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Exercise-Induced Bronchoconstriction in Asthmatic Children

A Comparative Systematic Review of the Available Treatment Options

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Contents

Abstract

The aim of this article is to critically review the efficacy and safety data from randomized controlled trials (RCTs) using inhaled corticosteroids (ICSs), long- or short-acting β_2-adrenoceptor agonists (LABAs, SABAs), parasympatholytics

and oral leukotriene receptor antagonists in the management of exercise-induced bronchoconstriction (EIB) in children with persistent asthma (EIA).

The studies with sufficient information on patient characteristics and outcomes were chosen using a MEDLINE search. Results from the individual searches were combined and repeated. Studies were also found by reviewing the reference lists of the articles not included in this review. Studies focusing solely on individuals with asthma and other allergic co-morbidities (i.e. a degree of bronchial reversibility) were considered in this review. To make the paper evidence-based, the design and the quality of different studies were assessed employing the Sign criteria (evidence level [EL] and grades of recommendation [GR]). No additional statistical analyses were performed. Most of studies included paediatric patients with underlying EIA.

We need to distinguish children with recurrent asthma symptoms in whom EIB is also present (patients with EIA) from asthmatic subjects whose symptoms appear only as a result of exercise (patients with EIB). Further controller treatment is indicated in patients with EIA and further reliever treatment in patients with EIB. ICSs are the first-choice controller drugs for EIA in children with persistent asthma (Sign grade of recommendation [GR]:A). In children with EIA without complete control with ICSs, SABAs (GR:A), leukotriene receptor antagonists (LTRAs) [GR:A] or LABAs (GR:A) may be added to gain control. Treatment with relievers such as SABAs (GR:A), parasympatholytics (GR:B) or, eventually, LABAs (GR:A), administered 10–15 minutes before exercise is the most preferable method of preventing EIB symptoms in children; however, not as monotherapy in children with EIA.

The disadvantages and controversy relating to inhaled β_2-adrenoceptor agonist use lie in the development of tolerance to their effect when they are used on a regular basis, and the possibility of a resulting underuse of ICSs in patients with EIA. Researchers and guidelines recommend that if any patient requires treatment with a β_2-adrenoceptor agonist more than twice weekly, a low dose of ICSs should be administered. Inhaled parasympatholytics may be effective as preventive relievers in some children with EIB or EIA, especially among those with increased vagal activity. LTRAs have a well balanced efficacy-safety profile in preventing the occurrence of EIB symptoms in children. Compared with LABAs, LTRAs produce persistent attenuation of EIB and possess an additional effect with rescue SABA therapy in persistent asthmatic patients with EIA. A disadvantage of LTRAs is a non-response phenomenon. There are still insufficient data on the efficacy-safety profiles of ICS/LABA combination drugs in the treatment of EIA in children to recommend this treatment without caution. Safety profiles of inhaled SABAs, anticholinergics and montelukast in approved dosages seem sufficient enough to recommend use of these drugs in the prevention of EIB symptoms in children. Many researchers agree that treatment of EIA in children should always be individualized.

1. Exercise-Induced Bronchoconstriction (EIB) in Asthmatic Children

Physical activity is an important trigger of asthma symptoms for most patients, including children.[1,2] Exercise-induced bronchoconstriction (EIB) can also be a unique asthma phenotype.[3] Exercise-induced asthma (EIA) and EIB are terms used to describe a transient narrowing of the airways that follows vigorous exercise.[4]

However, there is a difference between EIB in an asthmatic individual and EIB in an individual without asthma. The term EIA is used to describe symptoms of asthma provoked by exercise and EIB describes a reduction in lung function after an exercise test or natural exercise.[4]

EIA occurs in up to 90% of asthmatic patients and in 40% of patients with allergic rhinitis; among athletes and in the general population it has a prevalence of between 6% and 13%.[5] The mechanism of EIB may involve changes in airway osmolarity resulting from water loss and/or changes in airway temperature that could lead to bronchoconstriction and bronchospasm.[3,4] However, the pathogenesis of EIB is a more complex problem involving the release of mediators from the mast cells and other inflammatory cells of the airways due to the change in osmolarity of the periciliary fluid, which lines the surface of the respiratory mucosal membranes.[4] It is thought that biochemical events associated with regulatory volume changes of the cells in response to an osmotic stimulus are associated with the biochemical events involved in the release of mediators.[4] This indicates that there is a relationship between EIB and airway inflammation.[4]

