Inhaled Corticosteroids in Asthma Management

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Summary

Asthma is a disorder of the lower airways, characterized by bronchial hyperresponsiveness and airflow limitation, the pathogenesis of which is yet to be fully understood. Regardless of its triggers, asthma’s hallmark is a state of inflammation that, when uncontrolled, results in persistence of symptoms. Inhaled corticosteroids are established as the mainstay of asthma therapy. This paper examines what is currently available among this class of drugs, features of the ideal inhaled corticosteroid, the delivery systems, dose-response relationships, adverse effects, combination with long-acting $\beta$ agonists, equipotent doses among the different types, and several special scenarios that involve the apparent incomplete or lack of response to treatment with inhaled corticosteroids among certain subgroups of patients, such as smokers and obese individuals, and we will discuss the scientific basis of such resistance and suggest alternative approaches to therapy. Key words: asthma, persistence, inhaled corticosteroids, inflammation, delivery systems, smokers, obese, long-acting $\beta$ agonists. [Respir Care 2008;53(5):625–633. © 2008 Daedalus Enterprises]

Introduction

Asthma is a complex, heterogeneous disorder characterized by reversible obstruction of the lower airways. The pathogenesis of asthma is yet to be fully understood. Regardless of the phenotype, in asthma the airways are in a state of chronic, dysregulated inflammation. The inflammatory process in asthma involves the increased expression of a wide variety of pro-inflammatory chemokines, cytokines, growth factors, lipid mediators, adhesion molecules, enzymes, and increased numbers of resident and invading inflammatory cells. That milieu leads to persistent or recurrent symptoms that require daily anti-inflammatory treatment to maintain appropriate symptom control and quality of life. At all levels of persistent asthma, inhaled corticosteroids (ICSs) are well established as the mainstay of therapy in both children and adults, and are...
Mechanism of Action

ICSs are believed to exert their effects after translocation into the nucleus of the respiratory epithelial cell and other cells in the airway, via the glucocorticoid receptor.4 The steroid-receptor complex within the nucleus promotes transcription of genes that decrease inflammation and inhibit transcription of genes that encode proteins that increase inflammation. There is also evidence that ICSs may facilitate the action of β-adrenergic agonists by increasing the concentrations of β-adrenergic receptors on smooth-muscle cells5 and decreasing airway smooth-muscle cell hyporesponsiveness to β agonist.6 Regardless of the structure differences of the various ICSs, they all work through these mechanisms. Differences in the chemical structure of the various ICSs cause differences in their pharmacokinetic and pharmacodynamic properties, which can prove advantageous for clinical efficacy and safety.

Features of an Ideal Inhaled Corticosteroid

The characteristics of an ideal ICS include optimal clinical efficacy and minimal to no toxicity in combination with a convenient and easy-to-use inhaler (Table 1).7,8 To achieve this optimal profile an ICS should have the following properties: a high affinity for and potency at the glucocorticoid receptor; high level of serum protein binding for the systemically absorbed fraction; high volume of distribution; prolonged retention in the lung; minimal or no oral bioavailability; and rapid, complete systemic inactivation (ie, high first-pass hepatic inactivation).8,9 All these features confer a higher therapeutic index that should manifest as prolonged anti-inflammatory activity in the lung and minimal systemic adverse effects. An ICS with properties that permit once-a-day administration is also likely to improve patient adherence to therapy by simplifying the treatment regimen (only mometasone and ciclesonide are currently labeled for once-daily use). The formulation and type of inhaler are also important considerations. Inhalers should provide maximum lung deposition, in both large and small lower airways, with little to no deposition or absorption outside the lung (ie, in the oropharynx or gastrointestinal tract).10 It is also critical to evaluate ICSs for administration with several different delivery devices, to ensure ease of use by patients of all ages and with different asthma severities, to offer both control and prevention of asthma symptoms and exacerbations.

