

Long-term effects of asthma medications in children

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Purpose of review

This review describes recent studies in children that evaluated long-term outcomes of controller asthma medications.

Recent findings

The literature is replete with studies demonstrating the immediate profound effects of inhaled corticosteroids on symptom control, reduction in morbidity and mortality rates, improvement in lung function, bronchial hyperresponsiveness, and inflammatory markers. Recent evidence supports that even this most effective class of medication does not alter the progression of recurrent wheeze to asthma, and that its effects on decline in lung function are limited. The lack of evidence supporting the superiority of lower dose inhaled corticosteroids combined with a long-acting β -agonist over a full dose inhaled corticosteroid with respect to long-term efficacy measures and growth effects suggests that monotherapy with acceptable inhaled corticosteroid dose is the preferred treatment in children with mild to moderate persistent asthma. Montelukast has been shown to significantly reduce asthma exacerbations and lower use of supplemental inhaled corticosteroids compared with placebo.

Summary

There is mounting evidence that the currently available medications for childhood asthma have a substantial impact on multiple dimensions of asthma control. No drug in our current armamentarium, however, has been found to alter the natural progression of childhood asthma nor halt progressive airway damage in the more susceptible children.

Keywords

asthma, inhaled corticosteroids, long acting β -agonists, montelukast, pulmonary function tests

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Introduction

Historically, according to the clinical guidelines in the National Heart Lung Blood Institute's (NHLBI) National Asthma Education and Prevention Program's (NAEPP) Expert Panel Report [1] and the Global Initiative for Asthma [2], a stepwise approach in the management of asthma is based primarily on the assessment of the patient's recent symptom frequency and intensity, and functional limitation (i.e. nighttime awakenings, need for short acting β -agonists for quick relief, work/school days missed, ability to engage in normal or desired activities, and quality of life assessments). For school-age children and youths, measurement of airflow compromise is an added tool. While the basis for initiation of medications is measured against these parameters, the ultimate goals of therapy include reducing the symptom burden and use of rescue medications, improving quality of life, and more importantly, maintaining 'normal' lung function and preventing exacerbations with minimal or no medication adverse effects. Most of these goals may be considered short term and easier to monitor, but long-term effects of therapy, which include reducing exacerbations,

preventing deterioration in lung function over time and airway remodeling, inducing remission or preventing the development of asthma in high-risk population, are more difficult to study and evaluate. These are the essential goals that motivate patients and families, if indeed interventions can alter the natural history of their disease.

In the last 1–2 years, there have been a few important studies that have addressed the long-term outcomes of current available medications in the pediatric age group: regular and as needed use of inhaled corticosteroids (ICSs), long-acting β -agonists (LABAs), and leukotriene receptor antagonist (LTRA). The appropriate age for intervention and mechanisms by which these medications affect children long term remain very important questions in the management of childhood asthma that this review attempts to answer.

Inhaled corticosteroids

The Childhood Asthma Management Program remains the longest, randomized, placebo-controlled clinical trial in pediatric asthma ever published. It compared

long-term effects of ICS therapy and nedocromil to placebo [3]. Consistent with numerous other studies demonstrating superiority of ICS therapy over placebo for persistent asthma, better symptom improvement, lower rescue β -agonist use, and lower bronchial hyper-responsiveness were seen in the budesonide-treated group. Long-term effects relating to reduction of exacerbations favoring not only the ICS but also nedocromil over placebo were also found. Specifically, compared with placebo, children treated with an ICS over 4–6 years had fewer hospital admissions, urgent care visits, and prednisone courses. Nedocromil-treated children, compared with placebo, had significantly reduced urgent care visits and courses of prednisone. Children who were in the budesonide group had a significantly smaller decline in the forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) ratio (0.2% versus 1.8%) compared with the placebo-treated group. There was, however, no significant difference between both treatment and placebo in the primary outcome: the degree of change in the postbronchodilator FEV_1 expressed as a percentage of the predicted value. Another important observation was that measurements of asthma control and bronchial hyperresponsiveness in the budesonide-treated group were similar to the placebo group upon discontinuation of treatment during the washout period, indicating that sustained effects of low-dose ICSs were not found. Although still speculative, the effects of long-term ICS or nedocromil therapy on inducing remission may be unlikely.

