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Pediatric Asthma Controller Therapy

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Contents

Abstract

The treatment of children with asthma has historically relied upon expert opinion using data extrapolated from adult studies. Over the past few years, landmark studies have been completed providing healthcare professionals with evidence on which a reasonable approach can be made for children suffering from this common and serious disease. Asthmatic phenotype in children, unlike adults, tends to differ according to age, which must be taken into account as well as triggers, severity, and level of control. The care of the child with asthma is complex, but accumulating data have demonstrated that we are on the right path for optimizing control while reducing the burden of side effects.

The newest Global Initiative for Asthma (GINA) guidelines, as well as recent updates from the landmark CAMP (Childhood Asthma Management Program) study and information from the PACT (Pediatric Asthma Control Trial) and budesonide/formoterol controller and reliever studies, along with recent comparisons of higher dose inhaled corticosteroids (ICS), and ICS/long-acting β_2-adrenoceptor agonist (LABA) combination and leukotriene receptor antagonist (LTRA) therapies in children have clarified a few of the big questions in pediatric asthma. For children with asthma aged 5 years and older, the CAMP trial demonstrated that regular use of ICS reduces the frequency of symptoms; however, height was adversely affected and there is no evidence for altering the natural history of asthma. In patients aged 6 years and over whose asthma is uncontrolled on ICS alone, combination therapy with ICS and a LABA has been recently compared with the use of higher dose ICS and the addition of an LTRA in pediatric patients. The addition of a LABA statistically will be of most benefit; however, some children will have optimal control with doubling the baseline dose of ICS or addition of an LTRA. Use of budesonide/formoterol as a controller and reliever therapy extends the time to first exacerbation versus contemporary use of this medication in patients aged 4 years and older. Ciclesonide, a newer ICS, has demonstrated acceptable efficacy but has the added benefit of not affecting growth. Certainly, with mounting evidence, the care-map in pediatric asthma control is becoming clearer.

Initially thought to be primarily a disease of bronchospasm, scientific and clinical research on asthma has demonstrated that inflammation is a predominant factor, and treatment of asthma has shifted accordingly. Historically, patients with asthma were treated in a step-wise fashion according to the severity of illness. This approach ignored the ongoing fluctuations in asthma

symptoms depending on environmental changes, respiratory infections, and various other factors. Therefore, there has been a paradigm shift towards assessment of control as opposed to severity.

In terms of childhood asthma, pediatricians have long asserted that children are not small adults; however, pediatric asthma care has mainly been modeled on adult experience and investigations. Recently, primary pediatric studies have been completed that have allowed more appropriate care for young asthmatics. Like adults, inflammatory control is at the core of pediatric asthma care, but long-term follow-up has not uniformly demonstrated that the beneficial effects of inhaled corticosteroids (ICS) continue after treatment is finished and adherence is limited by concerns regarding the long-term safety of ICS.

More recent data have emphasized that while regular use of certain ICS in children have an effect on growth, poor control is always a worse scenario for patients in the short- and long-term. Newer strategies, including using additional non-ICS controllers as well as newer ICS without growth effects will extend the benefits of long-term asthma control while diminishing the unwanted effects of treatments. This review examines recent developments in controller therapies for pediatric asthma. The original literature search was performed on 3 June 2010, using PubMed with the search terms 'Pediatric' AND 'Asthma' AND 'Controller' with no limits, with an updated search on 4 October 2010 using the same search terms with 92 results. Relevant articles were chosen by the author. Additional references were specifically searched for by the author.

1. The Global Initiative for Asthma

In 1993, the Global Initiative for Asthma (GINA; www.ginasthma.org) was developed to network various organizations in terms of the care of asthmatic patients and incorporating results of research into asthma care using continuous review of published scientific investigations. The first comprehensive workshop report was published in 1995.[1] The 2005 report heralded a major change in that the philosophy driving asthma care was radically changed. Historically, asthma patients were classified into disease severity groups based on symptoms and objective measures at diagnosis (table I).[3] Patients with persistent and severe asthma would be given more intense treatment. While this initial division may be helpful in the initial assessment of a patient, it did not address the fact that asthma patients tend to have cyclical severity. The 2005 guidelines suggested that, after initial severity assessment, ongoing care should include continual assessment of the patient's asthma control in terms of real-life activities. This approach uses a cycle of detailed assessment and intervention to achieve and maintain asthma control. Symptoms during day-time activities, symptoms at night, frequency and severity of exacerbations, as well as days missed of work or at school are part of the detailed history to determine if the patient is well controlled. Quantification of use of rescue medication as well as objective lung function is also recorded. Using this information, patients can be stratified into groups depending on whether they are controlled, partly controlled or uncontrolled (see table II). The level of control at the time of the routine follow-up visit would determine if a change in controller therapy is required. The 2005 guidelines enforced the need for complete control of asthma for all patients and that the relationship between the medical expert and the patient/family is the key to success. Self-recognition of difficulty with asthma control and then initial management changes in the home are emphasized. The 2008 update[4] is similar but includes single-inhaler combination and rescue therapy using budesonide/formoterol.

