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Current concepts on the use of glucocorticosteroids and beta 2-adrenoreceptor agonists to treat childhood asthma

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Abstract

Purpose of Review—This article reviews current concepts regarding the clinical and scientific rationale for the combined use of glucocorticosteroids (GC) and beta2-adrenoreceptor (β2AR) agonists in the treatment of childhood asthma.

Recent findings—Several studies have demonstrated that inhaled corticosteroids (ICS) and β2AR-agonists are the most effective medications for the management of asthma in children. Given substantial evidence of an increased clinical benefit when these agents are used together, new studies are being pursued to establish the efficacy and safety of this combinational therapy in infants and children. Ongoing research is also investigating the mechanisms of β2AR and GC signaling and their molecular interactions. This new knowledge will likely lead to novel therapeutic approaches to asthma control.

Summary—There is increasing evidence demonstrating that the combination of long-acting β2AR-agonists and ICS may be more effective than high dose ICS therapy alone in the management of children with uncontrolled asthma. In addition, the use of a single inhaler containing ICS and a quick-acting β2AR-agonist might be a convenient alternative to prevent and treat asthma exacerbations. Future investigations should be designed to more specifically evaluate the efficacy and safety of these therapies in the different asthmatic phenotypes of infants and children.

Keywords

Glucocorticosteroids; inhaled corticosteroids; beta2-adrenoreceptor agonists; long-acting β2-agonists; childhood asthma

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Introduction

Reversible airflow obstruction, bronchial hyperresponsiveness, and airway inflammation are the characteristic features of asthma [1]. Notwithstanding these common features, there exist phenotypic differences between children and adults with asthma (2). Specifically, childhood asthma is not a homogenous entity and its expression reflects the manifestation of various pathophysiological processes. Accordingly, viral infections, allergic airway inflammation, and exposure to a host of aeroallergens and pollutants can evoke airway hyperresponsiveness and exacerbations of asthma via different mechanisms [3–5]. Interestingly, despite these varied etiological mechanisms, glucocorticosteroids and beta2-adrenoreceptor (β 2AR) agonists remain the mainstay of therapy to prevent and reverse asthma exacerbations in children [1]. In this review, we discuss the latest insights into the use of glucocorticosteroids and beta2-adrenoreceptor agonists to treat childhood asthma, with emphasis placed on the clinical efficacy, safety, and molecular mechanisms underlying the therapeutic benefit of the combined use of these medications.

Glucocorticosteroids and the management of preschool wheezing and asthma: The importance of asthma phenotyping

Wheezing in early life needs to be carefully evaluated in order to decide the best strategy of treatment. In this regard, a phenotypical differentiation of preschool wheezing based on symptom pattern has been recently proposed by the European Respiratory Society (ERS) Task Force [6**]. The ERS Task Force divides preschool wheezing into either episodic (viral) or multiple-trigger wheezing. The major advantage of this phenotypical distinction is that it allows for a rational approach to treatment planning. This is particularly true when the clinician is deciding how to treat episodic viral-induced wheezing in preschool children. In this context, a recent meta-analysis concluded that infants and preschoolers with recurrent wheezing or asthma had less exacerbations and improved lung function and symptoms during treatment with inhaled corticosteroids (ICS) [7**]. This evidence notwithstanding, when viral-induced wheezing is evaluated in individual studies, the evidence is less convincing. A double-blind, randomized, placebo-controlled trial conducted by Panickar et al. [8**] found no significant benefit of oral prednisolone in preschool children hospitalized with acute virus-induced wheezing when compared to placebo. These results are similar to those of a previous study that reported that there is no clear benefit of a short course of parent-initiated oral prednisolone for viral wheezing in children aged 1–5 years [9].

