

The Role of Inhaled Corticosteroids in Asthma Treatment: A Health Economic Perspective

Dennis L. Spangler, MD

Asthma affects approximately 23 million Americans, including almost 7 million children (as of 2008),^{1,2} and it is estimated that by 2025 that number will grow by more than 100 million worldwide.³

Asthma is responsible for almost 15 million physician office and hospital visits, and nearly 2 million visits to emergency departments, every year.⁴ In addition, results from the survey Asthma in America indicate that the United States is not meeting asthma goals set forth by the National Heart, Lung, and Blood Institute, which consist of no sleep disruption, no missed school or work, no (or minimal) need for emergency department visits/hospitalizations, maintenance of normal activity levels, and normal or near-normal lung function.⁵ This lack of control has contributed to the annual economic costs associated with asthma, which have been estimated to be as high as \$56 billion.⁶

Asthma Treatment: ICS Monotherapy as the Gold Standard

Current guidelines recommend long-term treatment with inhaled corticosteroids (ICS) because of their superior effectiveness in managing the chronic airway inflammation that characterizes persistent asthma.^{7,9} Additionally, the US Food and Drug Administration (FDA) issued a warning in February 2010 that long-acting beta agonists (LABAs) should never be used alone to treat asthma, specifying that when they are used, they should be administered only for the shortest duration possible and then discontinued.¹⁰ This warning resulted from analyses showing that LABA use was associated with an increased risk of severe exacerbations leading to hospitalization in both children and adults, with a possibility of death.¹⁰

The National Asthma Education and Prevention Program (NAEPP) Expert Panel Report (EPR)-3 Guidelines recommend a stepwise approach to asthma treatment:

1. ICS monotherapy as first-line controller treatment for persistent asthma (mild, moderate, and severe) for both adults and children.
2. If asthma remains uncontrolled with low-dose ICS monotherapy, only then should physicians consider a medium-dose ICS or adding a LABA to a low-dose ICS regimen.

Abstract

Asthma affects approximately 23 million American children and adults, resulting in almost 15 million physician office and hospital visits, and nearly 2 million emergency department visits each year. Despite the publication of National Asthma Education and Prevention Program guidelines, asthma remains poorly controlled, with annual costs estimated at up to \$56 billion. Current guidelines recommend long-term treatment with inhaled corticosteroids (ICS) because of their superior effectiveness in managing the chronic airway inflammation that characterizes persistent asthma. ICS monotherapy should be explored before alternatives such as leukotriene modifiers and long-acting beta agonists (LABAs) are attempted, especially after the US Food and Drug Administration's 2010 warning that LABAs should never be used alone to treat asthma due to the increased risk of severe exacerbations leading to hospitalization in both children and adults, with a possibility of death. In the past, asthma treatment focused solely on the central airways, rather than the small, more distant airways, and most traditional ICS therapies are aerosols which deliver large particles to the central airways. Today, the importance of the role of small airway disease in asthma, particularly inflammation, is known. Targeting the small airways may help improve clinical outcomes and reduce healthcare utilization and costs. The ICS beclomethasone dipropionate HFA does not require a spacer and is characterized by small particle sizes that result in more of the drug being deposited in both the large and small airways. Studies have demonstrated that beclomethasone dipropionate HFA is clinically effective and cost efficient compared with other asthma monotherapies or combination therapies.

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3. Increasing the ICS dose may reduce the risk of severe exacerbations and hospitalizations compared with approaches that involve adding a LABA.¹¹ A study of more than 64,000 patients¹¹ found treatment to be more successful among those who were given “stepped up” ICS monotherapy compared with patients given ICS/LABA combination treatment (odds ratio [OR] 0.75 vs 0.96). Patients given ICS only were 31% less likely to be hospitalized for respiratory issues than those receiving ICS/LABA treatment.¹¹

The National Institute for Health and Clinical Excellence (NICE), which is based in the United Kingdom, recommends ICS treatment as step 2 (with a short-acting beta agonist [SABA] as step 1 for mild intermittent asthma) if the patient meets the following requirements:

- Continued asthma exacerbations within the past 2 years
- The patient is using a SABA at least 3 times per week. This does not include use for exercise-induced asthma
- The patient has symptoms at least 3 times per week
- The patient wakes at night due to symptoms

Despite these recommendations, however, the use of ICS monotherapy has been shown to be suboptimal. Although LABA/ICS therapy is not recommended as first-line treatment, and ICS therapy is less costly than LABA/ICS treatment or leukotriene modifiers, evidence indicates physicians are still predominately prescribing LABA/ICS regimens or a leukotriene modifier rather than attempting to utilize the full potential of ICS monotherapy.¹²

