Management of asthma in preschool children with inhaled corticosteroids and leukotriene receptor antagonists

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Current Opinion in Allergy and Clinical Immunology 2008, 8:158–162

Purpose of review

The aim of this article is to review the recently published studies addressing various treatment approaches for asthma in preschool children.

Recent findings

The heterogeneity of wheezing in the preschool years complicates the study of asthma in this age group. Once children at highest risk for persistence of wheezing are identified, various management strategies may be thoroughly studied. Several recent studies have confirmed the efficacy and safety of both inhaled corticosteroids and leukotriene receptor antagonists in the management of early childhood asthma. In addition to examining clinical efficacy, studies investigating the effects of these treatment modalities on the underlying airway inflammation have recently increased in number and quality and confirm the anti-inflammatory actions of these therapeutic strategies in the preschool child with asthma.

Summary

Evidence for the preferred treatment strategies for persistent asthma in young children remains incomplete. Based on the current body of evidence, there is rationale for further investigation of these management strategies, including direct comparisons between inhaled corticosteroids and leukotriene receptor antagonists, as well as the role of long-acting β-agonists, potentially targeting the subpopulations of early childhood with wheezing who are at highest risk for persistence of asthma symptoms.

Keywords

asthma, inhaled corticosteroids, leukotriene receptor antagonists, preschool children

Curr Opin Allergy Clin Immunol 8:158–162
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1528-4050

Introduction

Asthma has its origins during the preschool years, with approximately 50% of children experiencing at least one wheezing illness during the first 6 years of life [1] and 80% of adults with asthma report onset of asthma symptoms during the first 5 years of life [2]. The prevalence of self-reported 12-month or current asthma in the United States among the 0–4-year age group has increased dramatically over the past two decades, rising from 369 000 children in 1980 to 1 120 000 children in 2004 [3•], and approximately 65% of those children experienced an asthma attack within the past month. The preschool age group experiences significant morbidity related to asthma, as evidenced by 1 910 000 physician office visits for asthma, 336 000 emergency department visits, 120 200 hospitalizations, and 36 asthma deaths in 2004 [3•]. Until recently, the principles guiding management in the preschool age group were extrapolated from data derived from school age children and adolescents. Fortunately, there has been a recent increase in study of various management strategies in the preschool age group. This review examines the current literature addressing inhaled corticosteroids and leukotriene receptor antagonists as treatment options for asthma in preschool children.

Inhaled corticosteroids

Administration of budesonide inhalation suspension to children 6 months to 8 years of age with mild [4] or moderate [5] persistent asthma resulted in significantly lower symptom scores and rescue medication use relative to placebo over a 12-week period. Bisgaard and colleagues [6] examined the safety and efficacy of inhaled fluticasone propionate in children 12–47 months of age with recurrent cough or wheezing who were symptomatic 3 days/week on average prior to the trial. While this study was an open-label randomized trial designed primarily to assess the safety of fluticasone propionate 100 μg twice daily by metered dose inhaler through the Babyhaler for 52 weeks relative to disodium chromoglycate, secondary efficacy outcomes demonstrated significant reductions in the proportions of children who experienced at least one exacerbation or a severe exacerbation in the fluticasone propionate group relative to the comparator group. Carlsen *et al.* [7] studied the efficacy and safety of

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fluticasone propionate 100 μg twice daily versus placebo in 167 children 12–47 months of age with recurrent cough, wheeze or doctor-diagnosed asthma in a randomized, double-blind, placebo-controlled 12-week trial. Fluticasone propionate therapy led to significantly more symptom-free 24-h periods than placebo, but no differences in terms of rescue albuterol use, daytime or nighttime symptom scores, or caregiver quality of life scores.

Two recent trials have further examined the safety and efficacy of fluticasone propionate delivered by metered dose inhaler with a valved holding chamber in preschool children with asthma [8••,9••]. Wasserman and colleagues [8••] studied the effect of fluticasone propionate chlorofluorocarbon (CFC) 44 μg twice daily or 88 μg twice daily compared to placebo via a valved holding chamber over a 12-week treatment period in 332 children 24–47 months of age with asthma. Eligible participants experienced two or more episodes of increased symptoms requiring medical attention and pharmacotherapy in the preceding year or rescue albuterol use at least twice weekly during the 3 weeks before screening. Children who received fluticasone propionate 88 μg twice daily experienced significantly greater increases in the percentages of symptom-free and albuterol-free days compared to placebo, and significant decreases in rescue albuterol use, whereas children receiving fluticasone propionate 44 μg twice daily were similar to those receiving placebo in these outcomes. Furthermore, the asthma exacerbation rate in the fluticasone propionate 88 μg twice daily group was approximately half that experienced by those receiving placebo. Adverse events were comparable between the two groups except for a higher rate of oral candidiasis among the fluticasone propionate 88 μg twice daily group (5 versus 2% in placebo group). Growth velocities and 12-h urine cortisol excretion rates were comparable across the three treatment groups.