2. Inhaled Corticosteroid Therapy (ICS)

2.1 Efficacy

GINA recognizes that the regular long-term use of inhaled corticosteroids (ICS) is the cornerstone of pediatric asthma care. The CAMP (Childhood Asthma Management Program) study, a double-blind, placebo-controlled trial that randomized

Table I. Asthma severity at initial visit; information from Global Initiative for Asthma (GINA) guidelines[2]

Disease severity group	Symptoms and objective measures at diagnosis		
	symptom frequency	exacerbations	nocturnal symptoms
Intermittent	<1 per week	Brief	≤2 per month
Mild persistent	>1 per week <1 per day	May affect activity and sleep	>2 per month
Moderate persistent	Daily	May affect activity and sleep	>1 per week
Severe persistent	Daily	Frequent	Frequent

Table II. Asthma control criteria; information from Global Initiative for Asthma (GINA) guidelines[2]

Characteristic	Level of control		
	controlled (all present)	partly controlled (any of the below present in any week)	uncontrolled
Daytime symptoms	≤2 per week	≥2 per week	Three or more features of partly controlled asthma present in any week
Activity limitation	None	Any	
Nocturnal awakening	None	None	
Reliever use	≤2 per week	≥2 per week	
PEF or FEV_1	Normal	<80% predicted or personal best	
Exacerbations	None	≥1 per year	One in a week

FEV_1 = forced expiratory volume in 1 second; **PEF** = peak expiratory flow.

1041 children 5–12 years of age to receive budesonide 200 μg twice daily, nedocromil 8 mg twice daily or placebo for 4–6 years was the first to prove that inflammation control improved asthma control in children.[5] While the group treated with nedocromil had a significant reduction in urgent care visits and courses of prednisone versus the placebo group, the number of hospitalizations and methacholine response were no different between these groups. The group treated with budesonide had fewer hospitalizations, urgent care visits, and courses of systemic corticosteroids, a reduction of β_2-adrenoceptor agonist (β_2-agonist) use, and lower airway responsiveness to methacholine compared with the placebo group. The CAMP study established the efficacy of ICS therapy in children.

2.2 Safety of Long-Term ICS Therapy

Height was followed closely during the CAMP study (see section 2.1) and, at the end of the study, treatment with budesonide caused a small but statistically significant decrease of 1.1 cm in height compared with the placebo group. There was an initial decrease in growth velocity which normalized during the study, but the height difference remained evident at the end of the trial. Initial conclusions were that, in keeping with data from Agertoft and Pederson,[6] children would reach their targeted adult height, but to date a large, placebo-controlled study of ICS in children and final adult height has yet to be published. As the CAMP participants age, further data have been accrued. Two follow-up studies were conducted using the CAMP cohort to further evaluate the long-term safety profile of budesonide.

As a post-trial investigation in 2009, Strunk et al.[7] published results after following the CAMP study partipicants for 9 years post-randomization. The improved measures of asthma control during the trial did not continue after cessation of ICS therapy. In terms of lung function, there was no improvement in any parameter at the end of the post-trial follow-up in the treatment group compared with the placebo group. At the same time, a great decline in both the number of oral corticosteroid courses and urgent care visits was noted in all patients as they aged from a mean of 8.9–18.1 years, evidence of a decrease in the incidence in exacerbations over time in the group. In terms of growth, there remained a 0.9 cm difference between those who received ICS during the CAMP study versus those who did not. Of interest, after separation of the data in terms of sex, height was more affected in girls (1.7 cm) than boys (0.3 cm).

The CAMP study also followed longitudinal bone mineral density. In 2008, Kelly et al.[8] reported that in the CAMP participants, multiple bursts of systemic corticosteroids for asthma exacerbations created a dosage-dependent risk for decreased bone mineral accretion and increased the risk for osteopenia in boys, while the use of ICS over a mean of 7 years reduced bone mineral accretion, but did not increase the risk of osteopenia. These investigators suggested that the risk of reduced bone mineral accretion during long-term ICS therapy is less than the effect of multiple oral corticosteroid bursts that would be needed in uncontrolled asthma or asthma controlled less effectively with a mast-cell stabilizer. Overall, it would seem that children who are in need of multiple courses of oral corticosteroid therapy would benefit from long-term ICS to decrease the frequency of exacerbations. Children on long-term ICS therapy should be continually reassessed as they age, as the incidence of exacerbations in the group lessens over time.