EIB typically develops within 5–10 minutes after completing the exercise.[1] Patients experience typical asthma symptoms (or sometimes a nasty cough) that disappear spontaneously within 30–45 minutes.[1] An 8-minute running protocol is easy to perform in clinical practice and can establish a firm diagnosis of EIA.[1,6] The preferred modes of exercise are the motor-driven treadmill with adjustable speed and gradient, or the electromagnetically braked cycle ergometer.[6] Conditions, methods and interpretation of the exercise challenge test are now standardized and fully described by the American Thoracic Society.[6] The presence of EIB is defined by plotting forced expiratory volume in 1 second (FEV_1) as a percentage of the pre-exercise baseline FEV_1 at each post-exercise interval.[6] A decrease below 90% of the baseline FEV_1 (a 10% decrease) is the lower limit accepted for EIB.[6] However, there is some discordance in the matter of FEV_1 diagnostic decrease after exercise. Some authors prefer to use more specific (although less sensible) thresholds, such as 15%, which is more diagnostic of EIB, particularly if the exercise has been performed in the field and the study is performed for epidemiological purposes.[7] Moreover, in order to establish or compare drug efficacy in clinical studies, more than even a 20% of FEV_1 decrease may be needed.[8] Various important diagnoses of EIB that should be taken into account are cardiac arrhythmias, vocal cord dysfunction and hyperventilation induced by exercise.[4] It is known that a normal cardiovascular fitness does not completely prevent the EIB;[9] therefore, it seems reasonable to plan a specific pharmacological therapy in order to prevent EIB in children with asthma. According to Price,[2] 25 years ago the techniques for exercise testing in asthmatic children were undergoing a process of standardization.

The studies performed during that period showed there were several different compounds, which when given prior to a free running exercise, reduced the consequent fall in lung function. In the years since, treatment methods have developed from pre-exercise treatment with short-acting β_2-adrenoceptor agonists (SABAs), parasympatholytics, cromones and theophylline, through to regular controller therapy with inhaled corticosteroids (ICSs) and leukotriene receptor antagonists (LTRAs), or reliever therapy with long-acting β_2-adrenoceptor agonists (LABAs), to methods based on combining these drugs according to the latest guidelines.[1]

Before starting any treatment, there is always a need to classify patients in order to select the appropriate therapy. A question to be addressed is whether the patient is a child with recurrent asthma symptoms in whom EIB is also present (patients with EIA) or whether he/she is an asthmatic individual whose symptoms appear only as a result of exercise (patients with EIB). This may indicate further controller (anti-inflammatory) treatment of patients with EIA and reliever treatment of patients with EIB (premedication before exercise and treatment of symptoms). However, there is no evidence supporting different treatment for EIB in asthmatic athletes and nonathletes.[10] Recent important guidelines even suggest that the principles of asthma

management in general may be applicable to EIA as well.[11,12]

The purpose of this article is to discuss the efficacy and safety data from randomized controlled trials using LABAs such as formoterol and salmeterol, SABAs such as salbutamol (albuterol), parasympatholytics such as ipratropium bromide, ICSs and LTRAs, such as montelukast, in the management of EIB in children.

2. Methods of Literature Review and Scope

The studies reported in this review were chosen using a MEDLINE search. Most studies included paediatric patients with underlying persistent asthma (EIA). The search terms were: 'exercise-induced bronchoconstriction', 'exercise-induced asthma', 'children', 'adolescents', 'fluticasone', 'beclomethasone', 'budesonide', 'cyclesonide', 'mometasone', 'long-acting β_2-agonist', 'formoterol', 'salmeterol', 'short-acting β_2-agonist', 'albuterol', 'parasympatholytics', 'ipratropium bromide', 'leukotriene receptor antagonists', 'montelukast', 'combined treatment', 'formoterol/budesonide', and 'salmeterol/fluticasone'. Results from the individual searches were combined to include a LABA, a SABA, a parasympatholytic, an ICS and a LTRA; for example, formoterol, albuterol, ipratropium bromide, budesonide and montelukast; salmeterol/fluticasone, albuterol ipratropium bromide and montelukast; and salmeterol, budesonide, albuterol, ipratropium bromide and montelukast. These combined searches were repeated for the LABAs formoterol and salmeterol; the SABA albuterol; the ICSs beclomethasone, budesonide, cyclesonide, fluticasone, mometasone; and a LTRA, montelukast. Every search included the following terms: 'exercise-induced bronchoconstriction', 'exercise-induced asthma', 'children' and/or 'adolescents'; all citations found in the search were checked and studies that were not specifically connected with those terms were not included in this review. Other studies were also found by reviewing the reference lists of the articles not included in this review, to ensure that no studies were skipped in the original search. Only the articles with sufficient information on patient characteristics and outcomes were included. Studies that included only individuals with asthma and other allergic co-morbidities (i.e. a degree of bronchial reversibility) were considered. Studies using unlicensed doses of ICSs, LABAs, SABAs, parasympatholytics or LTRAs were excluded. To make the article evidence-based, the design and the quality of the different studies were assessed employing the Sign criteria (evidence level [EL] and grades of recommendation [GR]). No additional statistical analyses were performed.