In the past, asthma treatment tended to focus solely on the central airways, rather than the small, more distant airways (airway diameter ≤ 2 mm). Today, the importance of the role of small airway disease in asthma, particularly inflammation, is now known.^{13,14} Initially thought to be “the quiet zone of the lungs,” contributing little to total lung resistance, more recent technology such as fiber optic bronchoscopy¹⁴ has given way to an understanding that the small airways contribute significantly to airway resistance.¹⁵ Among patients with mild asthma having normal spirometry, small airway resistance was increased up to 7-fold when compared with controls.¹⁵ Patients with asthma who are asymptomatic can also show significant increases in small airway resistance, in most cases caused by poorly treated distal lung inflammation.¹⁵ The inflammatory process in the central and distal airways is similar (infiltrates contain activated T lymphocytes and eosinophils, increased mucus plugging, and smooth muscle hyperplasia), with one important difference. The small airways are a major site of airway

obstruction because of their small diameter, and because smaller amounts of inflammation result in a greater degree of airway narrowing and may contribute significantly to airway hyperresponsiveness.^{13,14} Remodeling can also occur in the small airways of patients with asthma.¹³ A study showed that among patients with asthma who had died, most were taking large-particle ICS; autopsy data indicated that airway remodeling was not altered by large-particle ICS therapy.¹⁶ These structural changes that occur amid airway hyperresponsiveness may result from “long-standing” or undertreated airway inflammation.¹⁶ The use of small-particle ICS has been shown to reduce small airway inflammation.

Targeting the small airways can help improve clinical outcomes, reduce healthcare utilization/costs, and improve quality of life. Diagnosing small airway dysfunction and treating the patient early may reverse airway remodeling, progression to airway fibrosis, and irreversible airway damage in patients with mild-to-moderate asthma.¹⁵ Although ICS treatment is the gold standard for treating asthma, aerosol particle size is crucial, with only small, less dense particle sizes having the ability to reach the small airways. Particles between 0.6 and 0.3 μ m are likely to be exhaled, and therefore of less therapeutic benefit.^{13,17} Although delivery method and dosage vary between ICS products, most traditional ICS therapies are aerosols that deliver large particle sizes (2.4 to 4.5 μ m) to the central airways, resulting in relatively low total lung deposition.^{13,18-20} Large-particle metered-dose inhalers, pressurized inhalers, or dry-powder inhalers have not shown great efficiency, delivering drug to the smaller airways at no more than 30% of the administered dose.²¹

Improper technique by patients is another common problem when administering ICS, and many physicians advise patients to use a spacer when administering an ICS. The combination of larger particle sizes with poor inhaler technique leads to much of the drug settling in the oropharynx. Beclomethasone dipropionate HFA does not require a spacer and is provided in a liquid solution, resulting in small particle sizes (1.1 μ m).²² Consequently, it has been shown that more of the drug reaches the entire lung, including both large and small airways (and reducing oropharyngeal adverse effects), even if the patient exhibits poor technique.²³

Comparison of Current Agents and Differences Between ICS Therapies

Relatively new in the United States, comparative effectiveness research (CER) is another effort by managed care toward providing quality, cost-effective care, and \$1.1 billion has been earmarked for CER and allotted to such organiza-

tions as the Agency for Healthcare Research and Quality, the US Department of Health and Human Services, and the National Institutes of Health.²⁴ As defined by the Patient Protection and Affordable Care Act, CER is “research evaluating and comparing health outcomes and the clinical effectiveness, risks, and benefits of 2 or more health care interventions, protocols for treatment, care management, and delivery, procedures, medical devices, diagnostic tools, pharmaceuticals (including drugs and biological agents), integrative health practices, and any other strategies or items being used in the treatment, management, and diagnosis of, or prevention of illness or injury in individuals.”²⁵ CER examines original research, evidence synthesis, and evidence dissemination concerning the comparative harms and benefits of existing pharmacologic and nonpharmacologic interventions so that healthcare decision makers may select the best therapy for an individual patient as well as the best way to deliver it.²⁵

The United Kingdom–based NICE is an organization that has issued CER recommendations since 1999, and usually advises the least costly product as long as it is appropriate for an individual. NICE examined 7 asthma treatments (5 monotherapies: beclomethasone dipropionate HFA, budesonide, fluticasone propionate, mometasone furoate, and ciclesonide; and 2 combination therapies: fluticasone propionate/salmeterol and budesonide/formoterol fumarate),²⁰ and concluded that all ICS therapies were similar in regard to efficacy. However, beclomethasone dipropionate HFA in particular was found to be both cost efficient²⁰ (the least expensive compared with the other ICS therapies)²⁰ and clinically effective: NICE concluded that beclomethasone dipropionate HFA use led to improved lung deposition because of its delivery of smaller ICS particles.²⁰

A real-world observational study²⁶ conducted in the United Kingdom compared beclomethasone dipropionate HFA and fluticasone among primary care patients with persistent asthma who received either a first prescription or a dose increase of either beclomethasone dipropionate HFA or fluticasone. Results of the study showed that although approximately 80% or more of patients in each treatment group in both cohorts achieved asthma control, fluticasone was prescribed at significantly higher doses than beclomethasone to achieve control ($P \leq .001$). Patients taking beclomethasone had a similar or greater chance of reducing exacerbations and achieving asthma control with lower doses.²⁶ Relative to fluticasone, the adjusted OR for achieving asthma control in the beclomethasone dipropionate HFA initial therapy cohort was 1.30 (95% confidence interval, 1.02-1.65).²⁶ Among patients in the stepped-up cohort,

the adjusted OR for patients receiving beclomethasone dipropionate HFA and achieving asthma control was 1.22 (95% confidence interval, 0.66-2.26).²⁶ This study reinforces guideline recommendations to begin asthma treatment with ICS monotherapy and increase the ICS dose as necessary. According to the authors, the study results suggest that improved lung deposition improves a patient’s chances of achieving effective asthma control; also, ease of inhalation may have been a contributing factor.