Within the context that ICS may not alter the natural history of preschool wheezing [10–12], the use of ICS in infants and children with episodic viral-induced wheezing requires careful consideration of benefits and potential side effects. This tradeoff was recently demonstrated by Ducharme et al. [13**] in a study that evaluated the use of a high dose of fluticasone in preschool-age children with moderate-to-severe virus-induced wheezing. Although the high dose ICS treatment reduced the use of rescue oral corticosteroids compared to placebo, it was also associated with a decreased rate of growth with respect to both height and weight. Given the possibility of these unfavorable side-effects with prolonged high-dose ICS treatment, there is increasing interest in exploring alternatives to the management of viral wheezing in this age group. In this connection, recent clinical trials have reported that leukotriene receptor antagonists (LTRAs) may be effective for the treatment of viral-induced wheezing in preschool children [14,15], but that the greatest effect of LTRA use is in patients with a negative family history of asthma and a serum IgE less than 130 [14]. These results suggest that LTRA may not be as effective an alternative for children with atopic phenotypes, which represents a group of patients in which ICS appear to be highly effective [16**].

Inhaled glucocorticosteroids (ICS): The first line of pediatric asthma management

Once the diagnosis of asthma has been established, there is little controversy that glucocorticosteroids are the most effective therapy to control asthma symptoms and reduce moderate-to-severe exacerbations. The most recent asthma guidelines from the Expert Panel Report 3 (EPR-3) [1] are the first to provide evidenced-based recommendations for the management of asthma in children 0–4 years of age, 5–11 years of age and youths >12 Years old. The EPR-3 concludes that ICS are the most potent and consistently effective long-term control medications for patients who have persistent asthma in all age groups [1]. More recent studies have further supported this notion. The Inhaled Steroid Treatment As Regular Therapy in Early Asthma (START) study [17**], a 5 years follow-up of a large cohort of 7241 combined pediatric and adult patients with recent-onset, mild persistent asthma, has demonstrated that early intervention with inhaled budesonide is associated with improved asthma control and a lesser need for additional asthma medications. These results complement the findings of previous randomized, double blind clinical trials in children such as the Childhood Asthma Management Program (CAMP) study [18] and the Prevention of Early Asthma in Kids (PEAK) study [19] both of which demonstrated that ICS are effective in preventing asthma exacerbations in children > 2 years of age.

Another important consideration pertaining to chronic ICS therapy in children is the potential for adverse side-effects, particularly from the use of high doses [13**]. In this regard, there has been an increasing interest in determining which clinical criteria can best predict the optimal response to ICS and therefore help to identify the most appropriate high-risk children who may benefit most from maintenance ICS therapy. A recent multivariable analysis of the participants in the PEAK trial found more favorable responses to ICS in preschool children with an emergency department (ED) visit or hospitalization for asthma within the past year, children with aeroallergen sensitization, boys, and white subjects [16**]. In addition, the Pediatric Asthma Controller Trial (PACT) reported that in children with mild-to-moderate persistent asthma, the presence of increased exhaled nitric oxide (eNO) levels, low PC20 methacholine values and a parental history of asthma, predict the best long-term outcomes with ICS therapy when compared to treatment with leukotriene receptor antagonists alone [20**].

Use of beta2-adrenoreceptor (β 2AR) agonists alone and in combination with ICS

β 2AR agonists are commonly used medications in the management of asthma. Intermittent use of inhaled short-acting β 2AR-agonists (SABAs) is the drug of choice for treating acute asthma symptoms and exacerbations, and for preventing exercise-induced bronchospasm [1]. Alternatively, the daily use of long-acting β 2AR-agonists (LABAs) carries the potential risk of worsening of the asthmatic condition [21]. This was confirmed in a large clinical study, the Salmeterol Multicenter Asthma Research Trial (SMART), which reported that daily treatment with salmeterol resulted in an increased risk of asthma-related deaths in patients when compared with placebo [22]. Importantly, LABAs reportedly have a beneficial and safe role in the management of asthma when these agents are used in combination with ICS. In this regard, it is particularly noteworthy that Weatherall et al. [23**] recently conducted a meta-analysis of 215 randomized, controlled studies, encompassing a total of 106,575 subjects, to evaluate the risk of mortality with salmeterol and the effect of concomitant inhaled corticosteroid therapy. This meta-analysis concluded that salmeterol monotherapy in asthma increases the risk of asthma mortality but that this risk is ablated with concomitant ICS therapy.