Currently Available Inhaled Corticosteroids

Six ICSs, each with somewhat different pharmacokinetic/pharmacodynamic profiles and biologic characteristics, are currently available for clinical use (Tables 2 and 3): beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, mometasone fumarate, and triamcinolone acetate.12 A seventh ICS, ciclesonide, is available only outside the United States for treatment of asthma, but the nasal-spray version of ciclesonide (Omnaris) was recently cleared for treatment of allergic rhinitis.13 Whereas fluticasone, budesonide, and mometasone are active drugs, beclomethasone dipropionate and ciclesonide are pro-drugs with active metabolites. Beclomethasone dipropionate has relatively poor activity and is metabolized to 17-beclo- methasone monopropionate, which is the main active constituent.14 Ciclesonide is also converted at the airway cell

Table 1. Properties of the Ideal Inhaled Corticosteroid

<table>
<thead>
<tr>
<th>Properties</th>
<th>Pharmacokinetic/Pharmacodynamic or Pharmacologic Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Properties That Affect Efficacy</td>
<td></td>
</tr>
<tr>
<td>High pulmonary deposition</td>
<td>Greater pulmonary anti-inflammatory activity</td>
</tr>
<tr>
<td>Single isomer</td>
<td>Only active agent is given, so lower drug load</td>
</tr>
<tr>
<td>Conversion to active metabolite in lung</td>
<td>Targeted activity/efficacy in lung and not elsewhere</td>
</tr>
<tr>
<td>High glucocorticoid receptor affinity</td>
<td>High potency and efficacy at site of action</td>
</tr>
<tr>
<td>High pulmonary retention</td>
<td>Prolonged maintenance of targeted anti-inflammatory activity</td>
</tr>
<tr>
<td>Properties That Affect Safety and Tolerability</td>
<td></td>
</tr>
<tr>
<td>Low oropharyngeal exposure</td>
<td>Limited local adverse effects (eg, dysphonia and candidiasis)</td>
</tr>
<tr>
<td>Low oral bioavailability</td>
<td>Low systemic exposure, so limited systemic adverse effects</td>
</tr>
<tr>
<td>High protein binding</td>
<td>Steric inhibition leads to pharmacologic inactivation within the systemic circulation and limits systemic adverse effects</td>
</tr>
<tr>
<td>Metabolized elsewhere in the body</td>
<td>Hepatic metabolism destroys active compound, which limits systemic adverse effects</td>
</tr>
<tr>
<td>Rapid and extensive elimination</td>
<td>Removal of drug from body, which limits systemic adverse effects</td>
</tr>
</tbody>
</table>

(Adapted from Reference 7).
into its active metabolite, des-ciclesonide. Ciclesonide is only converted to its active form by enzymes found in the lower respiratory tract, and this accounts for the reported reduction in local adverse effects in the upper airway (thrush, dysphonia) and systemically. Ciclesonide may also have a more favorable safety profile regarding growth and adrenal suppression in pediatric patients.\(^{12}\)

Although there are few robust studies on differences in clinical efficacy between the different ICSs, in vitro there is a direct correlation between efficacy and affinity at the glucocorticoid receptor; and in most instances this is a reasonable marker for predicting clinical efficacy and likely safety profile. All ICSs can achieve the same clinical activity when given at equipotent doses. The equitherapeutic dose of different ICSs depends in part on the pharmacokinetic properties and delivery device used.\(^{15}\) Three delivery systems are available for ICSs: metered-dose inhaler (MDI), dry-powder inhaler (DPI), and small-volume nebulizer.\(^{16,17}\) MDI formulations are propelled by either chlorofluorocarbon or hydrofluoroalkane 134a (HFA). HFA formulations have a higher output of aerosol particles in the respirable range than do chlorofluorocarbon formulations. The aerosol particle size range 1.0–5.0 μm results in optimal deposition in the airways. MDIs emit particles of various sizes, some of which are outside the respirable range. A valved holding chamber increases the percentage