Qaqundah and colleagues [9••] reported a randomized double-blind placebo-controlled 12-week treatment trial comparing fluticasone propionate hydrofluoroalkane (HFA) 88 μg twice daily delivered via valved holding chamber to placebo involving 359 children aged 1 to <4 years with asthma. Similar to the study reported by Wasserman *et al.* [8••], eligible participants experienced two or more episodes of increased symptoms requiring medical attention and pharmacotherapy in the preceding year along with rescue albuterol use at least twice weekly during the 3 weeks before screening. The group receiving fluticasone propionate HFA 88 μg twice daily experienced significantly greater reductions in asthma symptom scores and nighttime symptom scores, and a prolonged time to treatment failure, compared to placebo. Both groups, however, had similar improvements in symptom-free days, daytime symptom scores, and rescue albuterol use. Safety measures were comparable between the two groups in terms of 24-h urine cortisol excretion and rates of adverse events. Both of these studies [8••,9••] demonstrated comparable magnitudes of improvements in asthma symptom scores. The findings reported by Qaqundah, however, differ from those of Wasserman *et al.* in the failure of inhaled corticosteroids (ICSs) to demonstrate improvements in symptom-free days and rescue albuterol use despite more severe disease among the population enrolled in the study by Qaqundah, as reflected by higher baseline albuterol use and symptom scores, higher rate of prior oral corticosteroid use (39–44% versus 14–23%), as well as a higher proportion of ethnic minorities (52–54% versus 26–37%). Taken together, these two trials [8••,9••] demonstrate the efficacy of low-dose fluticasone propionate in preschool children with asthma in terms of reduction of several measures of asthma symptom burden and exacerbations along with a favorable safety profile.

While the studies reported by Wasserman and Qaqundah and colleagues [8••,9••] support the efficacy of ICSs over a short-term 12-week period, the Prevention of Early Asthma in Kids (PEAK) trial examined the efficacy of ICSs over a substantially longer time period [10••]. The PEAK trial examined the effects of continuous ICS therapy among 285 preschool children (2 and 3 years of age) with recurrent wheezing at risk for asthma based upon the presence of a positive, modified Asthma Predictive Index consisting of frequent wheezing (at least four episodes in the prior year) and either one major risk factor (parental history of asthma, personal history of atopic dermatitis, or aeroallergen sensitization) or two minor risk factors (eosinophilia ≥4%, wheezing without colds, or allergic sensitization to food) [10••]. Children were randomized to receive fluticasone propionate CFC 88 μg twice daily or placebo via a valved holding chamber for a 2-year period. While the primary outcome for this trial was the proportion of episode-free days during the year after discontinuation of ICSs, this trial demonstrated that continuous ICS treatment for 2 years in children with positive asthma predictive indices resulted in a significantly greater proportion of episode-free days, a lower asthma exacerbation rate, and less supplementary controller medication use compared with placebo. In terms of adverse events, the ICS group experienced a significant reduction in growth velocity during the 2-year period (1.1 cm less growth among those receiving ICSs relative to placebo, $P < 0.001$). Despite the clear asthma control benefits associated with daily ICS therapy, once ICSs were discontinued, children who received ICSs for the first 2 years of the trial had similar symptom burden during the third year, suggesting that the beneficial effects of ICSs persist as long as therapy is continued, but disappear once therapy is withdrawn.

Most studies of ICS therapy in children have been focused on symptom control and prevention of asthma exacerbations. Fortunately, in the past several years, investigators

