Paediatric Respiratory Reviews 21 (2017) 80–85

Contents lists available at ScienceDirect

Paediatric Respiratory Reviews

Review

Concerns with beta2-agonists in pediatric asthma - a clinical perspective

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EDUCATIONAL AIMS

After reading this review, readers will be able to:

- Discuss the potential risks of treatment of childhood asthma with β2-agonists
- Understand the development of tolerance to β2-agonists
- Discuss potential mechanisms involved in the increase in asthma-related adverse events with regular β2-agonist treatment
- Understand the potential role of β2-adrenoreceptor polymorphisms in response to β2-agonist treatment

ARTICLE INFO

Keywords:
β2-agonists
Tolerance
Asthma
Genetic polymorphisms

SUMMARY

Beta2-adrenoreceptor agonists (β2-agonists) are extensively used in the treatment of childhood asthma. However, there have been concerns regarding their adverse effects and safety. In 2005, the FDA commissioned a "Black Box Warning" communicating the potential for an increased risk for serious asthma exacerbations or asthma related deaths, with the regular use of LABAs. In a meta-analysis of controlled clinical trials, the incidence of severe adverse events appeared to be highest in the 4-11 year age group. Several mechanisms have been proposed regarding the risk of regular use of β2-agonists, such as masking patients' perception of worsening asthma, desensitization and downregulation of the β2-adrenoreceptor, pro-inflammatory effects of β2-agonists, pharmacogenetic effects of β2-adrenoreceptor polymorphisms and age related differences in pathophysiology of asthma.

In this paper, we review β2-receptor pharmacology, discuss the concerns regarding treatment with β2-agonists in childhood asthma, and provide suggestions for clinical pediatric practice in the light of current literature.

INTRODUCTION

Short acting β2-agonists (SABAs) are the first choice as rescue medication during acute bronchoconstriction and provide protection against exercise induced bronchoconstriction (EIB) [1]. SABAs activate the β2-adrenoreceptor (β2AR) within 5 minutes and have a bronchodilator effect of 4-6 h [2]. Long acting β2-agonists (LABAs) have a longer (12-24 h) bronchodilator effect [2]. Currently, in clinical guidelines for children, LABAs are recommended as one of the step-up options for maintenance treatment in combination with

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Abbreviations: cAMP, cyclic adenosine monophosphate; BARGE, Beta Adrenergic Response by Genotype; β2AR, β2-adrenoreceptor; BHR, bronchial hyperresponsiveness; EIB, exercise induced bronchoconstriction; FDA, food and drug administration; FEV_1, forced expiratory volume in 1 sec; ICS, inhaled corticosteroid; LABA, long acting β2-agonist; LARGE, Longacting β2-Adrenergic Response by Genotype; LTRA, leukotriene receptor antagonist; PKA, protein kinase A; SABA, short acting β2-agonist; SAE, serious adverse events; SMART, Salmeterol Multi-center Asthma Research Trial; SNP, Single Nucleotide Polymorphism; SNS, Serevent Nationwide Surveillance.

http://dx.doi.org/10.1016/j.prrv.2016.05.006
1526-0542/

inhaled corticosteroids (ICSs) when asthma is not adequately controlled with ICSs alone [3,4].

In the past 20 years, concerns about the safety of LABAs caused an ongoing controversy among drug authorities, scientists and clinicians [5], as meta-analyses indicate a significantly higher risk of serious adverse events, such as life-threatening asthma exacerbations [6–11], in adults and children regularly taking LABAs. Particular concern has arisen about the risk of LABAs in childhood asthma [10,12].

In this paper, we discuss the concerns regarding treatment with β2-agonists in childhood asthma, review β2-receptor pharmacology, and focus on clinical recommendations for pediatricians in the light of current literature.

PHARMACOLOGY

The adrenoreceptors are a class of G-protein coupled receptors that are targeted by catecholamines. The β2AR predominates in the respiratory tract, where it is widely distributed, not only in airway smooth muscle cells (with a density of 30.000-40.000 receptors per cell), but also in lung epithelial cells, endothelial cells and inflammatory cells such as mast cells [2]. The β2AR density increases more distally throughout the respiratory tract with highest levels in the small airways and alveolar region [2].