The question regarding final adult height and ICS has not yet been answered with conviction. While the Agertoft and Pederson[6] study in the year 2000 prospectively followed children using inhaled budesonide 400 μg daily for a mean of 9.2 years, and demonstrated that participants on ICS met expected adult final height, the study had a major flaw. There were only 18 patients in the placebo group and 142 in the budesonide group who reached adult height. Hence, the comparison was with expected adult height instead of the placebo

control group, with which no definitive conclusions could be drawn. It would seem that until the CAMP participants reach adult age, this question will remain unanswered.

3. Other Treatment Options

3.1 Montelukast

While the regular long-term use of certain ICS compounds may affect growth of patients and bone mineral accretion (see section 2.2), refraining from the use of controller therapy carries the risk of uncontrolled asthma. There has been much investment into non-steroidal controller agents or medications that can reduce the amount of corticosteroid used.

Leukotrienes are potent bronchoconstrictors and mediators of inflammation. The PACT (Pediatric Asthma Control Trial) was a randomized, placebo-controlled trial in children with mild to moderate persistent asthma comparing three controller regimens: inhaled fluticasone propionate monotherapy, oral montelukast monotherapy, and a novel therapy using inhaled fluticasone propionate/salmeterol combination in the morning and inhaled salmeterol in the evening (PACT combination).[9] In terms of the primary outcome, days with good asthma control, both fluticasone alone and the PACT combination were significantly more effective than montelukast alone. There was no statistically significant difference in growth velocity among the three groups. Montelukast remains a reasonable choice as a controller therapy in mild asthma, but clearly the beneficial effects are less when compared with fluticasone propionate. The addition of a long-acting β_2-adrenoceptor agonist (LABA) to fluticasone propionate did not improve asthma control in the PACT; however, the method of LABA use in the PACT was quite unconventional and likely should not be used to determine the efficacy of LABA therapy in children.

Montelukast may have another role in pediatric asthma. As an add-on therapy to ICS in children, montelukast has been shown to provide asthma control equal to that of doubling the baseline dose of ICS; however, there is a higher exacerbation risk.[10] A systematic review of 13 randomized controlled trials involving adolescents and adults, including seven studies that compared montelukast/ICS versus ICS monotherapy, was published by Joos et al.[11] in 2008. The authors determined that the addition of montelukast as an add-on to ICS increased asthma-free days and decreased nocturnal awakenings and exacerbation events versus ICS alone.[11] Therefore, montelukast remains a reasonable add-on therapy to ICS or ICS-LABA combination therapy in patients who are not well controlled on ICS alone.

3.2 Long-Acting β_2-Agonist Therapy in Combination Format

Combination inhaled therapy comprises a mixture of ICS and a LABA and has been studied well in asthma patients aged 12 years and older. In the FACET (Formoterol and Corticosteroids Establishing Therapy) trial, the addition of formoterol to ICS therapy significantly reduced the estimated yearly rate of exacerbations and mean symptom score at night and during the day, and increased forced expiratory volume in 1 second (FEV_1). In this study, the benefit of the addition of formoterol to budesonide was present irrespective of the budesonide dose.[12] The GOAL (Gaining Optimal Asthma controL) trial demonstrated that the addition of salmeterol to ICS therapy in patients aged 12 years and older significantly decreased the mean annual rates of exacerbations requiring oral corticosteroids (OCS) and/or hospitalizations or emergency visits versus fluticasone propionate while improving asthma control.[13]

In children, there is less evidence. Recently, de Blic et al.[14] compared fluticasone 100 μg/salmeterol 50 μg fixed combination dosing given twice daily versus fluticasone 200 μg twice daily in a randomized non-inferiority trial, and reported equal efficacy with respect to individual clinical outcomes and overall asthma control in asthmatic children aged 4–11 years previously uncontrolled on low doses of ICS. While both salmeterol and formoterol (both LABAs presently available in combination with ICS) have been shown to be effective and have equal bronchodilatory capacity, formoterol has a much faster onset of action, equal to that of salbutamol.[15] This attribute has been exploited in terms of single inhaler use of budesonide/formoterol. In 2005, O'Byrne et al.[16] studied 2760 patients, aged 4–80 years, divided into three treatment groups in a randomized, double-blind, parallel group study. The first group used a double-dose of daily budesonide (400 μg twice daily) with terbutaline 0.5 mg as a reliever medication, while the second group used budesonide/formoterol twice daily (100 μg/6 μg) with terbutaline 0.5 mg as reliever medication as needed. The final group used budesonide/formoterol (100 μg/6 μg), one inhalation twice a day, as well as the budesonide/formoterol combination, one inhalation as needed, as a reliever medication; this was the combination therapy maintenance and reliever group. In this group, the maximum number of doses of the combination therapy was 10 inhalations per day for adults.[16] Children aged 4–11 years were enrolled in the study in a ratio of 1 : 8 adults and were given half of the adult daily maintenance dose in all groups. The maintenance and reliever pediatric group were allowed to use budesonide/formoterol up until a maximum of seven as-needed doses in 24 hours. The main outcome was severe asthma exacerbations, which were