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have begun to examine other measures of ICS efficacy in preschool children, including the effects of therapy on lung function and markers of airway inflammation. Teper and colleagues [11] studied 26 children 6–20 months of age with three or more episodes of wheeze responsive to bronchodilators along with personal or family history of asthma or atopy and decreased pulmonary function at baseline (V_{max}FRC Z-score lower than −1 SD). Children randomized to receive fluticasone propionate 125 μg twice daily via valved holding chamber for 6 months experienced significant improvements in lung function over the 6-week trial, whereas those receiving placebo did not experience a change in lung function. Hofhuis *et al.* [12] examined the effect of fluticasone propionate 200 μg daily compared to placebo in a randomized trial of 3 months duration. The 127 participants were 4–24 months of age with three or more reported wheezing episodes, or one or more period of persistent wheezing longer than 2 months. In contrast to the findings of Teper and colleagues [11], Hofhuis *et al.* [12] did not demonstrate a significant change in V_{max}FRC between the ICS and placebo groups. Symptomatic improvement was detected after 6 weeks of treatment but not at the end of the trial. Potential explanations for these differing findings include differing durations of therapy (3 months versus 6 months) and the heterogeneity of wheezing phenotypes in early childhood [1] and their varying responses to therapeutic interventions. Atopic disposition differed between the two studies, with the former study [11] including exclusively children with atopic dispositions, while the latter study [12] included 74% of children with atopy, thus potentially selecting populations with differing likelihoods of response to ICS therapy. Using impulse oscillometry to measure lung function, children in the PEAK trial receiving fluticasone propionate demonstrated significantly lower reactance at 5 Hz relative to those receiving placebo [10••]. Moeller and colleagues [13] examined the efficacy of ICSs in reducing the fractional exhaled nitric oxide (F_ENO) in 31 children 6–19 months of age with three or more episodes of wheeze per year, a baseline F_ENO over 10 ppb, along with a parental history of atopy. Children who were randomized to receive fluticasone propionate 100 μg twice daily via valved holding chamber for 4 weeks experienced a significant reduction in median F_ENO levels (35.0 to 16.5 ppb, $P = 0.01$) compared to the placebo group (35.2 to 30.2 ppb, $P = 0.8$), but there was no difference between the groups in terms of lung function [forced expiratory volume $(FEV)_{0.5}$] or symptom scores. Overall, in addition to the symptomatic benefits noted above, ICS therapy in preschool asthma also appears to improve pulmonary function and a biomarker of eosinophilic airway inflammation, F_ENO.

Leukotriene receptor antagonists

The cysteinyl leukotrienes (LTC4/LTD4/LTE4) contribute many of the pathophysiologic processes involved in asthma, including bronchoconstriction, mucus secretion, eosinophil migration to the airways, and increased vascular permeability. Several recent trials have examined the efficacy of montelukast in preschool children with asthma. Knorr *et al.* [14] examined the effects of treatment with montelukast over a 12-week period in children 2–5 years of age with physician-diagnosed asthma consisting of three or more episodes of asthma symptoms during the past year. Relative to children receiving placebo, montelukast therapy was associated with significant reductions in multiple symptoms relative to placebo, as well as lower rescue bronchodilator and oral corticosteroid use.

Bisgaard [15] reported on the effects of montelukast in participants with a history of intermittent asthma symptoms in the context of upper respiratory tract infections, but who had no symptoms or rescue β-agonist use in a typical week over the prior 3 months. This double-blind study enrolled 549 children 2–5 years of age who were randomized to receive either montelukast or placebo daily for 48 weeks. Montelukast therapy was associated with a significant reduction in exacerbations (31.9%) and a prolonged time (approximately 2 months longer) to first exacerbation. Despite these findings, oral corticosteroid use did not differ between the two groups (0.53 courses/year in montelukast group versus 0.64 courses/year in placebo group), although this finding may have been influenced by the relatively mild level of disease in the participants as reflected by the relatively low rate of oral corticosteroid use (approximately 67% did not receive oral corticosteroids) in the past year.

A recent trial by Robertson and colleagues [16••] examined an alternative strategy of managing intermittent asthma in young children. These investigators enrolled 220 children 2–14 years of age (of whom approximately 80% were 2–5 years of age) with physician-diagnosed intermittent asthma who were asymptomatic between episodes and received no asthma medications between episodes. Parents began study medication at the onset of asthma symptoms or the first sign of upper respiratory infection (URI) in those children in whom a URI was usually followed by asthma. Participants received montelukast or placebo once daily for a minimum of 7 days or until symptoms had resolved for 48 h up to a maximum of 20 days. The montelukast group experienced 28.5% fewer healthcare utilizations than the placebo group, along with modest reductions in symptoms, school and parental work missed, but no differences in β-agonist or oral corticosteroid use.

Johnston and colleagues [17••] reported the findings of a trial focusing on the utility of adding montelukast to usual therapy during the yearly 'epidemic' of asthma worsening typically seen in September. The investigators enrolled