3. Clinical Efficacy of Controller Treatment

3.1 Therapy with Inhaled Corticosteroids (ICSs)

Maintaining proper asthma control is strictly related to the treatment of airway inflammation. ICSs are the mainstay of asthma therapy in children, and there are a lot of data about their effectiveness in protecting against EIB in children (figure 1).[1,3,12-18] However, there are limitations to preventing EIB using ICSs alone. It needs to be remembered that treatment with doses of ICSs that are too low sometimes leads to the onset of EIA.[13] Moreover, evidence exists that monotherapy with ICSs does not fully cover the needs of paediatric patients with EIA.[19-21] The latest

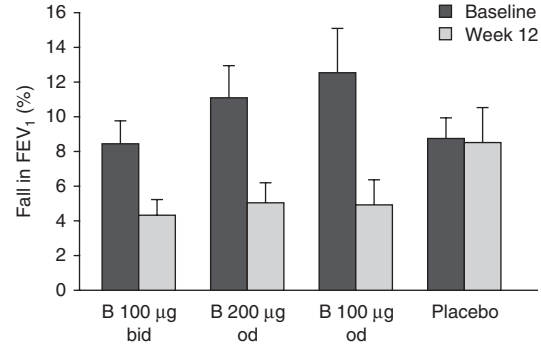

Fig. 1. Protection against exercise-induced bronchoconstriction of different doses of inhaled budesonide (B) in children after exercise testing. Comparison between treatments on maximum fall in the forced expiratory volume in 1 second (FEV_1) after exercise (% fall from pre-exercise value) from baseline to week 12 (reproduced from Jonasson et al.,[16] with permission). **bid** = twice daily; **od** = once daily.

Cochrane analysis showed that the relative benefits of ICSs compared with other forms of EIB treatment remains unclear (EL:2+).[22] This is the reason why the remaining part of this article concentrates on the currently available, additive therapies in children with asthma and EIB.

3.2 Therapy with Leukotriene Receptor Antagonists (LTRAs)

In 1992 in what was probably the first study on the topic, Robuschi et al.[23] showed that in adults, 800 μg of inhaled peptidoleukotriene receptor antagonist effectively attenuated EIB for as long as 24 hours after a single dose (EL:1+). Since then, there have also been some studies testing the effectiveness of LTRAs for protection against EIB in adolescents and children. However, there is still a lack of longitudinal studies involving a larger paediatric population.

One of the first important studies was a trial that examined the effect of montelukast on EIB in 6- to 14-year-old asthmatic children (n = 27) [EL:1].[24] The authors found that montelukast significantly attenuated EIB at the end of the dosing interval. It reduced the post-exercise percentage fall in FEV_1 over 60 minutes, which was measured as the area above the post-exercise fall in FEV_1 versus time curve and the maximum percentage fall in FEV_1. The authors underlined that the improvements in the post-exercise efficacy endpoints from pre-randomization baseline were also evident after the patients received placebo. Nevertheless, even with this effect, the between-group differences (montelukast vs placebo) in efficacy endpoints were significant. However, when the challenges were performed 24 hours after the latter of the two consecutive doses, montelukast did not provide complete protection against EIB.[24]

An important issue regarding treatment with LTRAs, and especially montelukast, is that it is usually prescribed on a regular basis. However, patients who manifest EIB symptoms only after strenuous activity could potentially be treated with LTRA 'as needed' in addition to, or instead of, other drugs.[25] This issue was investigated in a study by Peroni et al.[25] to evaluate the timing of the onset and duration of activity of a single oral-dose treatment with montelukast compared with placebo on EIB prevention in asthmatic children (n = 19) [EL:1]. Children (aged 7–13 years) with stable, mild asthma undertook three consecutive treadmill exercise tests 2, 12 and 24 hours after a single-dose administration. The analysis of the degree of protection showed montelukast had significant efficacy compared with placebo only at 12 hours; montelukast showed a significant protective effect 12 hours after dosing, but no effect after 2 and 24 hours. These authors suggested that the timing of administration of a single dose before exercise should be carefully considered in order to obtain the maximal drug efficacy.[25] In another study, Peroni et al.[26] found that the addition of loratadine to the montelukast treatment did not result in significant additive bronchoprotective effects on EIB in children with asthma (EL:1).