### Table 2. Pharmacokinetic and Pharmacodynamic Features of Inhaled Corticosteroids

<table>
<thead>
<tr>
<th></th>
<th>Beclomethasone Dipropionate</th>
<th>Beclomethasone Monopropionate</th>
<th>Budesonide</th>
<th>Fluticasone Propionate</th>
<th>Ciclesonide</th>
<th>Des-ciclesonide</th>
<th>Mometasone Furoate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral bioavailability (%)</td>
<td>&lt;1</td>
<td>26</td>
<td>11</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pulmonary deposition (%)</td>
<td>51</td>
<td>*</td>
<td>28</td>
<td>16</td>
<td>52</td>
<td>*</td>
<td>14</td>
</tr>
<tr>
<td>On-site activation</td>
<td>Somewhat</td>
<td>Somewhat</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Receptor binding affinity(^{†})</td>
<td>53</td>
<td>1,345</td>
<td>935</td>
<td>1,800</td>
<td>12</td>
<td>1,200</td>
<td>2,200</td>
</tr>
<tr>
<td>Protein binding (%): free fraction (%)</td>
<td>87:13</td>
<td>87:13</td>
<td>88:12</td>
<td>90:10</td>
<td>99:1</td>
<td>99:1</td>
<td>98–99; approx 1</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>0.5</td>
<td>2.7</td>
<td>2.8</td>
<td>7.8</td>
<td>0.36</td>
<td>3.4</td>
<td>4.5</td>
</tr>
<tr>
<td>Volume of distribution (L)</td>
<td>20</td>
<td>424</td>
<td>183</td>
<td>318</td>
<td>207</td>
<td>897</td>
<td>152</td>
</tr>
<tr>
<td>Clearance (L/h)</td>
<td>15</td>
<td>120</td>
<td>84</td>
<td>69</td>
<td>152</td>
<td>228</td>
<td>53.5</td>
</tr>
</tbody>
</table>

*Beclomethasone monopropionate and des-ciclesonide are the active metabolites of beclomethasone dipropionate and ciclesonide; they only exist in the airways and are the products of enzymatic conversion from the inhaled parent compounds, so only beclomethasone dipropionate and ciclesonide are inhaled and therefore have deposition data.

†Receptor binding affinities values are relative to 100, which is the affinity of dexamethasone.

(Adapted from Reference 7)

### Table 3. Inhalable Corticosteroids

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Delivery System(s)</th>
<th>Brand Name</th>
<th>Year Cleared by FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone</td>
<td>HFA MDI</td>
<td>QVAR</td>
<td>2000</td>
</tr>
<tr>
<td>Budesonide</td>
<td>DPI</td>
<td>Pulmicort Turbuhaler and Flexhaler</td>
<td>1997</td>
</tr>
<tr>
<td></td>
<td>SVN(^{†})</td>
<td>Pulmicort Respules</td>
<td>2000</td>
</tr>
<tr>
<td></td>
<td>HFA MDI</td>
<td>Symbicort</td>
<td>2006</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>CFC MDI</td>
<td>Aerobid</td>
<td>1984</td>
</tr>
<tr>
<td></td>
<td>HFA MDI</td>
<td>Aerospin</td>
<td>2006</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>DPI</td>
<td>Advair Diskus</td>
<td>2000</td>
</tr>
<tr>
<td></td>
<td>HFA MDI</td>
<td>Advair</td>
<td>2006</td>
</tr>
<tr>
<td></td>
<td>MDI</td>
<td>Flovent</td>
<td>2004</td>
</tr>
<tr>
<td>Momethasone</td>
<td>DPI</td>
<td>Asmanex Twishtaler</td>
<td>2005</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>CFC MDI</td>
<td>Azmacort</td>
<td>1982</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>HFA MDI</td>
<td>Alvesco</td>
<td>Not yet cleared*</td>
</tr>
</tbody>
</table>

*Ciclesonide is not yet marketed in the United States

†May not be reformulated with an HFA propellant.

HFA = hydrofluoroalkane (MDI propellant)

MDI = metered-dose inhaler

DPI = dry-powder inhaler

SVN = small-volume nebulizer

CFC = chlorofluorocarbon

(Adapted from Reference 11.)
of inhaled particles that are within the respirable range and captures larger particles and thus prevents their deposition in the oropharynx.

In the new HFA formulations of flunisolide and beclomethasone dipropionate the drug component is in solution, whereas in the HFA formulations of fluticasone propionate and triamcinolone acetonide the drug component is in suspension. The HFA suspension formulations have the same particle size, deposition, and efficacy profiles as their chlorofluorocarbon-propelled counterparts. The HFA solutions, however, produce extra-fine aerosol particles that penetrate more effectively into the peripheral lung.18 The beclomethasone dipropionate HFA formulation has a smaller particle size and thus better lung deposition, but there is an attendant risk of greater systemic adverse effects at the same dose, which suggests that equal efficacy is possible at a lower dose.19 Because chlorofluorocarbon depletes the ozone layer in the upper atmosphere, this propellant is being phased out and will be banned in inhaled asthma medications by international law by the end of 2008.