hospitalizations, emergency room treatments, oral corticosteroid use or an increase in second ICS inhaler and/or a peak expiratory flow 70% or lower from baseline on 2 subsequent days. Using budesonide/formoterol for maintenance and symptom relief significantly increased the time to first exacerbation and reduced the risk of experiencing an exacerbation versus the other two groups.

Subsequent analysis of the pediatric patients in this study was published in 2006.[17] Of the 341 pediatric patients, 26% of the patients in the budesonide 200 μg/day group and 38% of the patients in the budesonide/formoterol 100 μg/6 μg/day fixed-dose group had an exacerbation, compared with only 14% of those in the single-inhaler maintenance and reliever therapy group, a significant difference. Exacerbations requiring medical intervention occurred in 8% of the single inhaler for maintenance and relief group versus 31% in the fixed-dose combination group and 20% in the fixed high-dose budesonide group. Both differences were statistically significant.

An interesting point of the above study and sub-analysis is the number of asthma control days. An asthma control day in the original study was defined as a day and night without symptoms or use of rescue medication. In the original study group of adults and children, as well as in the pediatric sub-analysis, using budesonide/formoterol as maintenance and relief significantly increased the percent of asthma control days versus fixed high-dose budesonide, but not versus fixed-dose combination therapy. In terms of side effects in the pediatric sub-population, children taking the combination therapy either as maintenance and reliever or just maintenance were at least 0.9 cm taller than those on fixed high-dose budesonide. For children whose asthma is uncontrolled on conventional therapy, the use of budesonide/formoterol for maintenance and relief will statistically provide the best defense against an exacerbation. There are some concerns with the study. Namely, the use of combination therapy as maintenance, while reducing exacerbation risk, did not actually improve control. Second, the maintenance dose of budesonide/formoterol in children was 100 μg/6 μg once daily, a dosing regimen for which there is little evidence. The following question is valid: why then are not all children on inhaled combination therapy?

There are two main responses to this question. In terms of safety, Cates et al.[18,19] published two meta-analyses of the safety data on formoterol and salmeterol used in the control of asthma in all patients, regardless of age. With respect to long-term use of salmeterol, there is a risk of serious asthma-related adverse events similar to regular use of short-acting β_2-agonist therapy when compared with placebo. Additionally, the use of salmeterol without concurrent ICS was associated with a risk of asthma-related death. Formoterol long-term use also carries a risk of asthma-related adverse events similar to regular use of short-acting β-agonists. There is no evidence of asthma-related death with formoterol long-term use in asthma. More recently, Cates et al.[20] reviewed published safety data on LABA-ICS combination therapy. In terms of formoterol-budesonide, after reviewing 14 adult and 7 pediatric studies, the group could not confirm that the addition of formoterol to regular ICS carries no risk of increasing mortality in comparison with ICS alone. There was no conclusive evidence of harm. Although there were more serious adverse events with the formoterol-ICS combination in children compared with ICS alone, the difference was not big enough to rule out a chance finding. In reviewing the pediatric studies, the authors submit that it is impossible to tell with certainty if the addition of ICS to formoterol abolishes the risk of adverse events.[20] In terms of salmeterol-fluticasone, serious adverse events were not significantly increased in adults or children when regular salmeterol was added to ICS as randomized treatment, but the results are too imprecise to conclude that there is no increased risk.[21]

At this time, it is prudent to use ICS alongside a long-term LABA in asthmatic children. Single use of a LABA long-term in pediatric asthma is dangerous.