It should also be remembered that it is advisable to take montelukast in the evening. However, one study from Pajaron-Fernandez et al.[27] hypothesized that the effect of the drug on the response to an exercise challenge test in asthmatic children should be comparable whether the drug was taken in the morning or evening. They sought to determine if this effectiveness could vary depending on dosage time (EL:1). Children receiving ICSs were excluded. The study revealed a significant effect of montelukast in protection against EIB, measured both as the percentage of a maximum fall in FEV_1 and as the area under the curve (AUC), independently of dosing time. The measured changes in forced expiratory flow 25–75% ($FEF_{25–75\%}$) showed that recovery was faster and the AUC was smaller when montelukast was taken in the evening, albeit this difference was not statistically significant. The authors concluded that according to the main outcome variable (maximum percentage fall in FEV_1), montelukast protects against EIB in 6- to 14-year-old children with EIB, and this protection is independent of dosage time. However, when the fall in $FEF_{25–75\%}$ was considered, there was a trend towards evening dosing of montelukast, which was believed to be somewhat more effective.[27]

Analysing $FEF_{25–75\%}$ as a way of detecting lower airway obstruction has also been suggested recently.[28]

Other studies have also focused on the long-term management of asthmatic children with EIB. Kim et al.[29] showed that 40 asthmatic children with EIB had significant improvements in asthma symptom score, maximum percentage fall in FEV_1 after exercise and time of recovery after receiving montelukast for 8 weeks compared with a placebo group (EL:1+). In the treatment group, even 8 weeks after stopping montelukast, all endpoints were still significantly improved. The authors concluded that montelukast may be useful for the long-term management of asthmatic children with EIB. However, the protection against EIB provided by montelukast in that study, with the maximal reduction in FEV_1 of 27.6% after montelukast, is still insufficient.[29] De Benedictis et al.[30] reported that montelukast provided significant protection against EIB, measured using the mean percentage drop of FEV_1 after exercise challenge, in 32 asthmatic children aged 6–12 years over a 4-week period, suggesting a lack of tolerance to its bronchoprotective effect (EL:1) [figure 2]. Percentage of protection was defined as (Pp–Pt)/Pp where Pp is the maximum percentage fall in FEV_1 after placebo test, and Pt is the maximum

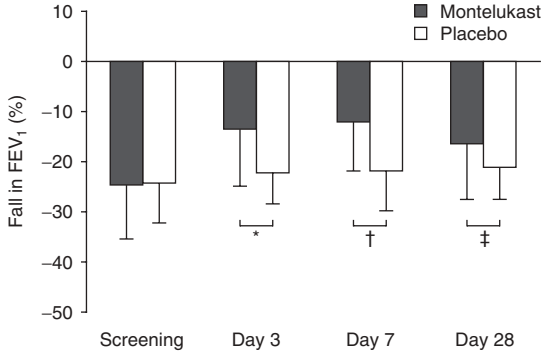

Fig. 2. Lack of tolerance to leukotriene receptor antagonist efficacy in children with exercise-induced bronchoconstriction. Mean percentage decrease of forced expiratory volume in 1 second (FEV_1) at screening and at different timepoints after treatment (reproduced from de Benedictis et al.,[30] with permission). * p = 0.026; † p = 0.005; ‡ p = 0.011.

percentage fall in FEV_1 after active treatment.[30] Despite the fact that the percentage of protection was in favour of montelukast when compared with placebo, resulting in 39%, 44% and 44% of protection after 3, 7 and 28 days of treatment, respectively, almost half of the patients in this study were nonresponders to montelukast. Only a few patients in each study group were receiving regular stable doses of ICSs, and there was no difference in lung function changes after exercise between patients who were receiving or not receiving ICSs in this trial. The authors stated that regular once-daily treatment with montelukast does not appear to reduce the protective effect on EIB over time and that it may be a preferential therapeutic option for long-term treatment of EIB in children.[30] However, in the light of these results, it should be remembered that the overall efficacy of montelukast treatment in the prevention of EIB was suggested to be <800 μg budesonide daily, as revealed in the study of Vidal et al.[8] performed in adolescents and adults (EL:1).

Considering that the exact mechanism of EIB is still unknown, some studies have shown that there may be a late-phase response, 3–8 hours after exercise, in a subset of asthmatic patients.[31-33] However, it is still debated whether a late-phase reaction to exercise really exists or if it represents fluctuations in bronchial tone.[34] Melo et al.[31] performed a study on 22 atopic asthmatic children aged 7–16 years with reproducible EIB. Most of them were treated continuously with ICSs in stable doses throughout the study period. Exercise challenges were performed while breathing cold dry air, and FEV_1 measurements were taken up to 8 hours after the exercise (EL:1). Reproducible, late-phase reactions occurred in 5 of 22 patients, which correlated with the extent of immediate response. After 1 week of treatment with montelukast, a significant decrease of immediate responses was observed. Compared with placebo, montelukast treatment was associated with a lower average decrease in the FEV_1 and a shorter time for recovery, independent of concomitant treatment with ICS (figure 3). Results from this study suggest that regular, once-daily treatment with montelukast attenuated the immediate-phase response and eradicated the