DPI ICSs have 3 brands of delivery system: Diskus, Twisthaler, and Turbuhaler. All DPIs are breath-actuated and therefore can be used only by cooperative older children and adults. When used properly the DPI deposits a relatively high concentration of active ICS particles in the airways. The proper technique for use involves a rapid, sustained inhalation. Aerosol particles from DPIs are usually within the range 0.5–5 μm, so lung deposition will be optimal as long as the inspiratory flow is ample (ie, Diskus ≥ 30 L/min, Twisthaler 30–60 L/min, Turbuhaler 60–90 L/min).

Small-volume nebulizers require a mask or a mouthpiece from which the patient inhales the aerosol. Only budesonide is available for delivery via small-volume nebulizer, which requires a compressor that can deliver ≥ 6 L/min and a high-efficiency nebulizer to produce an acceptable concentration of optimal particle sizes.

Clinical Effects

ICSs effectively and reproducibly suppress the inflammatory processes in the airways of most asthmatics. The versatile anti-inflammatory activity of ICSs down-regulates most pathways involved in synthesis of cytokines and other inflammatory mediators, with the exception of leukotrienes. Their clinical benefits include decreased asthma symptoms,20,21 fewer exacerbations,22,23 fewer hospitalizations,24,25 decreased airway hyperresponsiveness,26 improved pulmonary function,25,27 decreased exhaled nitric oxide,28,29 and fewer asthma-related deaths.30

Dose-Response and Adverse Effects

ICSs demonstrate a dose-response relationship for the majority of important clinical efficacy measures.25,27,31 In mild-to-moderate asthma, marked clinical improvement has been seen in most studies in the low-to-moderate dose range25,27,32 (Table 4). Doses in excess of that range increase the risk of systemic adverse effects.32,33 The ther-

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Table 4. Estimated Daily Doses of Inhaled Corticosteroid in Children and Adults

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Dose (μg) and Age Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Dose</td>
</tr>
<tr>
<td></td>
<td>0–4 y old</td>
</tr>
<tr>
<td></td>
<td>0–4 y old</td>
</tr>
<tr>
<td></td>
<td>0–4 y old</td>
</tr>
<tr>
<td></td>
<td>0–4 y old</td>
</tr>
<tr>
<td>Beclomethasone HFA MDI (40 or 80 μg/puff)</td>
<td>* 80–160</td>
</tr>
<tr>
<td>Budesonide</td>
<td>250–500</td>
</tr>
<tr>
<td>Powder formulation</td>
<td>* 180–400</td>
</tr>
<tr>
<td>Flunisolide HFA MDI (80 μg/puff)</td>
<td>* 160</td>
</tr>
<tr>
<td>Mometasone DPI (200 μg/puff)</td>
<td>*</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>* 300–600</td>
</tr>
</tbody>
</table>

*Not approved and no data available for this age group.
HFA = hydrofluoroalkane (MDI propellant)
MDI = metered-dose inhaler
DPI = dry-powder inhaler

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The therapeutic dose range for all clinical outcome measures in adults is 100–1,000 µg/d of beclomethasone monopropionate or budesonide. Meta-analysis including fluticasone propionate showed that 90% of clinical benefit was achieved with doses in the range of 150–250 µg/d, and the peak effect with a dose of approximately 500 µg/d. Those studies provide evidence on why ICSs should be titrated to the lowest effective dose once asthma symptoms are under control. However, some of these studies were dominated by adolescents and adults with mild-to-moderate asthma, which suggests that a trial of a higher dose may be indicated in a patient who has more severe asthma. Similarly, there are clinical situations in which a higher ICS dose is warranted for temporary treatment, such as following asthma exacerbation, and as a sparing agent in a patient with oral-steroid-dependent asthma, to enable reduction in oral steroid dose. Although most dose-response studies have been with patients with mild-to-moderate asthma, other studies have shown that even very high doses of ICS (2 mg of fluticasone) do not further improve forced expiratory volume in the first second or methacholine responsiveness in patients with moderate-to-severe asthma. In addition, as many as 25–30% of patients fail to respond to moderate-to-high doses of ICS and they may be considered steroid insensitive or resistant.