Second, the use of combination therapy is effective in reducing asthma exacerbations, but that is just one aspect of asthma control. In terms of the GINA guidelines, does the addition of a LABA actually improve control? The study by de Blic et al.[14] demonstrated non-inferiority of combination therapy at a lower ICS dose, but not superiority. When Bisgaard et al.[17] published the pediatric data from the budesonide-formoterol maintenance and reliever therapy study, the fixed-dose combination regimen was statistically superior to high-dose fixed budesonide in terms of asthma symptom score and percent of asthma control days (symptom free with no medication use); however, night-time awakenings and overall rescue medication use were similar. When comparing the formoterol-budesonide combination used as maintenance and reliever therapy versus high-dose budesonide, the only symptom that was statistically decreased with the single-inhaler regimen was the percent of night-time awakenings.[17] Therefore, the use of combination therapy both in conventional fixed-dose and maintenance and relief combination may reduce the frequency of exacerbations, but not necessarily improve overall asthma control.

Lemanske et al.[22] recently published a study of 182 children in the US, aged 6–17 years who were uncontrolled on fluticasone 100 μg twice daily. The participants were randomized to receive one of three 'step-up' therapies: fluticasone 250 μg twice daily (ICS step-up), fluticasone 100 μg plus salmeterol 50 μg

twice daily (LABA step-up) or fluticasone 100 μg twice daily plus montelukast 5 or 10 mg daily (leukotriene receptor antagonist [LTRA] step-up). The study used a triple crossover design and recorded three main outcomes: exacerbations, asthma controlled days, and FEV_1. In combining the pair-wise comparisons and the three main outcomes, nearly all the children demonstrated a differential response to each therapy. Comparing LABA step-up with LTRA step-up, the proportion of patients who had a better response to LABA step-up was 52% versus 32% with LTRA. LABA step-up also had a greater probability of a better response compared with ICS step-up (54% vs 32%; $p = 0.004$). Finally, the responses to LTRA and ICS step-up therapies were similar**.** The differential response to therapy is not predictable with each patient, highlighting the need for continual re-assessment and medication adjustments in uncontrolled patients.

3.3 Newer ICS

Presently, the risk of decreased growth velocity and reduced bone mineral accretion with ICS is easily balanced by the benefits of good asthma control. However, can the balance be tipped even further onto the side of regular ICS use? Ciclesonide, a newer ICS, has recently been approved in 45 countries as of 2008 for patients with asthma. In a double-blind, crossover study with increasing doses, ciclesonide did not significantly alter lower leg growth rate or urinary cortisol corrected for creatinine in comparison with placebo.[23] In a similar study, lower leg growth rate during fluticasone treatment was found to be significantly reduced compared with both placebo and ciclesonide.[24] In a 12-week study comparing budesonide and ciclesonide, both medications increased FEV_1 and asthma quality-of-life scores, as well as improved symptom scores, although there was a significant difference in body height in favor of ciclesonide at the end of the study.[25] In a 2006 study comparing the efficacy of ciclesonide versus fluticasone, both treatment groups demonstrated a significant improvement in terms of FEV_1, asthma symptoms, use of rescue medication, and asthma symptom-free days without any differences between the treatment groups in changes from baseline.[26] Ciclesonide is an effective ICS that may allay some of the concern about growth, although its long-term effect on bone mineralization is unknown to date.

4. Conclusions

Care of the asthmatic child has changed greatly in the past 20 years, with a focus on inflammation as the causative factor. The GINA guidelines remain an excellent resource for healthcare providers and the control-based approach allows more patient-responsibility in asthma care. There is now a reasonable foundation of research in pediatric asthma that has enabled the creation of a framework of care with literature support alongside expert opinion. ICS remain the standard of care in asthma, and long-term use improves control and reduces exacerbation risk. There is a decrease in growth velocity with chronic ICS use, and final adult height in the CAMP participants is anxiously awaited. While decreased bone mineral accretion has raised concerns, uncontrolled asthma with recurrent oral corticosteroid doses is more problematic. Montelukast has limited use as a single agent, but may have benefit as an add-on therapy in children not well controlled on ICS alone. Combination therapy with a LABA and ICS decreases the frequency of exacerbations in children and offers asthma control equal to that with higher doses of ICS, and is a reasonable alternative in carefully selected pediatric asthma patients not controlled on ICS alone. Long-term LABA use without ICS is not appropriate in children. Rapid-acting LABA therapy in combination with ICS used as maintenance and reliever therapy in a single inhaler decreases the frequency of exacerbations in children compared with conventional high-dose ICS and fixed-dose combination therapies but may not increase control as per the GINA guidelines, and a small percentage of patients are still at risk for a severe asthma exacerbation. Careful selection of patients eligible for combination therapy is indicated. Finally, newer and more site-specific ICS therapy that limits systemic effects will increase the benefit-risk ratio for these effective medications.

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