There is also recent evidence suggesting that the combination of LABA and ICS may be more effective than the use of high dose ICS therapy alone in children with uncontrolled asthma. The VIAPAED study group has published a multicenter study that compared the efficacy and safety of doubling the dose of ICS to that of adding a LABA to the ICS. This study found that in children and adolescents aged 4–16 years with uncontrolled asthma, treatment with fluticasone plus salmeterol (100/50 mcg) resulted in higher peak flow rates, less asthma symptoms, and better overall asthma control when compared to 8 weeks of treatment with double-dose fluticasone (200 mcg twice daily) [24**]. De Blic et al. [25**] reported similar results in another recent multicenter trial which reported that ICS/LABA treatment was associated with better lung function and asthma control when compared to 12 weeks of double dose ICS therapy in children with uncontrolled asthma. Both these clinical trials demonstrated that either ICS plus LABA or double ICS therapy were well tolerated, and no serious adverse events were reported. Finally, a recent meta-analysis of 25 randomised controlled trials suggested that the addition of LABA to ICS is superior to increased dose of ICS in children with persistent asthma [26*]. As previously established in adult patients [27–31], these new pediatric data suggest that the combination of ICS/LABA may provide a greater benefit than high doses of ICS alone in children with uncontrolled asthma.

New combined therapies: A single inhaler for maintenance and relief

The reported concerns about the safety of LABA preparations have motivated the development of new combinational therapies, including inhalers that contain an ICS together with a quick-acting β_2 AR agonist. These combined inhalers may be a convenient alternative to prevent and treat asthma exacerbations [32**]. Papi et al [33] recently investigated whether symptom-driven use of a combination of beclomethasone and albuterol in a single inhaler could be as effective as the regular use of inhaled beclomethasone and the as-needed use of albuterol in adult patients with mild asthma. The study demonstrated that symptom-driven use of a single inhaler containing beclomethasone/albuterol is as effective as the regular use of beclomethasone in patients with mild asthma. Moreover, the group treated with the beclomethasone/albuterol single inhaler had a lower 6-month cumulative dose of corticosteroid compared to the patients that used inhaled beclomethasone alone [33]. The latter finding may be of particular significance in the pediatric population given that cumulative corticosteroid levels may be associated with unfavorable side-effects (e.g., impaired growth development).

Another large clinical trial conducted by O'Byrne et al [34] reported that use of a single inhaler containing ICS plus a quick-acting LABA (budesonide/formoterol; 80/4.5 mcg) for both asthma maintenance and relief significantly reduced the risk and rate of severe asthma exacerbations, as well as the need for systemic steroids, when compared with the traditional use of a fixed dose of ICS. Importantly, in this large study that included 2,760 patients aged 4–80 years with moderate-severe asthma, the significant reduction in severe exacerbations was consistent in children, adolescents, and adults [34]. Furthermore, children (4–11 years) receiving the combined inhaler for maintenance and relief had significantly better growth (adjusted mean difference in growth of 1.0 cm; 95% CI, 0.3, 1.7; $p = 0.0054$) than those in the budesonide alone group. Notwithstanding this evidence, the potential benefits of the combined single inhaler approach are less clear in preschool children with wheezing. In this regard, a recent multi-center trial conducted in 276 preschool children aged 1–4 years with frequent wheezing (>3 episodes in the previous 6 months) by the BEclomethasone and Salbutamol Treatment (BEST) for Children Study Group [35] showed that the use of regular inhaled glucocorticoid was superior to combined therapy with respect to maintenance and symptom relief. Similar to previous studies, the cumulative dose of beclomethasone was lower in the beclomethasone/salbutamol combination treatment group. Taken together, the

information given by these clinical trials suggests that additional studies are clearly needed to further evaluate the effectiveness of these new combined inhalers in the management of childhood asthma. In addition, future investigations should be designed to specifically evaluate the efficacy and safety of these therapies in the different phenotypes of asthma in infants and children.