In a separate publication from the Childhood Asthma Management Program (CAMP) study [4^{••}], the effects of mild to moderate asthma on lung growth were evaluated. Sex and age-specific lung function measurements of the 1041 children enrolled in the CAMP study were compared with those of 5415 children without asthma involved in the Harvard Six Cities Study using repeated-measures multiple linear regression models. The FEV_1 /FVC ratio was significantly lower for both boys and girls with asthma compared with those without asthma ($P < 0.001$), with corresponding increases for children with asthma in FVC ($P < 0.001$). Boys with asthma had lower FEV_1 compared with boys without asthma ($P < 0.001$), and this difference was not found for girls with or without asthma. There was no difference in the patterns of lung growth for children with asthma treated for 4.3 years with budesonide or nedocromil and placebo during the CAMP trial. Therefore, from this longest placebo-controlled pediatric asthma clinical trial to date, the long-term effects of ICS therapy on patterns of lung growth are not remarkable.

It is possible that the effects of asthma on lung function could be modified by early intervention. A large, international, long-term randomized placebo-controlled study

(inhaled Steroid Treatment As Regular Therapy in early asthma – START) was undertaken to evaluate whether intervention with a low-dose ICS for 3 years in patients with less than 2 years of mild persistent asthma would prevent severe asthma-related events (SAREs) and accelerated decline in lung function. From an earlier publication, patients on active drugs had fewer asthma exacerbations, less courses of systemic corticosteroids and more symptom-free days than did those on placebo [5]. A separate paper focusing on children aged 5–10 years was published more recently [6[•]]. Data from 1000 children in the budesonide (200 μ g daily Turbuhaler; AstraZeneca) group compared with 974 in the placebo group showed a significant increase in the time to first SARE and a 40% reduction in the risk of SARE over the 3 years (hazard ratio 0.60, 95% confidence interval 0.40–0.90, $P = 0.012$). Children receiving budesonide also needed less intervention with other ICSs (12.3% versus 22.5% over 3 years; $P < 0.01$). Treatment effect was evident in that smaller mean declines from baseline for postbronchodilator $FEV_1\%$ predicted were found between the budesonide and placebo groups after 1 year (–0.78 versus –1.84%, respectively) and after 3 years (–1.84 versus –2.31%, respectively). Despite low-dose ICS, a deterioration in postbronchodilator $FEV_1\%$ predicted over time occurred [6[•]] and this was found in the other age groups (11–17 years and 18–66 years) as well, with the smallest decline apparent in adolescents [7]. These observations suggest that low-dose ICS therapy can improve asthma control and reduce risk of exacerbations long term, but there may be components of the disease that are not targeted by these medications (nor the dose used) which manifest as progressive deterioration in lung function.

Can early intervention before an asthma diagnosis is made alter the natural course? Three important reports were published in 2006 that sought to determine if treatment with an ICS therapy soon after the onset of early indicators of the disease would modify the course of asthma [8^{••}, 9[•], 10^{••}].

In the Prevention of Early Asthma in Kids (PEAK) study from the Childhood Asthma Research and Education (CARE) network sponsored by the NHLBI [8^{••}], approximately 300 children 2–3 years old at entry and at risk for persistent asthma, as determined by a positive modified Asthma Predictive Index, received either fluticasone propionate 88 μ g via pressurized metered dose inhaler (pMDI) or matching placebo twice daily for 2 years. The primary outcome was the proportion of episode-free days during the third year observation period. The study showed no difference in the proportion of children with active wheezing between the two treatment groups during the third year observation period, after study medications were discontinued. In addition, no difference in lung