Stimulation of the β2AR in airway smooth muscle cells induces a signal transduction pathway, resulting in increased intracellular cyclic-3′,5′-adenosine monophosphate (cAMP) [2]. cAMP catalyzes the activation of protein kinase A (PKA), which subsequently leads to phosphorylation of key regulatory proteins involved in the control of muscle tone. An increase in cAMP inhibits Ca^{2+} release from intracellular stores, reduces Ca^{2+} entry into the cells, and enhances sequestration of intracellular Ca^{2+}. The stimulated β2AR also directly interacts with potassium channels present in the airway smooth muscle cell membrane, without involving cAMP, resulting in airway smooth muscle relaxation (Figure 1). Stimulation of the β2AR by β2-agonists stabilizes mast cells, which are abundantly present in the asthmatic airways, through an increase in intracellular cAMP [13], inhibiting the release of pre-stored histamine and the synthesis of new mediators, such as cysteinyl leukotrienes and prostaglandin D2.

Stimulation of the β2AR on epithelial cells leads to an increased beat frequency of cilia and may therefore facilitate mucociliary clearance [14]. Furthermore, β2-agonists inhibit extravasation of plasma proteins in the airway wall, thereby reducing the airway wall congestion that contributes to airway obstruction in asthma [14].

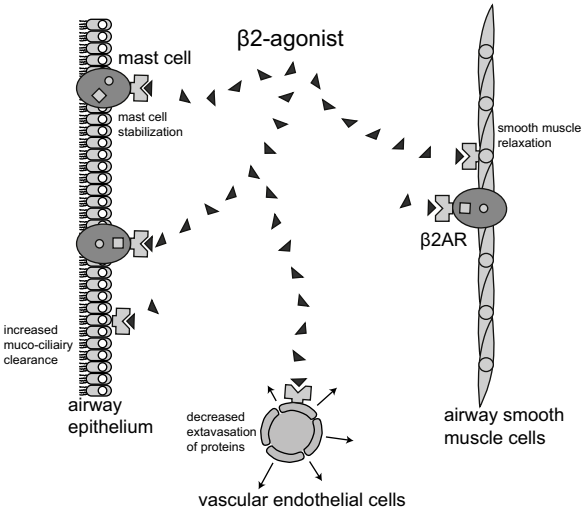

Figure 1. Physiological effects of β2-agonists in the airways.

β2AR-mediated vasorelaxation, and possibly bronchodilation, decline with age due to a decrease in affinity for agonists, suboptimal receptor signaling and a decline in cAMP production [15].

Prolonged exposure to an agonist desensitizes G-protein-coupled receptors. In homologous desensitization, within minutes of binding of a ligand to its receptor, G-protein receptor kinase is activated. This kinase phosphorylates the carboxyterminal portion of the G-protein-coupled receptor, which changes the receptor conformation and leads to decoupling of the receptor from the G-protein, resulting in receptor subsensitivity. In heterologous desensitization, that for example happens after allergen challenge [16], the receptor is phosphorylated by a non-specific kinase that is activated by binding of a ligand to a different G-protein coupled receptor.

The phosphorylated receptors are bound by β-arrestin, after which they are internalized by endocytosis. The internalized receptors can be recycled to the cell membrane. However, when exposure to the ligand or agonist continues, the total transit time for the recycling of receptors increases [2] and part of the receptors will be degraded in lysosomes. After hours of agonist exposure there is a net loss of receptors, called downregulation. The receptors can only be replaced by re-synthesis of new receptors through transcription of the β2AR-gene [2,14]. Therefore it takes hours to days to overcome downregulation.

Corticosteroids increase β2AR-gene transcription and regulate both the number of receptors and the coupling to adenylate cyclase, reversing β2AR downregulation [2].

CONCERNS WITH REGULAR B2-AGONIST TREATMENT

No large efficacy and safety studies were performed when SABAs were introduced. Two epidemics of asthma related mortality, after the marketing of isoproterenol in the 1960s in the United Kingdom [17] and fenoterol in the 1970s in New Zealand [18], rose concern about regular SABA treatment. It was assumed that the relationship between asthma mortality and isoproterenol (a non-selective β-agonist) resulted from cardiac toxicity, and that the dose related effect of fenoterol on asthma mortality [19] reflected increased SABA use due to more severe asthma. However, a prospective trial by Sears et al. in adolescent and adult asthmatics (aged 15-64y) in 1990 demonstrated worse asthma control when fenoterol was used regularly compared to when it was used as rescue, as-needed therapy [20]. Several placebo controlled studies have since then compared the effect of regular treatment with a SABA to as-needed treatment in asthmatic adults [21]. Overall, there was little evidence to support regular use of SABAs [21] and SABAs are therefore advised to use only on an 'as needed' basis. Increased use is considered to indicate a deterioration of asthma control and the need to step-up treatment.