ICSs are safe, and if properly administered have relatively few adverse effects. The main local adverse effects of ICSs are oral candidiasis, cough at the time of inhalation, hoarse voice, and dysphonia. The cough is due to a local irritant effect and often may resolve by changing the delivery device, using a valved holding chamber, or slowing the rate of inhalation. Oral candidiasis is dose-related, occurs in <5% of treated patients, and can be prevented by rinsing the mouth with water. However, topical antifungal for small doses of ICS might be required in some individuals. Dysphonia and hoarseness are both dose-related and may be due to steroid myopathy of the laryngeal muscles. Both are worse with DPIs than with MDIs. In a study on the incidence of oral candidiasis, ciclesonide at 640 µg/d had an oral candidiasis incidence of <1%, compared to 11% with fluticasone at 880 µg/d. This is attributed to significantly less oral deposition of ciclesonide in clinical studies.

Systemic adverse effects of ICSs are dose-related. The more drug deposited in the lung, the greater the systemic absorption and the greater the systemic adverse effects (Table 5). Although the results reported in the literature on the adverse effects of ICSs conflict and the studies have often been restricted to a small number of cases with limited follow-up, an important adverse effect is dose-related suppression of the hypothalamic-pituitary-adrenal axis. In adults, biochemical adrenal suppression seems to occur at doses above 800 µg/d (beclomethasone dipropionate equivalent). There are also reports and case series of substantial adrenocortical suppression in children at ICS doses above the licensed dose for fluticasone propionate. Other dose-related adverse effects, such as osteoporosis, glaucoma, and cataracts are largely restricted to adult patients treated long-term with high-dose ICS.

A major concern of parents and providers is growth suppression from ICSs; however, the 2007 National Asthma Education and Prevention Program’s Expert Panel Report 3, Guidelines for the Diagnosis and Management of Asthma (2007 NAEPP guidelines), asserts that ICSs at the recommended doses are not likely to have long-term, clinically important, or irreversible effects on linear growth. The growth rate slows down in the first year of treatment, but children resume their growth pattern within 2–4 years and ultimately achieve their predicted adult height.

Two studies support the assertion that ICSs do not significantly affect growth: the Childhood Asthma Management Program study and the Prevention of Early Asthma in Kids study, in which the children were using budesonide and fluticasone, respectively. In the former study, children using inhaled budesonide were 1.1 cm shorter than the controls at the end of the 4-year treatment phase. However, the children are expected to reach their adult final height, based on similar data from a long-term treatment trial of budesonide at an average dose of 400 µg/d for up to 9 years. In the Prevention of Early Asthma in Kids trial the difference in growth rate was significant between the fluticasone and control groups in the first year of the study, but not during the second year of treatment, when active drug was withdrawn. In the third-year observation period, the children who had been regularly treated with ICS grew more quickly than the children in the control group. Although the apparent safety of low-dose ICS in pre-pubertal children with respect to growth suppression seems evident, it remains important to monitor linear growth in all children who take ICS long-term, at any dose.

Although current recommendations for ICSs indicate that daily dosing is necessary, there is some evidence that acceptable asthma control can be achieved with intermittent use. A study of 225 adults with mild asthma randomized to receive either daily inhaled budesonide or as-needed...
budesonide and daily zafirlukast or placebo showed no clinically important difference among the 3 treatment groups with respect to morning peak flow.45 However, patients in the daily-ICS group reported 26 more symptom-free days per year than did the patients on the other treatments, although asthma exacerbations did not differ significantly among the groups. Remarkably, the group assigned to as-needed budesonide took the drug for an average of only 0.5 weeks per year. These data suggest that some patients with mild asthma might have acceptable, albeit not ideal, asthma control with as-needed ICS.

Special Cases

Though most patients respond well to conventional asthma therapy, as outlined in the 2007 NAEPP guidelines,2 about 25–35% of patients with asthma may be relatively or completely unresponsive to inhaled steroid.46 Persistent immune activation and airway inflammation, which to varying degrees is resistant to glucocorticoid therapy, appears to define the immunologic abnormality underlying steroid-resistant asthma.4 Recent studies that used molecular biology techniques identified both ligand-binding and deoxyribonucleic-acid-binding defects that might account for steroid resistance at the molecular level, such as alterations in histone deacetylase.47

Issues that require exploration in the setting of apparent steroid resistance include poor patient adherence to therapy, improper inhaler technique, inadequate anti-inflammatory therapy, incorrect diagnosis, and environmental factors. Patients who exhibit steroid resistance need a thorough and systematic workup to check for diseases that mimic asthma, such as chronic obstructive pulmonary disease, vocal cord dysfunction, emphysema, gastroesophageal reflux, or congestive heart failure.