function using impulse oscillometry was shown. While on treatment with an ICS for 2 years compared with placebo, however, improvement in symptom control and fewer asthma exacerbations were demonstrated. A reduction in growth velocity was observed in the ICS-treated group during the first 8 months (6.6 ± 1.0 versus 7.3 ± 1.0 cm/year between 1 and 8 months, $P = 0.005$) and a difference in the mean increase in height (4.5 ± 1.1 versus 4.9 ± 1.1 cm between 4 and 12 months, $P = 0.001$). During the last 12 months of the treatment phase, the growth velocity was similar between the study groups, and during the observation year, the growth velocity in the ICS group was greater than that in the placebo group (7.0 ± 0.8 versus 6.4 ± 0.9 cm/year, $P = 0.001$).

Another study (Inhaled Fluticasone propionate in Wheezy Infants – IFWIN) [9[•]] evaluated whether early institution of ICS therapy in infants with wheezing could prevent active asthma and loss of lung function later in childhood. A total of 200 children from a birth cohort (mean age of 1.2 years at entry) with two documented episodes of wheeze or one prolonged episode of more than 1 month duration and a parental history of atopy were randomized to receive fluticasone propionate 100 µg or matching placebo twice daily. The study cohort was followed until age 5 years, at which time, lung function and airway reactivity were assessed. The investigators found no difference in the proportion of children with current wheeze, physician-diagnosed asthma, use of supplemental open-label ICS (fluticasone 100 µg twice daily), number of exacerbations, lung function, and airway reactivity at age 5 years in children treated with an ICS compared with those treated with placebo. They also reported transient reduction in growth velocity in children who received active treatment, particularly after 6–12 months.

The third study (Prevention of Asthma in Childhood – PAC) [10^{••}] evaluated if early intervention using intermittent administration of an ICS, when initiated at the first episode of wheezing and during subsequent episodes, could alter the development of asthma. Of 411 infants born to mothers with asthma enrolled at 1 month of age, approximately 300 children received at least one 14-day course of budesonide 400 µg/day or matching placebo administered via pMDI and holding chamber (mean age at the first course of study medication was 10.7 months). For every acute illness, children were to start either treatment after 3 days of wheezing. Upon completion of this 3-year study, a similar percentage of symptom-free days between treatment groups (83% versus 82% for the budesonide and placebo groups, respectively) was found. Furthermore, there was no difference in the percentage of children with persistent wheezing (24% versus 21%, respectively) at the end of treatment. In addition, the mean duration of each acute wheezing

episode was not reduced by budesonide therapy. There was also no difference in height between the groups. Thus, intermittent ICS failed to either alter the natural history of asthma in infants at risk for asthma or reduce the duration of the acute wheezing episodes.

These three studies differed in subject entry criteria, frequency of past wheezing episodes, and mode and duration of treatment; yet they all demonstrated that early intervention with ICS therapy in preschool children with recurrent wheezing does not alter the natural history of asthma. ICS can be indicated to improve asthma control but should not be intended at preventing the development of asthma, even for high-risk children.

Long-acting beta agonists

Primarily indicated as an add-on therapy for children with moderate persistent asthma and for children whose asthma remains uncontrolled on low-dose ICS therapy, the long-term effects of long-acting β -agonists in children are still not quite established. The recent Pediatric Asthma Controller Trial (PACT) also from the NHLBI-funded CARE network compared three controller regimens in mild to moderate persistent childhood asthma administered for 48 weeks. A total of 285 children (aged 6–14) were randomized into one of three double-blind 48-week treatments: fluticasone 100 µg twice daily, fluticasone 100 µg/salmeterol 50 µg in the morning and salmeterol 50 µg in the evening (PACT combination) and montelukast 5 mg in the evening [11^{••}]. During the 48 weeks of the study, the percentage of asthma control days averaged 64.2% for fluticasone monotherapy, 59.6% for the PACT combination and 52.5% for the montelukast monotherapy. Both fluticasone monotherapy and PACT combination achieved greater improvements in asthma control days than montelukast but PACT combination was not as effective as fluticasone monotherapy with respect to improvement in number of asthma control days, time to prednisone burst and time to treatment failure. There was no significant difference between fluticasone monotherapy and PACT combination in regard to Asthma Control Questionnaire (ACQ) score improvement. The unadjusted and intent to treat mean increase in height from baseline over 48 weeks was 5.3 ± 1.8 cm with fluticasone, 5.3 ± 1.5 cm with PACT combination, and 5.7 ± 2.0 cm with montelukast. Therefore, the greater beneficial effects with fluticasone monotherapy compared with PACT combination and the lack of any differences in growth effects between these two controller regimens despite a lower dose ICS in the PACT combination do not support the use of this particular combination regimen as an ICS-sparing strategy in children.