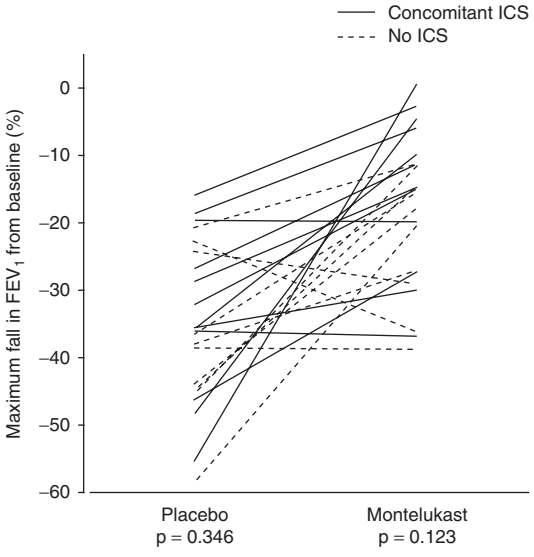

Fig. 3. Montelukast prevents exercise-induced bronchoconstriction in children, independent of concomitant treatment with inhaled corticosteroids (ICSs). Forced expiratory volume in 1 second (FEV_1) maximum percentage decreases after exercise challenge in patients treated with placebo or montelukast for 1 week (n = 22). The same degree of protection with montelukast was observed regardless of the use of ICSs (reproduced from Melo et al.,[31] with permission from Elsevier).

late-phase response induced by exercise challenge in asthmatic children. However, results of this study also showed that four patients were considered nonresponders to treatment. The authors explained that this phenomenon probably occurred because of the complexity of the pathophysiology of EIB, and suggested that leukotrienes do not seem to be the only elements involved.[31]

In another study, 30–40% of paediatric patients with asthma and EIB did not respond to therapy with montelukast.[35] The complexity of the EIB pathophysiology mentioned previously was studied in light of a possible lack of response to LTRAs in children with asthma, since protection against EIB with this treatment varies from around 40–50%[24] or even to almost 70% in the other study.[35] For example, Kim et al.[36] studied the influence of genetic polymorphism of the tromboxane A2 receptor (TBXA2R) on the efficacy of montelukast in preventing EIB in Korean children with asthma given that TBXA2R negatively regulates leukotriene C_4 synthase activity.[37] In their study, 100 children with asthma were recruited, and EIB was measured before and after an 8-week treatment with montelukast 5 mg.[36] It was found that children with the specific polymorphisms TBXA2R+924T>C homozygote (TT) and TBXA2R+795T>C hetero-or homozygote (CT or CC) genotypes had a significantly smaller response to an 8-week montelukast treatment with respect to maximum percentage fall in FEV_1 after exercise when compared with the paediatric patients with asthma, possessing common alleles.[36] Their findings underline that TBXA2R polymorphisms may play the role of a disease-modifying gene in children with asthma.[36] Moreover, the authors showed that by using the TBXA2R genotype, it is possible to predict the clinical response to LTRAs in children with asthma and EIB.[36] Drug responsiveness to LTRA in children with asthma was also studied in terms of the association of this phenomenon with interleukin (IL)-13 polymorphisms.[38] IL-13 is known to induce bronchial hyperreactivity, damage of epithelial cells, hyperplasia of goblet cells, hyperproduction of mucus and eosinophilia.[39,40]

LTRAs are able to decrease the ability of IL-13 to induce this phenomenon in tissue. Thus, Kang et al.[38] assessed the connection between IL-13 polymorphisms, clinical phenotypes and LTRA responsiveness in 100 Korean children with asthma and EIB. Subjects received montelukast for 8 weeks and the authors included 80 children from that group in the drug responsiveness analysis. The +2044G/A polymorphism located in the coding region of the *IL13* gene was associated with total IgE and the maximum percentage fall in FEV_1 in children with asthma and EIB, which suggests that the IL-13 polymorphism may modulate the severity of EIB in Korean children with asthma and EIB. A significant association between LTRA responsiveness and the IL-13 –1112C/T polymorphism was also shown. Moreover, a haplotype (CTA) consisting of three risk alleles of IL-13 occurred with a higher frequency in nonresponders than in responders to montelukast therapy.[38] This study indicates that LTRA responsiveness depends on the IL-13

–1112C/T polymorphism and the CTA haplotype of IL-13 polymorphisms, which could be useful as a target for the modulation of LTRA responsiveness.[38]

4. Clinical Efficacy of Reliever Treatment

National Asthma Education and Prevention Program (NAEPP) guidelines should be followed in patients with EIB or EIA. They recommend that if a patient requires treatment with a β_2-adrenoceptor agonist more than twice a week, a low dose of ICSs should also be administered.[41]