Pharmacoeconomic Evidence

The ability of beclomethasone dipropionate HFA to treat chronic small airway inflammation may enhance symptom management, leading to fewer asthma exacerbations and reducing healthcare resource utilization (physician visits, etc). A retrospective study by Lage et al²⁷ examined data from 13,968 patients, of whom 3223 took beclomethasone dipropionate HFA and 10,745 took fluticasone. Total medical costs were found to be significantly less for patients taking beclomethasone dipropionate HFA (\$5063 vs \$5377 for the fluticasone group), most likely due to significantly lower drug and emergency department costs, as well as lower asthma-related outpatient costs (\$191 vs \$224, respectively; $P < .0001$) and asthma-related emergency department costs (\$28 vs \$45, respectively; $P < .0001$).²⁷ Patients who took beclomethasone dipropionate HFA were less likely to go to the emergency department for any cause or for reasons related to asthma (a 17% and 30% reduction, respectively) during the 1-year follow-up.²⁷

Zeiger et al conducted a large retrospective analysis of cost and resource utilization for more than 96,000 asthma patients, which found adjusted total and asthma inpatient costs were significantly less for patients using ICS monotherapy compared with other monotherapy agents and all combination therapies ($P < .001$ for all). Asthma-related resource utilization (eg, hospitalization/emergency department visits) was lower for patients using ICS monotherapy compared with patients using leukotriene modifiers and combination therapies.²⁸

A study by Wang et al found that asthma was a significant predictor of absenteeism and presenteeism (loss of productivity while at work). Excess absenteeism days related to asthma totaled 10.6 days, with excess presenteeism at 18.3 days. These results suggested less than adequate asthma control.²⁹ Another study by Lamb et al found that absenteeism and presenteeism costs associated with asthma resulted in total lost productivity of \$702,998 in a survey of 8267 employees.³⁰ Absenteeism costs were \$779 higher in patients with persistent asthma ($P < .01$) than in patients without, according

to a study by Colice et al.³¹ Another study by Colice et al reinforced ICS monotherapy as the least expensive treatment option compared with leukotriene modifiers or ICS/LABA combination treatment.¹² This was mainly due to differences in drug acquisition costs; however, research showed that patients taking ICS monotherapy had lower mean medical costs and total direct medical costs compared with patients taking leukotriene modifiers or ICS/LABA combination treatment.¹²

Conclusion

ICS monotherapy is recommended as first-line treatment for persistent asthma for all age groups, including children. The full potential of ICS monotherapy should be explored before alternative treatments such as leukotriene modifiers and LABAs are attempted, especially given the FDA's 2010 warning on LABA use.

Targeting the small airways may help improve clinical outcomes and reduce healthcare utilization and costs. The ICS beclomethasone dipropionate HFA, which does not require a spacer and is characterized by small particle sizes that result in more of the drug being deposited in both the large and small airways, has been shown in studies to be both clinically effective and cost efficient. Beclomethasone dipropionate HFA treatment has been associated with a reduction in total medical costs, a direct consequence of its lower drug costs and fewer hospital and outpatient visits.

About Beclomethasone Dipropionate HFA Inhalation Aerosol

Beclomethasone dipropionate HFA inhalation aerosol is indicated in the maintenance treatment of asthma as prophylactic therapy in patients 5 years of age or older. Beclomethasone dipropionate HFA inhalation aerosol is also indicated for asthma patients who require systemic corticosteroid administration, where adding beclomethasone dipropionate HFA may reduce or eliminate the need for systemic corticosteroids.

Important Safety Information for Beclomethasone Dipropionate HFA Inhalation Aerosol

Important Safety Information for beclomethasone dipropionate HFA inhalation aerosol includes: Beclomethasone dipropionate HFA inhalation aerosol is not a bronchodilator and is not indicated for relief of acute bronchospasm. Common side effects associated with the use of beclomethasone dipropionate HFA inhalation aerosol and placebo in clinical trials include, but are not limited to, headache (12% and 9%, respectively) and pharyngitis (8% and 4%,

respectively). An important CAUTION found in the FDA-approved labeling for beclomethasone dipropionate HFA inhalation aerosol is that adrenal insufficiency may occur when transferring patients from systemic steroids. A reduction in growth velocity in growing children and teenagers may occur as a result of inadequate control of chronic diseases such as asthma or from use of corticosteroids for treatment.

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Address correspondence to: Dennis L. Spangler, MD, 12 Ball Creek Way, Atlanta, GA, 30350. E-mail: dspangler@atlantaallergy.com.

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