Leukotriene receptor antagonists

Recent studies have been done in the past 5 years to evaluate the long-term effects of a leukotriene receptor antagonist (continuous [12,13] and intermittent [14]), with respect to occurrence of exacerbations. The Montelukast Study of Asthma in Children, a 12-month, randomized, double-blind, multicenter trial, was designed as a 1-year noninferiority trial with the primary endpoint defined as rescue-free days (RFDs) [12]. For montelukast to be considered inferior, there had to be more than 7% difference in RFDs following treatment with montelukast versus fluticasone propionate. Almost 1000 children with mild persistent asthma were randomized to receive treatment with either fluticasone propionate 100 µg twice daily or montelukast. Treatment with fluticasone propionate resulted in an increased percentage of RFDs from 64% to 86.7%, while percentage RFDs following montelukast increased from 64% to 84%. This represented a difference in RFDs of only 2.8% in favor of fluticasone propionate. Secondary endpoints including change in FEV₁, days requiring β-agonist use, quality of life and patients requiring systemic corticosteroids for acute worsening all favored treatment with fluticasone propionate.

In a 12-month, double-blind, parallel study which was designed to investigate the role of montelukast in the prevention of viral induced asthma exacerbations in children aged 2–5 years with a history of intermittent asthma symptoms [13], patients were randomized to receive daily oral montelukast 4 or 5 mg (by age) ($n=278$) or placebo ($n=271$) for 12 months. During the trial, montelukast significantly reduced the rate of asthma exacerbations by 31.9% compared with placebo. Montelukast delayed the median time to first exacerbation by approximately 2 months and the rate of ICS courses compared with placebo.

A randomized, double-blind, placebo-controlled study was performed on 200 children aged 2–14 years with intermittent asthma also over a 12-month period, using either intermittent montelukast or placebo at the onset of asthma or upper respiratory tract infection symptoms for a minimum of 7 days [14]. The montelukast group had 163 unscheduled healthcare resource utilizations for asthma compared with 228 in the placebo group (odds ratio 0.65, 95% confidence interval 0.47–0.89). There was a nonsignificant reduction in specialist attendances and hospitalizations, duration of episode, and β-agonist and prednisolone use.

These studies suggest that intermittent or persistent therapy with montelukast for children with intermittent asthma symptoms is effective in reducing risk of exacerbations compared with placebo, and its regular use is comparable to ICS therapy in regard to symptom control.

Conclusion

Childhood asthma is a complex, heterogeneous chronic disease with a variable course. There are numerous significant endpoints used in clinical trials that determine successful response to therapy. For a substantial majority of children with asthma, the greatest risk is having severe exacerbations, and not so much the prospect of a progressive disease, unlike that seen in other chronic diseases such as hypertension and diabetes. Fortunately, our current pharmacotherapeutic interventions for asthma are able to reduce this risk of severe or frequent exacerbations. No therapy, however, is yet able to alter the natural progression of the disease, such as preventing the development of persistent asthma and inducing remission, nor to prevent significant airway damage in the few susceptible cases. Anti-immunoglobulin E is now recommended as an adjunct therapy for older children and adults with severe persistent allergic asthma (step 5 and 6) [1]. This treatment, however, is still not indicated for children under 12 years of age. Hence, the long-term effects in the younger pediatric group with airways that are probably more vulnerable to damage and repair remain to be seen. Future studies in immunologic and cellular markers for airway inflammation may hold the answer for individualized patient care and targeted therapy to prevent the complications of asthma and its resultant lung damage.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 210).