4.1 Therapy with Short-Acting β_2-Adrenoceptor Agonists (SABAs)

SABAs are the most common drugs administered before exercise to relieve EIB symptoms in children with asthma. This is because they offer an immediate onset of action and, thus, a fast effect on EIB symptoms. For example, salbutamol is a β_2-agonist with an onset of action beginning in <15 minutes and a duration of action of approximately 6 hours after a single dose (EL:2).[42,43] Bronsky et al.,[44] in their study in children with asthma and EIB (n = 44), revealed that salbutamol, both as aerosol and Rotacaps® formulations, prevented EIB symptoms in almost 100% of patients compared with 57% of patients in the placebo group. It also reduced mean post-exercise FEV_1 by 6% independent of formulation group (EL:2). Pretreatment with salbutamol prevented EIB in 100% of children (n = 11) in the latest study of Raissy et al.[45] Salbutamol is also known to significantly improve fitness parameters in children with asthma and EIB (e.g. maximum oxygen uptake, ventilatory anaerobic threshold, ventilation and energy costs of running) compared with placebo.[46] There is also evidence that bronchodilation after salbutamol increases with age in children with asthma (EL:1).[47] Other studies supplied similar data on the efficacy of SABAs in children with asthma (EL:2).[48-52] The latest data from adults showed that a regular 16-week treatment with salbutamol in patients with a genetic polymorphism that results in homozygosity for arginine (Arg/Arg) at amino acid residue 16 of the β_2-adrenergic receptor worsened the long-term response to salbutamol use.[53] The authors of this study suggest that bronchodilator treatments avoiding salbutamol may be more effective for patients with this genotype.[53] These data argue that salbutamol is an 'as needed' drug. A recommended single dose of salbutamol in children is 0.1–0.2 mg.[1]

There are also limitations on the use of SABAs in children. Unfortunately, this group of inhaled medications is characterized by short-term real protective effect. A study of adolescents and adults demonstrated that the protective effect of salbutamol diminishes rapidly after dosing and it reaches effectiveness of placebo 4 hours after dosing.[42] This phenomenon was confirmed in another study of SABAs in children.[54] It was shown in the study of Inman and O'Byrne,[55] and it should always be remembered that the regular use of salbutamol four times a day for 1 week worsens EIB. Nevertheless, it remains extremely effective in preventing EIB when used immediately before exercise. It should be remembered that many asthma-provoking physical activities take place at school and, in many schools, children are not encouraged by teachers to keep their inhalers with them.[2] Another problem is they may not wish to take any medicine to school in order to not show their 'weakness' to their schoolmates.[56]

4.2 Therapy with Long-Acting β_2-Adrenoceptor Agonists (LABAs)

LABAs are characterized by a longer duration of protection against EIB symptoms in children than SABAs, and there are a lot of studies that showed this difference in children.

4.2.1 Formoterol

Boner et al.[57] compared the duration and effectiveness of formoterol 12 μg with salbutamol 200 μg in 15 children with EIB (EL:1+). The patients performed exercise tests 3 and 12 hours after dosing. Formoterol was more effective than salbutamol and placebo after both tests, and the effect of salbutamol did not differ from the effect of placebo after 3 and 12 hours.[57] The same

study model was partly repeated in the trial of Daugbjerg et al.[58] with a larger dose of salbutamol (400 μg) in 16 asthmatic children using pressurized metered-dose inhalers (pMDI) [EL:1+]. Similarly, formoterol was almost twice as protective against EIB than salbutamol after 3 hours and almost seven times more protective after 12 hours.[58]

Using a similar methodology, another study compared the action of formoterol via Turbuhaler® (4 μg and 9 μg) and terbutaline via Turbuhaler® (500 μg) for EIB in 27 asthmatic children aged 7–18 years (EL:1+).[59] Terbutaline produced a significantly better protection than placebo 15 minutes after drug administration, but the effect declined and reached the same level as placebo during the exercise test performed 4 hours after administration. Both formoterol and terbutaline produced significant protection against EIB compared with placebo 15 minutes after drug administration. However, only formoterol provided protection that lasted for 12 hours. Despite the fact that in this study the majority of children were regularly using inhaled ICSs, they showed symptoms of EIB after a baseline exercise test and, as the authors underline, a single dose of formoterol, no matter how large, provided the protection against EIB that they needed.[59]

Ferrari et al.[60] revealed a rapid (15-minute) protective effect against EIB of formoterol administered via dry-powder inhalers (DPIs) in young asthmatic athletes with an average age of 16.8 years (but including adults). Another study performed in adolescents and adult patients (age range 13–41 years; n = 20), compared the effect of single doses of formoterol (12 μg and 24 μg) via a DPI and salbutamol (180 μg) via a pMDI (EL:1+).[42] Forty-five percent of the patients studied were also taking inhaled or nasal corticosteroids during the study. Exercise challenge tests were conducted after drug administration, and both doses of formoterol produced a significantly greater inhibition of FEV_1 decreases at all timepoints than placebo. Moreover, formoterol had a rapid onset of action similar to that of salbutamol. The effect of salbutamol on EIB was the same as placebo 4 hours after dosing. There was no difference between the effectiveness of the two formoterol doses (12 μg and 24 μg) in preventing EIB, including in adolescents with asthma.[42] Bronsky et al.[61] showed a similar effect of formoterol in 17 adolescents and adults with asthma and EIB, while more extensive and precise results on the rapid effect of formoterol in children with EIB were presented by Hermansen et al.[62] (EL:1+). These authors performed a trial in 24 children (aged 7–15 years) with EIB, which tested the effectiveness of formoterol 9 μg and terbutaline 500 μg, administered via DPI, in preventing the decrease of EIB spirometric indexes. Both formoterol and terbutaline produced the same bronchodilatory effect 3 and 5 minutes after dosing, the same mean increase from each predrug baseline and almost the same median times of recovery to within 5% of baseline FEV_1, with a small shift in favour of formoterol. The authors concluded that formoterol is at least as effective as a SABA and can be considered an alternative in the treatment of acute EIB in school children.[62]