Since the introduction of LABAs there have been concerns regarding their adverse effects and safety. Among the first studies to examine LABA safety were the Serevent Nationwide Surveillance Study (SNS) [22] and Salmeterol Multi-center Asthma Research Trial (SMART) [23]. The SNS study was a 16-week, double-blind study in 25,180 subjects aged ≥ 12y that reported a statistically insignificant increase in the number of asthma-related deaths in patients treated with salmeterol twice daily compared to four times daily salbutamol (RR 3.0, 95% CI 0.7–20). The SMART trial was a 28-week, randomized trial in 26,355 subjects aged ≥ 12y that reported a significantly increased risk for asthma-related death (RR 4.37, 95% CI 1.25–15.3) and respiratory related death (RR 2.16, 95% CI 1.06-4.41) in patients treated with salmeterol compared to placebo. On subgroup analysis, this increased risk

was only found in African-Americans. SMART was not adequately designed to determine whether or not ICS use affected the incidence of asthma related deaths, but 9/13 deaths occurred in patients who did not receive ICS.

These observations led to a "Black Box Warning" by the FDA in 2005 communicating the potential for an increased risk for serious asthma exacerbations or asthma-related death with the regular use of LABAs. Subsequently, over a dozen meta-analyses investigating the adverse effects of LABAs in adults and children were published, providing an equivocal picture [6–11,24–29]. Some of these meta analyses demonstrated an increased risk of serious adverse events, such as asthma exacerbations requiring hospitalization, life-threatening exacerbations and asthma-related death with LABA use compared to placebo [6–11], while others did not [24–29]. This inconsistency is probably due to differences in background therapy and heterogeneity in study design and study populations.

The FDA performed a meta-analysis of controlled clinical trials comparing the risk of LABA use with no LABA use for different age categories [10]. They found that the composite outcome of asthma-related death, intubation, or hospitalization had the highest incidence in the 4-11y age group (30.4 events per 1000 patient years, 95% CI 5.7–55.1). Compared to 4-11y old children not on LABAs the RR was 1.67 (Figure 2). These results were similar for patients who reported concomitant use of ICSs, though adherence to ICSs was not checked. In the small subgroup of patients who were assigned ICSs as study medication and whose adherence was checked, there did not seem to be an increased risk.

A pediatric meta-analysis in which 82% of patients used ICSs, reported no significant difference (RR 1.05, 95% CI 0.61-1.83) in asthma-related hospitalizations in 4-11y old children on formoterol compared to no LABA [28]. A 2012 Cochrane analysis on the safety of formoterol and salmeterol in asthmatic children (aged 4-17y) concluded that regular LABA/ICS combination therapy is likely to be less risky than LABA monotherapy [29]. However, another Cochrane analysis reported a trend towards an increase in asthma related deaths in adults (OR 3.6, 95% CI 0.79-16.3) and non-fatal serious adverse events in children (OR 1.62, 95% CI 0.80-3.28) on formoterol with ICS compared to ICS monotherapy [25].

The important question that remains is whether the benefits of combination therapy in children outweigh the risks. LABA/ICS combination therapy is recommended as a third step in asthma treatment for children >6 years by clinical guidelines [3,4].

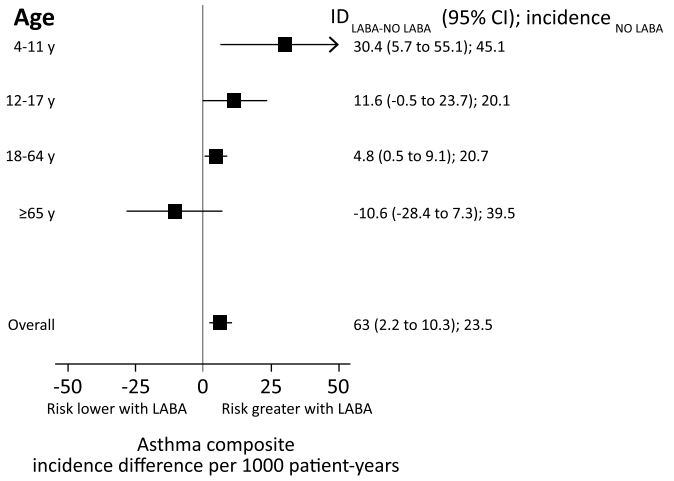

Figure 2. Incidence difference (ID) per 1000 patient-years for composite outcome of asthma-related death, intubation, or hospitalization, according to age for LABA versus no-LABA therapy.
$Incidence_{No\ LABA}$ = incidence in No LABA group per 1000 patient-years.
Figure adopted from McMahon et al., Pediatrics 2011 [10] with permission.