The obese asthmatic presents an interesting scenario in that, though obesity does not cause asthma, it may be a risk factor for development and severity of asthma.48 Obesity also might exacerbate persistent symptoms through comorbidities such as gastroesophageal reflux and sleep-disordered breathing. Management of steroid-resistant asthma is challenging, and conventional therapy with high-dose inhaled and daily oral steroid should be tried prior to embarking on alternative therapies such as anti-immunoglobulin E monoclonal antibody,49 methotrexate,50 or other immunomodulatory agents, which are not only expensive but potentially toxic.

Active cigarette smoking also blunts ICS response in asthma patients.51,52 Proposed mechanisms include enhanced neutrophil-mediated inflammation, increased level of tumor necrosis factor alpha, and smoking-induced glucocorticoid receptor insensitivity. Lazarus et al,53 in a study to determine if response to inhaled beclomethasone monopropionate and oral montelukast is attenuated among smokers, also identified corticosteroid insensitivity in patients with asthma who smoke, and they suggested that leukotriene antagonists may be beneficial in such patients. This observation is consistent with other studies that found increase in 15-lipoxygenase activity in the airways of smokers.54 A higher ICS dose may be necessary to adequately control symptoms in asthmatics who are also active smokers.

ICS in addition to standard treatment with inhaled β agonist and oral steroid may have benefit in asthma exacerbations. High-dose ICS reduces the likelihood of hospital admission and repeated exacerbation when added to standard treatment administered in the emergency department.55 However, some studies have not supported that conclusion, especially in pediatric patients.56 The exact mechanisms of the ICS effect in acute asthma are unclear. Experimental data suggest a role for the microcirculation and rapid effects of ICS on reducing airway mucosal hyperperfusion.57,58 This is probably due to a nongenomic mechanism of action that involves a direct membrane effect of ICS on enhancing noradrenergic vasoconstriction by blocking non-neuronal uptake of norepinephrine.59,60

Combination With Long-Acting β agonists

Against the background of greater adverse effects with greater ICS dose in moderate-to-severe asthma, the long-acting β agonists (LABAs) formoterol and salmeterol became available in the early 1990s. LABAs provided an alternative to increasing the ICS dose in patients with persistent symptoms, as their duration of action is up to 12 hours. They are marketed in fixed combination inhalers, such as Advair (fluticasone propionate plus salmeterol) and Symbicort (budesonide plus formoterol). These drugs have a steroid-sparing effect in combination with ICS.60–62 Treatment with ICS plus LABA improves lung function, increases the number of days and nights without symptoms, decreases the frequency of use of rescue medication, and decreases exacerbations at a lower daily dose of ICS. Some studies on the effects of LABAs on the airway suggest that LABAs may enhance the anti-inflammatory effect of ICS and decrease airway inflammation, via both anti-neutrophilic and anti-eosinophilic effect.63,64 However, other studies reported only improved clinical indices of asthma activity, with no change in differential cell counts or mediator levels in bronchoalveolar lavage fluid.65 Whatever the specific role of LABAs is in combination therapy, there is a strong scientific and clinical rationale for their use, at least in adults and adolescents with moderate persistent asthma who remain symptomatic on moderate-to-high doses of ICS, or to avoid increasing the ICS dose above the low-to-moderate range.5–3 LABAs should not be used as monotherapy for asthma, in view of recent con-
cerns about an increased risk of death in some patients treated with LABAs alone.66

Recommendations regarding LABAs as add-on therapy in children, according to the 2007 NAEPP guidelines,2 largely derive from studies of adults. The data from studies of children are scanty.67–69 Most children with persistent asthma have adequate control with an ICS dose equivalent to $\leq 250 \mu g/d$ of fluticasone propionate or HFA-propelled beclomethasone dipropionate, and should not require LABAs. Before prescribing higher-dose ICS or adding another drug, such as a LABA, it is important to ensure that the child has an appropriate ICS inhaler, acceptable inhaler technique, and adequate adherence to previously prescribed ICS. Addition of a leukotriene receptor antagonist is another alternative treatment. Use of the LABA formoterol in combination with an ICS (mometasone) may be a better combination treatment for younger children, and may even be more effective if used as both a controller and rescue medication. This strategy was associated with a decrease in exacerbations in a large prospective trial.67