The development of tolerance to the bronchoprotective effect of formoterol is a well known phenomenon in adult patients with asthma and EIB. García et al.[63] showed the development of tachyphylaxis to the protective effect of formoterol against EIB after 4 weeks of regular treatment in adults. This tolerance was shown to begin on the 14th day of treatment with formoterol and did not progress after another 2 weeks of treatment.[63] Some important studies performed in adult populations have indicated that the tolerance to formoterol tends to develop only during the early stages of treatment (weeks),[64] and the progressive tolerance does not develop during the next 6 months of treatment.[65] Thus, a decreasing efficacy of this drug in preventing the EIB in children still remains at least questionable. Moreover, when formoterol is used three or fewer times per week, the tachyphylaxis phenomenon is rarely seen.[66]

The pharmacological parameters of formoterol efficacy as a preventive drug for EIB in children are of great value; therefore, it is crucial to remember how important the proper technique in taking inhaled drugs is in the case

of children with EIB.[67] In one study involving 16 children with EIB, formoterol inhaled from the aerolizer at the low flow rate showed placebo efficacy; thus, in children, obtaining the highest possible value of inspiratory flow rate during drug inhalation must be taken into account (figure 4).[67]

4.2.2 Salmeterol

The first study on the effect of a single dose of inhaled salmeterol given via a pMDI and spacer in 13 asthmatic children with EIB was conducted in 1992.[68] In this study, salmeterol improved all measured spirometric parameters of EIB, with the onset of action starting within 5 minutes and lasting 9 hours with similar effectiveness (EL:2).[68] Since then, many studies in both children and adults, have confirmed the prolonged efficacy of salmeterol for EIB.[69-72] In particular, studies of salmeterol via Diskhaler® and Discus® in children showed a bronchoprotective effect against EIB lasting for 12 hours in children with asthma,[73,74] independent of low or high peak inspiratory flow rates (EL:2).[73]

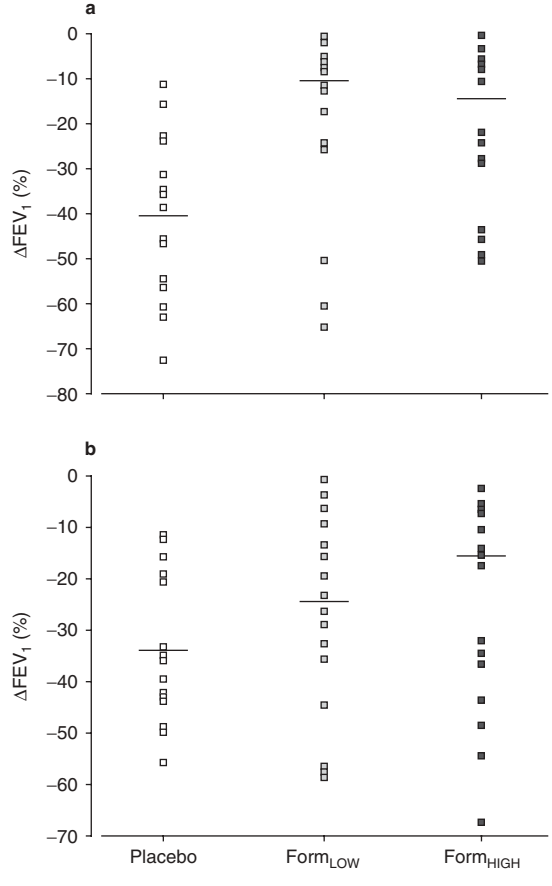

Fig. 4. Formoterol inhaled from an aerolizer at a low flow rate may show placebo efficacy in children with exercise-induced bronchoconstriction. Maximum percentage decrease in forced expiratory volume in 1 second (ΔFEV_1) after exercise in 16 children: (**a**) 3 hours and (**b**) 12 hours after inhalation of placebo, formoterol inhaled at low flow rate ($form_{LOW}$) and formoterol inhaled at high flow rate ($form_{HIGH}$). Medians are indicated by horizontal lines (reproduced from Nielsen et al.,[67] with permission).