In adults, the addition of a LABA to an ICS improves pulmonary function and symptoms, reduces the use of rescue medication and improves quality of life [30,31]. However, in children the evidence in favor of LABAs is far less certain, with wide confidence intervals including both superiority and inferiority of LABA/ICS combination therapy compared to adding a leukotriene antagonist or doubling the dose of ICSs [30,31].

It has been postulated that larger trials are necessary to determine the benefits and risks of LABA/ICS combination therapy. In 2011, the FDA issued a requirement for all manufacturers of LABAs to conduct controlled clinical trials to assess the safety of LABA/ICS combination therapy compared to ICS monotherapy [32]. Results from these studies in patients aged 4-11 years are expected in 2017.

POSSIBLE MECHANISMS OF INCREASED ADVERSE EVENTS WITH REGULAR Β2-AGONISTS

Several mechanisms have been proposed to explain the increase in adverse events with regular β2-agonist treatment: masking patients' perception of asthma worsening, desensitization and downregulation of the β2AR, pro-inflammatory effects and, finally, pharmacogenetic interactions.

Asthma worsening may be masked, as β2-agonists provide good acute symptom relief. Patients may rely on them too much, preventing them from taking sufficient anti-inflammatory treatment, unaware of their underlying disease state and obscuring a possible worsening of their asthma. Furthermore, patients may neglect to avoid allergens, and engage in bronchoprovocative behaviour such as smoking, as they experience no acute symptoms because of the bronchodilator effect of β2-agonists, causing a more severe late inflammatory response.

Desensitization and downregulation of the β2AR result in tolerance to the bronchoprotective and bronchodilator effects of β2-agonists. A loss of bronchoprotection could make children more vulnerable to asthma exacerbations in response to allergen, exercise, airway infections or non-specific stimuli. A loss in the bronchodilator effect of β2-agonists could result in failure of rescue SABA treatment during an exacerbation. The enhanced need for rescue SABAs could lead to even more receptor downregulation (Figure 3). Theoretically, corticosteroid stimulated transcription of the β2AR-gene may compensate for receptor downregulation [33]. Both systemic corticosteroids [34] and a single high dose of ICS (1600 μg budesonide) [35] have been shown to reverse bronchodilator tolerance. However, in clinical studies tolerance to the bronchoprotective effects of β2-agonists developed despite concomitant treatment with conventional doses of ICSs [36–38].

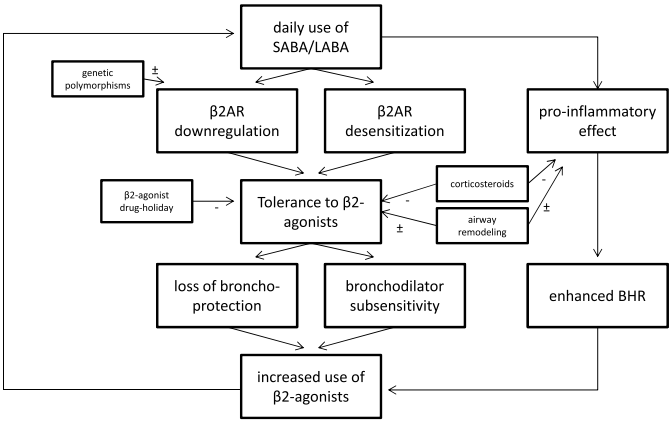

Figure 3. Schematic representation of vicious circle that could occur with frequent β2-agonist use.

It was postulated that LABAs may induce pro-inflammatory effects. β2-agonists induce a shift in peripheral blood mononuclear cells' cytokines toward a Th2-lymphocyte response [39]. Regular use of β2-agonists can increase sputum inflammatory cells [40]. Sustained exposure to β2-agonists increases airway smooth muscle contractility [41] and augments the effects of broncho-constrictive mediators [42] and pro-contractile signaling pathways. Clinically, these observations do not appear to be relevant, as a meta-analysis investigating the effect of LABAs on inflammation in adults or children concluded they did not have a clinically important anti- or pro-inflammatory effect [43].

