

Issues and challenges in pediatric asthma

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Much recent attention has been focused on pediatric asthma, with regard to both epidemiological trends and appropriate treatment (1). With regard to the former, statistics on the rising asthma-associated morbidity and prevalence indicate a disproportionate effect on children. With regard to the latter, recent studies have clearly documented a state of chronic airway inflammation in asthma in its mildest forms and in children. As such, attention to the reduction of inflammation therapeutically is increasing substantially via the introduction of new and improved drugs/delivery methods. However, it is of interest that alarming epidemiological trends are occurring at a time of unprecedented increase in the level of understanding of asthma pathogenesis and the spectrum and number of very effective therapies in the asthma marketplace. This suggests that currently available therapies are not being used effectively. For these therapies to be effective, both education and behavioral modification for both prescribing physicians and patients will be essential (2). With regard to behavioral modification, physicians must modify their prescribing habits, which are often driven by convenience and time constraints, and patients must modify behaviors that lessen their adherence to prescribed therapies.

For certain drug classes a difference exists between “efficacy” and “effectiveness”. For example, a drug that had demonstrated “efficacy” in published controlled clinical trials may have poor “effectiveness” in patients treated in a practice because it tastes unpleasant. Efficacy is established under optimal, controlled conditions. The enrolled patients are healthy (other than the disease under study) and must adhere to therapy during a typical 12-week period. Moreover, they receive extensive teach-

ing about medication use to achieve optimal inhaled drug delivery. In a clinical “real-world” practice where a drug is used for many months or years without close monitoring, many or all of these parameters are often not controlled and patients therefore do not experience the potential benefit of a drug prescription. They often do not understand the risks and benefits of a given drug and how to achieve optimal benefit. It thus behoves clinicians to consider patient-driven factors that gain effectiveness from a drug with established efficacy when they choose daily controller therapy for asthmatics, especially in children (3). These adherence-promoting factors include ease of use and provision of the minimal required level of education about the benefit/risk of the drug.

Guidelines and inhaled corticosteroids

As a consequence of the above information, all national and international guidelines (1, 4) are recommending long-term controller therapy for any form of persistent asthma at virtually any age with inhaled corticosteroids (ICS). Children with mild persistent asthma are included in this recommendation. As such, it is possible and very likely that a very young asthmatic child will be treated with low, medium or even high doses of ICS from infancy through to adulthood. The impact of such long-term treatment has not been delineated across broad populations, with regard to both beneficial effects on the airways, including long-term prevention of remodeling, and systemic adverse effects.

As such, use of ICS gains more widespread acceptance through dissemination of guidelines while modification

of prescribing physician behavior, balancing the safety and efficacy of ICS and other current therapies becomes of paramount importance. ICS are the most well-studied and potent agents for treating asthma. They affect virtually all aspects of the asthma phenotype, including symptoms, inflammation, lower airway function and hyperactivity and hospitalization rates. Despite these immense benefits distinguishing ICS as the “gold standard” in asthma therapy, certain problems with their use are apparent that compromise “effectiveness”. Compliance is low (30–50%), reflecting patient concerns about side-effects and a perceived lack of need for therapy when asymptomatic (5). Achieving adequate drug delivery to the airways using currently available metered dose inhaler/spacer ($\pm$ mask) or dry powder devices can also compromise therapeutic effectiveness of ICS in children. Indeed, even most adults do not use these delivery devices correctly (6).

A step-down approach to ICS treatment has been recommended, involving an initial high ICS dose to gain rapid control followed by regular, gradual stepping-down of the dose to the minimal effective dose over time (1, 4). However, whether or not busy practitioners spending on average 7 min with a patient actually dose-reduce patients on a regular basis is unknown. If they do not, as suspected, a patient may be exposed needlessly to unnecessarily high and potentially harmful ICS doses. Moreover, whether or not the established minimal effective dose for a given patient actually controls both symptoms and inflammation or merely controls symptoms and allows progression of inflammation (7) is unknown. This is, of course, confounded by the low compliance with ICS.

Systemic adverse effects are also possible in association with the routine use of higher ICS doses for longer periods of time in children with milder levels of disease. In that regard, recent studies have shown conclusively that children with mild-moderate asthma who adhere to inhaled beclomethasone treatment (400 mcg/day) for 1 year grow (on average) 1–1.5 cm/year less than control groups (8–12). Effects of some other ICS were evident, but to a lesser degree. As a result, the FDA recently announced class labeling for all intranasal and inhaled corticosteroids regarding the possibility of growth suppression. Most of these studies have been conducted using fixed doses for 1 year with high medication compliance in mild persistent asthmatics. The patent airways of such children may permit a high degree of intrapulmonary deposition (13) of ICS (relative to those in more severe asthmatics), which is the major source of systemic bioavailability and systemic adverse effects. Such growth suppression appears rare in clinical practices, due perhaps to the low compliance with ICS.