- 1 National Asthma Education and Prevention Program: Expert Panel Report 3 (EPR 3). Guidelines for the diagnosis and management of asthma 08-4051; 2007.
- 2 Global Initiative for Asthma: GINA report. Global strategy for asthma management and prevention; 2006.
- 3 Long-term effects of budesonide or nedocromil in children with asthma. The Childhood Asthma Management Program Research Group. *N Engl J Med* 2000; 343:1054–1063.
- 4 Strunk RC, Weiss ST, Yates KP, *et al.*, for the CAMP Research Group. Mild to moderate asthma affects lung growth in children and adolescents. *J Allergy Clin Immunol* 2006; 118:1040–1047.
- The CAMP cohort represents the longest and largest study in children with asthma. Results derived from this sentinel study provide important evidence for therapeutic management and its long-term effects on children with asthma.
- 5 Pauwels RA, Pedersen S, Busse WW, *et al.*, START Investigators Group. Early intervention with budesonide in mild persistent asthma: a randomized, double blind trial. *Lancet* 2003; 361:1071–1076.
- 6 Chen YZ, Busse WW, Pedersen S, *et al.* Early intervention of recent onset mild persistent asthma in children aged under 11 yrs: the Steroid Treatment As Regular Therapy in early asthma (START) trial. *Pediatr Allergy Immunol* 2006; 17 (Suppl 17):7–13.
- This is a well written study that investigates the role of early intervention with ICSs in children younger than 11 years old.
- 7 O'Byrne PM, Pedersen S, Busse WW, *et al.* Effects of early intervention with inhaled budesonide on lung function in newly diagnosed asthma. *Chest* 2006; 129:1478–1485.

- 8** Guilbert T, Morgan W, Zeiger R, *et al.* Long-term inhaled corticosteroids in preschool children at risk for asthma. *N Engl J Med* 2006; 354:1985–1997.

This is a well written, well designed study that provides crucial evidence of the lack of efficacy of ICSs in young children in altering the progression to persistent asthma.

- 9** Murray C, Woodcock A, Langley S, *et al.*, for the IFWIN Study Team. Secondary prevention of asthma by the use of Inhaled Fluticasone propionate in Wheezy Infants (IFWIN). *Lancet* 2006; 368:754–762.

This study provides additional evidence for the efficacy of ICSs in very young children who may develop asthma later in life.

- 10** Bisgaard H, Hermansen M, Loland L, *et al.* Intermittent inhaled corticosteroids in infants with episodic wheezing. *N Engl J Med* 2006; 354:1998–2005.

This study corroborates previous studies on early intervention using ICSs. This study looks at ICSs delivered intermittently.

- 11** Sorkness C, Lemanske R, Mauger D, *et al.*, for the Childhood Asthma Research and Education Network of the National Heart, Lung and Blood Institute. Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: the Pediatric Asthma Controller Trial. *J Allergy Clin Immunol* 2007; 119:64–72.

This is a unique well designed study that compares the three major medications used in childhood asthma: ICSs, LABAs and montelukast.

- 12** Garcia Garcia L, Wahn U, Gilles L, *et al.* 6 to 14 year old patients with mild asthma: the MOSAIC Study. *Pediatrics* 2005; 116:360–369.

- 13** Bisgaard H, Zielen S, Garcia Garcia L, *et al.* Montelukast reduces asthma exacerbations in 2 to 5 year-old children with intermittent asthma. *Am J Respir Crit Care Med* 2005; 171:315–322.

- 14** Robertson C, Price D, Henry R, *et al.* Short-course montelukast for intermittent asthma in children. *Am J Respir Crit Care Med* 2007; 175:323–329.