B2AR-gene polymorphisms result in changes in the amino acid sequence of the β2AR, leading to alterations of its properties. It was hypothesized that rare variants of the β2AR gene could account for the rare incidence of asthma-related life threatening events in patients receiving regular β2-agonists. Two single-nucleotide polymorphisms (SNPs) in specific coding regions, glycine for arginine at codon 16 and glutamic acid for glutamine at codon 27, have been more extensively studied since they are relatively prevalent in Caucasian populations. The minor allele of this SNP (Arg16) has a reported frequency of approximately 40% in Caucasians [44]. In vitro, receptors with the homozygous Arg16 genotype show enhanced susceptibility for homologous desensitization and receptor downregulation [45], which could account for an increase in β2-agonist tolerance in Arg16 homozygotes.

Both retrospective and prospective analyses of data in adults have demonstrated adverse effects of the Arg16 homozygous variant on asthma symptoms [46], BHR [47] and exacerbations [48] after receiving a SABA as regular therapy. In the Beta Adrenergic Response by Genotype (BARGE) trial the response to 16-weeks regular albuterol was compared to placebo plus ipratropium rescue treatment in asthmatic adults in a prospective, genotype-stratified, cross-over design [46]. In this study, Arg16 homozygotes did not experience an improvement in peakflow and demonstrated a deterioration of symptom control during albuterol treatment, in contrast to Gly16 homozygotes.

Studies searching for the effect of β2AR genotype on the response to treatment with LABAs have shown conflicting results which appear to relate to the age of the study group. In adults, a large retrospective study in 2250 patients (aged ≥12y) showed no association between treatment with salmeterol or formoterol and clinical outcomes after stratification by Arg16Gly genotype [49]. In the Longacting β2-Adrenergic Response by Genotype (LARGE) trial the response to 18-weeks twice daily salmeterol (added to ICS) was compared to placebo in a prospective, genotype-stratified, cross-over design [50]. In this study, both Arg16 and Gly16 homozygotes experienced an improvement in lung function, but only Gly16 homozygotes were protected against BHR provoked by metacholine [50]. This loss of bronchoprotection to methacholine after 1-2 weeks of regular LABA use in Arg16 homozygotes was previously described in a retrospective analysis of data from adult asthmatics [51]. A prospective trial found no association between Arg16Gly genotype and loss of bronchoprotection to EIB after 2 weeks treatment with salmeterol [52].

In children, an increased risk for exacerbations in Arg16 homozygotes in a cohort of 1182 patients (aged 3-22y) on daily salmeterol was reported [53]. An increase in oral corticosteroid use and emergency department visits was found in 597 Arg16 homozygotes (aged 4-12y) on LABA/ICS combination therapy, compared to Gly16 homozygotes [54]. A prospective randomized controlled study in asthmatic children aged 5-18y showed that in Arg16 homozygotes adding montelukast compared to salmeterol to inhaled fluticasone significantly improved asthma symptoms, asthma related school absence and quality of life (Figure 4) [55].

The increased risk of exacerbations associated with regular LABA treatment in children compared to older age groups could result