The use of ICS in moderate and severe persistent asthma is unquestioned, as benefits far outweigh known risks. Even in these severity categories, however, ICS dose reduction or minimization techniques should be

implemented. These include attention to environment (smoke/allergen reduction), appropriate vaccination (influenza), treatment of concomitant illnesses (gastro-esophageal reflux disease, allergic rhinitis, sinusitis) and maximizing add-on therapies. In contrast, a favorable benefit–risk ratio for ICS is not nearly as well established for mild persistent asthma. Aside from the higher pulmonary deposition in these patients (mentioned above), doses needed to control their inflammation and airway remodeling over the long term have not been well-established. If such doses do suppress growth in children, risk could potentially outweigh benefit, especially considering the availability of potentially effective non-steroid alternatives for this subgroup. Clearly, other agents that fill in some or all of the apparent therapeutic gaps inherent with ICS use are needed.

Leukotriene receptor antagonists

The leukotrienes are very potent mediators of inflammation and clearly play a role in asthma (14). Their production increased during episodes of acute and exercise-induced asthma (15, 16) and reportedly did not decrease during treatment with glucocorticosteroids (17). An important advance in the treatment of pediatric asthma has been the availability of the leukotriene receptor antagonists. Treatment with montelukast (Singulair), a once daily non-steroidal pill with demonstrated efficacy and safety in children (18, 19) alleviate many of the above concerns/limitations with ICS. The efficacy in activity-induced asthma (19) is especially valuable, considering the frequency and unpredictability of exercise in children, as well as the tolerance that develops with daily use of salmeterol, but not montelukast. The development of such tolerance with salmeterol was not prevented by concomitant ICS use or a reduction of the usual salmeterol dose by 50% (2).

Compliance with oral pills is approximately 80% (vs. <50% for inhalers) in patients with asthma (21). Indeed, a recent patient/parent preference/satisfaction study demonstrated superiority of montelukast over cromolyn in asthmatic children with regard to both compliance and parent/patient preference (22). In addition to benefits in clinical asthma control in children, reductions in peripheral blood eosinophil counts were also noted during montelukast therapy (18). The latter finding supports an anti-inflammatory effect of montelukast.

In standard “efficacy” trials, ICS have out-performed montelukast in improving FEV₁ over 12-week treatment periods that controlled factors to achieve optimal performance from ICS (23). However, in open-label 1-year extension trials, where ICS delivery techniques and adherence were not as closely monitored, the two drugs appeared more equally effective. In this circumstance (long-term, uncontrolled trial), a drug with excellent “efficacy” (ICS) had only good “effectiveness”,

and a drug with only good "efficacy" (montelukast) had excellent "effectiveness". Thus, prescribing physicians must consider both efficacy and effectiveness when choosing primary controller therapy for asthmatic patients depending on the severity level.

Based on the above lines of evidence, montelukast has utility in a number of circumstances in pediatric asthma:

- 1) primary therapy as a steroid-alternative in mild persistent asthma;
- 2) add-on therapy to gain more benefit from or dose-reduce inhaled corticosteroids in moderate or severe persistent asthma;
- 3) aspirin-sensitive asthma; and
- 4) exercise-induced asthma.

In addition to clinical trial results, the safety concerns and unknown long-term clinical benefits and risks of ICS primarily drive circumstance 1 in

this very mild, yet persistent, group. In this group of asthmatic children, balancing lung growth versus statural height growth is of paramount importance. Circumstance 2 is driven at least partially by the finding that leukotriene levels were not reduced during therapy with corticosteroids. Since leukotrienes are also mediators of the allergic rhinitis (24) experienced by most children with asthma, montelukast may provide additional benefit by simultaneously treating the upper airway. This may help minimize the dose of corticosteroids administered to both the nose and lungs in a large number of patients with concomitant asthma and allergic rhinitis. The importance of this opportunity is highlighted by the fact that such combined use of nasally and orally inhaled corticosteroids has not been previously studied for effects on growth in children. This unique drug represents an important advance for the treatment of children with asthma.

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