Summary

All ICSs work at an equipotent dose, and ICSs are the most effective asthma controller medication currently available (see Table 5). However, the ICS dose response plateaus in the low-to-moderate dose range. In addition, about 25–30% of asthmatics require high doses to obtain and maintain control. This subgroup includes smokers, obese individuals, and patients with a preponderance of neutrophilic inflammation. In such patients, even high doses of steroid might not control the persistent symptoms, which leads to consideration of add-on medications such as LABAs, oral steroid, and leukotriene antagonists. LABA is a good add-on, steroid-sparing therapy, especially in patients older than 12 years. Use of LABAs in patients less than 12 years old is controversial, due in large part to a paucity of data. Finally, although more study is needed, several randomized controlled trials suggest that in acute asthma ICS in addition to oral steroid may reduce admission rate and may be a useful adjunct in that venue.

REFERENCES


31. Adams NP, Jones PW. The dose-response characteristics of inhaled corticosteroids when used to treat asthma: an overview of Cochrane systematic reviews. Respir Med 2006;100(8):1297–1306.


36. Adams NP, Jones PW. The dose-response characteristics of inhaled corticosteroids when used to treat asthma: an overview of Cochrane systematic reviews. Respir Med 2006;100(8):1297–1306.


43. Adams NP, Jones PW. The dose-response characteristics of inhaled corticosteroids when used to treat asthma: an overview of Cochrane systematic reviews. Respir Med 2006;100(8):1297–1306.


Discussion

Stoloff:* In the IMPACT [Improving Asthma Control Trial] study,1 the symptom-free days—even with that very strange initiation of therapy with the prednisone and the higher dose of budesonide—the group who received daily low-dose budesonide had 26 more symptom-free days during the study than did the group that used intermittent therapy. When you look at impairment you have to take into account what you’re doing. In all the studies, including the one you presented, the educational event that took place on how to recognize and treat an exacerbation was entirely different than what occurs in the real world of day-to-day practice. And, as we’re all aware, the amount of time until someone recognizes their asthma worsening extends way beyond what we would like. One of our concerns in the NAEPPE guidelines2 was to address that. We stick with certain things because the refill rate on these medicines is so poor anyway; they’re already taking them intermittently.

Kercsmar: Those are great points, and I’m sorry I failed to mention that 26-day difference in symptom-free days. Note also that the patients in the intermittent-therapy group took their inhaled corticosteroids only a half a week out of that year of follow-up. So in the course of a randomized trial the patients were still only taking their medicine a few days a year. I think they only took the inhaled steroid rescue treatment regimen a little over half the time they should have taken it as well. So I agree that the risk in the real world, especially in patients who pay little heed to their symptoms and don’t act soon enough—on an intermittent basis—might be very risky in certain patients.

Sorkness: Yes, there are a lot of lessons from IMPACT. If you entertain as-needed ICS as a possible regimen, it should only be with a patient who’s been taught very well to activate a symptom-based action plan and who will actually do so. The disconnect is that, even if you believe that, some people still fail to initiate ICS when needed. One might consider that reality as justification that all asthmatics need to take ICS regularly. The other way of thinking about it is, “Well, I guess they really didn’t need it that bad.” They made a value judgment that those worsening symptoms were not important enough or serious enough for them to warrant activating an action plan.

Kecsmar: One of our concerns in the IMPACT conclusion was that in certain patients intermittent ICS can be a choice. The fact that people intermittently refill their prescriptions indicates that they make this choice all the time anyway. Maybe not everyone with asthma needs to be treated exactly the same.

Donohue: In adults, particularly in COPD [chronic obstructive pulmonary disease], we’re seeing a signal of pneumonia in patients receiving monotherapy with inhaled steroids, as well as in combination therapy. This was seen in the TORCH [Toward a Revolution in COPD Health] study,1 and although it pales in comparison to the reduction in exacerbations with ICS/LABA, it was also seen in the pivotal studies in Germany, by Kardos et al.2 Do you ever see that? Is there any risk of lower-respiratory-tract infection in asthma with inhaled steroids?

