects, all of whom had either continued exposure to allergens or had contracted an upper respiratory tract infection.

The hopes raised by the follow-up study by Juniper et al¹²⁶ have been diminished but not altogether dashed by subsequent studies. Haahtela et al¹¹⁷ also published a follow-up of their earlier study of adults with newly diagnosed asthma treated with placebo or high-dose budesonide (1200 $\mu\text{g}/\text{d}$) for 2 years. In their follow-up study, 37 subjects who had been treated previously with budesonide continued to receive a reduced dose of 400 $\mu\text{g}/\text{d}$ or were treated with placebo.¹¹⁷ The subjects whose ICS treatment was reduced continued to do well: FEV₁, PC₁₅, PEF, morning β_2 -agonist use, and symptom scores did not change. Those randomized to the placebo group did significantly worse. More specifically, the deteriorations in mean values for the several indices of asthma control were driven by deteriorations in 12 of the 18 subjects. Six subjects continued to do as well as they had while receiving budesonide. If the findings of this study are representative, they indicate that prompt, prolonged treatment of patients with newly diagnosed asthma with an ICS agent may lead to sustained remission of disease in about one third of these patients. It is possible that the dose required to induce remission is higher than the dose necessary to reduce symptoms and relieve airflow obstruction. Whether the induction of remission can be achieved by prolonged suppression of inflammation, which may require higher doses of ICS, is a matter of conjecture.¹²⁷

Other studies, unfortunately, suggest that even the modestly encouraging findings of Haahtela et al¹¹⁷ may not be representative, especially not of the course of asthma after ICS withdrawal from those whose untreated asthma was more severe.^{28,128-130} Gibson et al¹³¹ even published an article on the use of withdrawal of ICS therapy as a way of inducing a mild exacerbation of asthma for research studies. In addition, Chervinsky et al¹³² reported the return of markers of at least moderately severe asthma within 30 days of stopping treatment in 40 of 80 subjects. A summary of the effect of withdrawing ICS therapy in patients with asthma is shown in Table II.

TABLE III. Effects of ICS on the clinical consequences of asthma

Established effects
Reduction or elimination of need for systemic corticosteroids
Reduction of asthmatic symptoms and exacerbations
Improvement of lung function (spirometry, PEF readings)
Reduction in diurnal variation in lung function
Decrease in need for rescue bronchodilators
Reduction in nocturnal awakenings from asthma
Improvement of quality-of-life indices
Probable effects
Reduction in hospitalization and death
Reduction in rate of decline in lung function
Possible effect
Increase in likelihood of sustained remission of asthma

Remission of asthma is not easily achieved with ICS treatment, even when the definition of "remission" is eased to mean only the absence of symptoms for a prolonged period while therapy is continued, not after therapy is withdrawn. Van Essen-Zandvliet et al¹³³ observed this in their follow-up of a 22-month study showing the superiority of the addition of an ICS to regular treatment with an inhaled β_2 -agonist versus simple continuation of the β_2 -agonist alone in children with asthma. When the 58 children who had been receiving budesonide continued to receive the treatment for up to 36 months, 35 experienced at least one 8-month period free of asthma symptoms. Most of the children who achieved this remission had a relapse of symptoms at some later stage of the follow-up, even though inhaled budesonide was continued.¹³⁴ Thus as the authors concluded, ICS treatment for 28 to 36 months reduced symptoms and improved objective measures of lung function but did not cure asthma. These findings were underscored by the results of a subsequent study in which the same investigators found that withdrawing ICS from these patients was followed by a rapid reappearance of symptoms and a deterioration in lung function.¹³⁵

CONCLUSIONS

The recommendation for use of ICS in asthma treatment is grounded soundly on our knowledge of the mechanisms of action of the drugs and of the pathogenesis of the disease. It is also grounded soundly on a large and growing body of evidence of the efficacy of this treatment in reducing the consequences of asthma (Table III), a body of knowledge so far unapproached by that on any other treatment of asthma, including cromolyn, nedocromil, and the new leukotriene antagonists. ICS therapy is unique in its proven effects in reducing inflammation in the airway mucosa.^{136,137} For patients with more than mild asthma, the treatment may not be curative, but it reduces asthma symptoms and improves quality of life, airway caliber, and airway responsiveness. It reduces the risks of need for emergency care and hospitalization, and it almost certainly reduces the risk of death from asthma. For this group of patients, the risks of

treatment are offset by meaningful benefit; and the more severe the asthma, the more favorable is the cost-benefit ratio. This is true even when cost and benefit are defined narrowly in financial terms, for the costs of ICS treatment are offset by a reduction in the other costs of care. Again, the more severe the asthma, the more favorable is the exchange.

These issues are not quite so clear-cut in relation to the recommendation for using ICS for "mild persistent asthma," as defined by the NAEPP. The criteria for this category are quite inclusive, and most if not all of the studies of "mild" asthma or "newly diagnosed" asthma included patients with more severe disease than those in the new "mild persistent" category as defined by the NAEPP. ICS will certainly improve the modest severity of symptoms in this group and will reduce further an already low rate of risk of serious exacerbations. Those benefits may be sufficient to justify the low risk of side effects and the costs of treatment for these patients. If they are not, a case for using ICS can still be made from the evidence that such treatment may retard or prevent the development of changes in irreversible airflow obstruction. The hope that such treatment might also improve the chances for sustained remission after treatment is stopped remains just that—a hope—for a therapy for which other benefits are soundly established.

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