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194 children 2–14 years of age (only approximately 20% were 2–5 years of age) with physician diagnosed asthma who required a rescue inhaler in the past year, missed 1 day or more of school due to asthma or experienced significant activity limitation due to asthma, and had a history of exacerbations in the context of respiratory viral infections. Patients were randomized to receive either montelukast once daily or placebo from 1 September to 15 October in addition to their usual asthma therapy, which included an inhaled corticosteroid with or without a long-acting β-agonist in approximately 90% of participants. For the primary outcome, the proportion of days with worse asthma symptoms, the montelukast group experienced 53% fewer days with worse asthma symptoms than the placebo group, although the proportion of days with worse asthma symptoms was quite low in both groups (3.9% of days in the montelukast groups versus 8.3% of days in the placebo group, $P < 0.02$). The montelukast group had 78% fewer unscheduled physician visits (4 versus 18, $P = 0.011$) and fewer days with rescue β-agonist use (6.8 versus 9.4 days, $P = 0.05$). Effects were comparable among subjects who were and were not receiving concomitant inhaled corticosteroid therapy, but the addition of montelukast did not improve the primary outcome among those receiving ICSs plus a long acting β-agonist. In subgroup analysis, boys 2–5 years of age receiving montelukast had significantly fewer days with worse asthma symptoms than boys receiving placebo (0.4% of days versus 8.8% of days, $P < 0.001$), whereas in girls the difference was not significant (5.7% versus 6.9% of days), suggesting a more favorable response among preschool boys relative to girls.

In addition to the clinical trial data examining the efficacy of montelukast in preschool children with asthma, three recent studies have explored the effects of montelukast on indicators of airway reactivity and inflammation. Hakim and coworkers [18•] performed a double-blind randomized placebo-controlled crossover trial in 26 children 3–6 years of age with mild intermittent to mild persistent asthma. Children received 4 weeks of treatment with montelukast once daily or placebo with a 2-week washout period in between. Following the montelukast treatment period, the mean concentration of methacholine which produced a 20% fall in FEV_1 (PC_{20}) was significantly higher than following the placebo treatment period (4.79 mg/ml versus 2.07 mg/ml, $P = 0.001$), demonstrating a montelukast-related reduction in airway hyperresponsiveness among preschool children with mild asthma. Straub and colleagues [19] examined the effect of montelukast therapy on lung function and exhaled nitric oxide in preschool children in two separate reports. Among 24 children 10–26 months of age with recurrent wheeze, sensitization to either inhalant or food allergens, elevated F_ENO (>15 ppb) at baseline, and a positive family history of asthma, treatment with montelukast for 4 weeks was associated with statistically significant improvements in lung function ($FEV_{0.5}$), exhaled nitric oxide (F_ENO), and symptom scores, whereas no improvements were noted in these measures in the placebo group [19]. A second study by this group [20] enrolled 30 children 2–5 years of age with physician diagnosed asthma, sensitization to either inhalant or food allergens, and elevated F_ENO (≥15 ppb) at baseline. Following 4 weeks of therapy with montelukast, there were significant improvements in lung function (airway resistance, Rint) and exhaled nitric oxide (F_ENO). The absence of a control or placebo group in this trial, however, limits the interpretation of these findings. When taken together, these three trials [18•,19,20] add support to the anti-inflammatory properties of montelukast in preschool children with asthma.

Comparative trials between ICS and LTRA in school age children and adolescents have demonstrated greater improvements in lung function or symptom reduction with ICSs over leukotriene modifier in children [21–25]. Only recently has the first trial examining these two therapeutic strategies among young children with mild persistent asthma been reported [26••]. Szefler and colleagues randomized 395 children 2–8 years of age (approximately 65% ≤5 years of age) with mild persistent asthma or with three or more wheezing episodes in the past year lasting 1 day or more and affecting sleep, along with symptom scores of two or higher on three or more of seven consecutive days during the run-in period and short-acting β-agonist use on three or more of seven consecutive days during the run-in period, to receive either budesonide inhalation suspension 0.5 mg once daily or montelukast 4–5 mg once daily for 52 weeks in an open-label manner. The two treatment groups did not differ in the primary outcome of time for first additional asthma medication, which was initiated due to increasing symptoms indicative of an asthma exacerbation. Children receiving budesonide experienced 24.5% fewer exacerbations than children receiving montelukast, although the number of exacerbations requiring oral corticosteroids did not differ between the groups. Symptom scores were comparable between the two treatment groups, while morning and evening peak expiratory flows were significantly higher among the budesonide-treated children. There were no differences in adverse events, nor was there any evidence of difference in increases in height from baseline. The authors conclude that both treatment strategies provide acceptable asthma control, but overall, budesonide therapy was associated with better outcomes.

Conclusion

Recent studies have advanced our understanding as to the utility of ICS and LTRAs in the management of early

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childhood asthma. Both classes of agents are effective in improving symptom control and lung function, along with reductions in markers of airway inflammation. Unfortunately, many of the trials were relatively small in size and most had differing definitions for asthma, making comparisons between studies difficult. Further investigation should focus on young children at high risk for persistence of asthma symptoms (such as those with positive asthma predictive indices), direct head-to-head comparisons to help determine the relative efficacies of the available agents, alone and in combination, as well as the role of long-acting β-agonists in the preschool age group.

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 (pp. 200–201).

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