Sorkness: Yes, I believe there’s been a lot of discussion about how best to define and manage exacerbations. But the question of lower-respiratory-tract infection in asthma with inhaled steroids is a critical one.


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Kercsmar: I’m not aware of any pediatric trials that would suggest that. It’s been talked about, but I know of no data that would suggest that.

MacIntyre: Jim, I have trouble with the biologic plausibility of a reduction in exacerbations but an increase in pneumonias. Don’t pneumonias evolve out of exacerbations?

Donohue: That’s correct. This is one of the outcomes of the TORCH trial, where they had exacerbations defined per protocol, whereas pneumonia was simply an investigator checking off an adverse event based on the presence of rales and some deterioration. That’s an illogical construct. However, in TORCH the number of exacerbations (in that study of 6,200 people) that were reduced was 1,500. The number-needed-to-treat was 4. The total number of pneumonias was only in the 100s.

Hogg et al looked at the NETT [National Emphysema Treatment Trial] data. Remember, the people who had stopped smoking in the NETT who had lung resected for emphysema or solitary nodules for cancer, had in the 2-mm airways these inflammatory nodules plus exudate and mucus. And they hypothesized—but it’s just a hypothesis, so I don’t want to go too far with it—that those on inhaled steroids had fewer inflammatory nodules, yet were more likely to die. The death was related to the mucus and the exudate. So they postulated that the loss of a local innate immunity may be important. But I don’t know.

I’d have to say that the good outweighs the bad with ICS, particularly the combination of ICS and LABA. The survival is really dictated by exacerbations rather than pneumonia. The Food and Drug Administration is very concerned about pneumonia, and it was involved in the discussion of why Advair 500/50 was not approved at the hearing in July. There may be a dose-response with this adverse effect; more adverse effect may be seen with the higher dose. This has everybody in the adult COPD world concerned. We don’t know how big an issue it is. So it is semi-illogical, Neil, but that was the construct of the study, and I can’t give you a mechanism why an exacerbation would be different than pneumonia.


Stoloff: In the NAEPP guidelines we gave an evidence grade of D to the use of controller medication in children during the season that they have had exacerbations, just as a seasonal treatment to deal with the September epidemic in children, and in adults as well. So we said may consider—not should consider, but may consider—beginning the use of inhaled corticosteroids prior to the season, maintaining it through the season, and then discontinuing, in a defined population. It’s just put out there for thought.

Kercsmar: It’s an interesting paradigm. I think that it’s a prominent widespread clinical practice, particularly in young wheezy children who really might not have asthma. They may have virally induced wheezing that is not responsive to inhaled corticosteroids. In a population of wheezy infants and toddlers studied by the CARE [Childhood Asthma Research and Education] Network some data indicate that short-course or seasonally inhaled steroid is not that efficacious. It’s expensive medicine and therefore can be a burden on the family, for a minimal effect, so I think D is the evidence grade it deserves.


Enright: Note that FEV₁ [forced expiratory volume in the first second] is easily and accurately measured in the emergency department, even within the first hour of admission. Also note that in an asthmatic adolescent or adult who smokes, if their asthma is poorly controlled, it looks like instead of doubling their corticosteroid dose maybe we ought to be adding a pill, and I suggest that the pill is not Singulair, but Chantix.

Myers: In both the 1997 and 2007 NAEPP guidelines they talked about recommending ICS for persistent asthma, and I think everybody would agree that if the patient goes to the emergency department, that’s a lack of asthma control, yet we seem to have resistance from the emergency department to prescribe inhaled corticosteroids at discharge. They’re very quick to put systemic corticosteroids in their acute asthma exacerbation treatment and then send the patient home with a 5–7 day burst of that steroid, but they’re reluctant to prescribe inhaled corticosteroids. You alluded to studies on that. What’s it going to take to change that mentality?

Kercsmar: There are groups doing that. I think Rita Cydulka’s group (MetroHealth Medical Center, Department of Emergency Medicine, Case Western Reserve University, Cleveland, Ohio) has been trying to link emergency-department care to long-term care providers. The emergency-department group at Cincinnati Children’s Hospital is also launching a program to do that. It’s just not been the purview of emergency-department doctors, but that’s changing.

Stoloff: In the 2007 NAEP guidelines we recommend that emergency department physicians initiate controller medication at the time of discharge for patients who are new or are perceived as having persistent asthma.