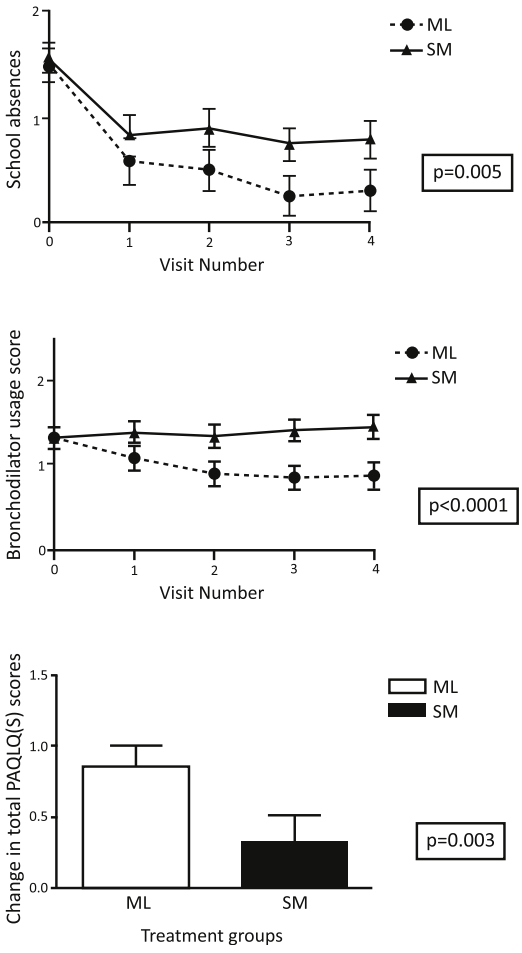

Figure 4. Changes in asthma-related outcomes in Arg16 homozygous children treated with fluticasone plus oral montelukast (ML) or salmetorol/fluticasone plus placebo montelukast (SM). Visits were every 3 months.
Top panel: change in asthma-related school absences.
Middle panel: change in use of salbutamol reliever.
Bottom panel: change in total pediatric asthma quality of life questionnaire score after 12 months treatment.
Error bars are 95% CI. P values are shown for the comparison between groups after 12 months.
Figure adapted from Lipworth et al. [55] with permission.

from differences in the pathophysiology of asthma between adults and children [56,57]. Airway smooth muscle in children might have a shortened response and relaxation time [58]. Younger asthmatic children have a higher reactivity to methacholine [59] and a faster maximal bronchoconstriction post-exercise than adults [58–60]. In epidemiologic studies, asthmatic children have a higher incidence of exacerbations than adults [61]. This increased responsiveness of the airway smooth muscle might wane with ageing. Possibly adult asthmatics are less vulnerable to the negative effects of β2-agonists due to more airway wall rigidity, caused by remodeling of the bronchoconstrictive apparatus, or due to less atopy, a lower number of inflammatory cells or receptors, or a decreased affinity of β2ARs to their agonists.

CONCLUSIONS AND SUGGESTIONS FOR CLINICIANS

Despite the fact that β2-agonists are the most effective bronchodilators currently used, their place in the treatment of childhood asthma needs to be carefully considered, taking into account possible genetic and environmental influences. For as-needed therapy, SABAs remain the first choice. However, based on the available evidence from clinical trials, it can reasonably be

concluded that daily use of SABAs and/or LABAs, whether used for protection or as rescue therapy, in the absence of ICS can have adverse effects on asthma control. At the moment, there is no consensus on how to balance benefits and risks of regular LABA/ICS combination therapy, especially in children under the age of 12, due to a paucity of randomized clinical data for children. The currently available data on concomitant LABA/ICS use in children appears reassuring [10]. More research in children < 12y is necessary to provide evidence based recommendations. Based on current evidence and guidelines we would like to suggest the following:

As recommended by the FDA [31] and clinical guidelines [3,4] we should refrain from LABA monotherapy, as it does not treat the underlying inflammation, could mask a deterioration of asthma control and is associated with an increased risk of serious adverse events. Combination therapy should be used as a single inhaler to prevent periods of LABA monotherapy due to poor compliance with ICSs.

LABA/ICS combination therapy should be used with caution in children aged < 12 years. In children aged < 12y, few studies have been performed to compare step-up options when asthma is not well controlled on low-dose ICSs. In contrast to data in adult studies, studies performed in children do not show a significant superior effect of adding a LABA compared to a double dose of ICS on asthma control, quality of life, BHR and risk of asthma exacerbations [30]. Although addition of a LABA to ICS treatment improves lung function, it may pose a risk due to a reduced effect of rescue SABAs during acute airway narrowing. Concomitant use of ICSs possibly mitigates the risk of asthma-related serious adverse events [10], yet the number of pediatric studies is limited and these studies should be interpreted with caution. We suggest to reserve LABA/ICS combination therapy for children aged < 12y whose asthma is inadequately controlled on a higher dose of ICSs alone, with or without using a leukotriene receptor antagonist.

Finally, as we are moving towards precision medicine, a randomized clinical trial comparing a pharmacogenetic approach to asthma medication prescription guided by the patients β2AR genotype compared to the traditional step up approach in all patients is urgently needed.

CONFLICT OF INTEREST STATEMENT

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

FUTURE RESEARCH DIRECTIONS

- More research on the safety and efficacy of long acting β2-agonists in children < 12y is necessary to provide evidence based recommendations.
- A randomized clinical trial comparing a pharmacogenetic approach to asthma medication prescription guided by the patients β2AR genotype compared to the traditional step up approach is needed.

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