New insights into β 2AR agonists: Understanding their pro-asthmatic potential

Although β 2AR agonists are highly effective for the acute relief of bronchoconstriction, the deleterious effects of their chronic use in asthma have raised important questions about the pathobiology of the disease. Previous studies have reported that prolonged β 2AR stimulation induces not only “tolerance” to the bronchodilatory effect of β 2AR-agonists, but also enhanced reactivity to bronchoconstrictor agents [36–38]. Recent investigations have demonstrated that sustained exposure to β 2AR-agonists [39*] or other cyclic AMP (cAMP) elevating agents [40] induces pro-asthmatic changes in airway smooth muscle (ASM) contractility and relaxation that are mediated by upregulated phosphodiesterase 4 (PDE4) activity. These observations are consistent with previous evidence that implicates upregulated PDE4 activity in mediating airway hyperreactivity (AHR) in asthmatic subjects [41] and in animal models of allergic asthma [41–46]. Furthermore, the link between β 2AR signaling and the pathogenesis of asthma has been recently extended. For instance, Nguyen et al. described that, in a murine model of asthma, β 2AR signaling is required for the full development of the asthmatic phenotype [47]. There was a significant decrease in antigen-driven AHR and airway inflammation seen in β 2AR-null mice and in animals that received chronic treatment with nadolol, a β 2AR-blocker with inverse agonist properties. In addition, Hanania et al. recently published the first open-label study in mild corticosteroid-naïve asthmatics to evaluate the effects of nadolol (10–40 mg) on AHR [48]. This “proof of concept” study showed that after an expected acute worsening, chronic nadolol treatment (9 weeks) improved AHR in 8/10 subjects, as evidenced by a dose-dependent increase in the PC20 to methacholine. Taken together, these observations suggest that there may be a β 2AR-dependent signaling pathway that evokes airway hyperresponsiveness and, thereby, play a critical role in the generation of the asthmatic state.

New insights into the molecular interactions of glucocorticosteroids and β 2AR agonists in airway smooth muscle

There are also new insights into the mechanisms involved in mediating the beneficial effects of the combination of glucocorticosteroids and β 2AR agonists [49*] in the treatment of asthma. Previous investigations have established that this combinational therapy is associated with superior anti-inflammatory effect and better asthma control [27–30]. Consequences of the molecular interaction of glucocorticosteroids and β 2AR-agonists include both enhanced glucocorticoid receptor (GR)-mediated responses [50–52] and augmented β 2AR transcription and function [52–54]. Moreover, new data suggest that there are also complementary interactions between β 2AR and glucocorticosteroids signaling in regulating ASM contractility and relaxation. In this context, Cooper et al. reported that glucocorticosteroids completely reverse β 2AR tolerance in isolated human small airways exposed to a short-acting β 2AR agonist [55] and, more recently, we demonstrated that glucocorticoids protect ASM from the pro-asthmatic effects of prolonged LABA exposure on ASM contractility and relaxation [56**]. The mechanism underlying the latter protective action of glucocorticosteroids on ASM function was found to involve glucocorticoid-mediated inhibition of pro-asthmatic signaling via the mitogen-activated protein kinase (MAPK) signaling pathway due to the induction of MAPK phosphatase-1[56**]. In light of

this new evidence, future interventions targeted at this mechanism may yield new therapeutic approaches to improve asthma control.

Conclusion

Although glucocorticosteroids and β 2AR agonists remain the first line of therapy for asthma in children and adults, special consideration must be given to the use of corticosteroids to treat infants and young children. Some preschool wheezing phenotypes may not obtain significant clinical benefit, and there are potential serious side-effects associated with the use of high doses of ICS in this age group. Large clinical studies have shown that combinational therapy involving an ICS together with a β 2AR agonist can provide additional clinical benefits in asthma management, and the clinical efficacy of this therapeutic approach has been substantiated by recent newly identified molecular interactions between β 2AR and glucocorticosteroids signaling that modulate ASM contractility and relaxation. In addition, new clinical trials have suggested that a single inhaler containing an ICS plus a quick acting β 2AR may be a more convenient and equally effective alternative to prevent and treat asthma exacerbations. However, additional large pediatric clinical studies are needed to establish the efficacy and safety of this therapy in children.

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Papers of particular interest, published within the annual period of review, are followed by brief annotations in bold type and have been highlighted as:

*Of special interest

**Of outstanding interest

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