A study by de Benedictis et al.[75] performed in 12 children (aged 7–14 years) with EIB compared the efficacy of two doses of salmeterol via pMDI (25 μg and 50 μg). Both doses were found to be equally effective against EIB and it was suggested that a smaller dose may be suitable for most asthmatic children (figure 5).[75] However, this was not confirmed by the results of another study.[76]

The morning efficacy of salmeterol (25 μg and 50 μg) has been evaluated in 23 children after administration the evening before.[77] This study confirmed similar overnight protection of both drug doses (EL:2). However, salmeterol did not fully protect against EIB in eight patients from the salmeterol 25 μg group and 11 patients from the salmeterol 50 μg group, which suggests that, in children with EIB, additional protective drugs administered before exercise may be needed to fully control their symptoms.[77] Moreover, some trials have shown the problem of tolerance to salmeterol against EIB when administered regularly twice daily.[72] This was further investigated by Simons et al.[78] in a trial performed in 14 children (12–18 years old) with salmeterol 50 μg administered once daily via pMDI (EL:2). Excellent bronchoprotective efficacy against EIB was shown with the first dose of salmeterol at 1 and 9 hours after drug administration; however, after the 28th day of regular once-daily salmeterol treatment, the bronchoprotective effect of the drug reached placebo efficacy after 9 hours, despite concomitant use of ICSs. Indeed, this study revealed that the bronchoprotective effect of salmeterol may wane during the course of a regular once-daily treatment regimen even with

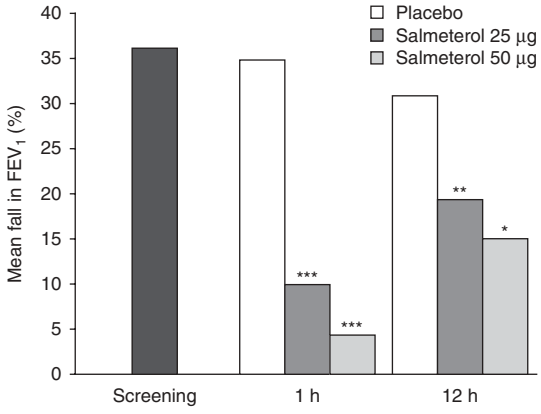

Fig. 5. Comparison of the efficacy of two salmeterol doses in preventing exercise-induced bronchoconstriction in asthmatic children. Mean percentage decrease in forced expiratory volume in 1 second (FEV_1) at screening and after the first and second exercise test with each treatment (reproduced from de Benedictis et al.,[75] with permission). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs placebo.

simultaneous regular treatment with ICSs.[78] This has also been shown in studies involving adults,[72,79,80] as well as another in adults and children.[79] Furthermore, in a study of adults with asthma, a regular 1-month treatment with salmeterol offered substantial protection against EIB; however, a decrease in drug activity time after a single dose was seen, which became evident after a 1-month treatment.[80] Tolerance to the effect of salmeterol has been shown to be present even within 24 hours of administration of the first two doses of salmeterol in adults.[81]

Salmeterol, like formoterol, has also been the subject of studies comparing its protective efficacy against EIB with SABAs. One study in 26 children (aged 4–11 years) compared the time of efficacy in protection against EIB of two doses (25 μg and 50 μg) of salmeterol versus salbutamol (180 μg).[76] After the first exercise challenge (1 hour after drug administration), the mean minimum percentage of predicted FEV_1 was significantly higher in the salbutamol group than the placebo and both salmeterol groups, and after two further exercise tests (6 and 12 hours after drug administration), salmeterol 50 μg produced higher mean minimum percentage of predicted FEV_1 values than placebo or salbutamol, which were similar. The authors of this trial concluded that salmeterol 50 μg provided effective protection against EIB for at least 12 hours in asthmatic children and its effect was more pronounced than salbutamol 180 μg.[76]

4.3 Restrictions on the Use of Inhaled β_2-Adrenoceptor Agonists in Relation to Sports

Children and adolescents active in sports and paediatricians treating such children should be aware of the regulations concerning the use of inhaled β_2-adrenoceptor agonists. Athletes (especially the young) are allowed to use them under special conditions.[11] Treatment with β_2-adrenoceptor agonists requires an abbreviated therapeutic use exemptions approval (TUE) according to the World Anti-Doping Association, or documentation of bronchial hyper-responsiveness, by reversibility to inhaled bronchodilators, positive exercise test, eucapnic hyperventilation test or cold air challenge according to a medical committee of the International Olympic Commission.[11] A concentration of urinary salbutamol ≥1000 ng/L is considered an adverse analytical finding regardless of any form of TUE.[11] More information regarding this topic is included in the latest papers of Carlsen et al.[11] and Weiler et al.[12]

4.4 Inhaled Anticholinergics (Ipratropium Bromide)

Anticholinergic drugs are now increasingly used by athletes with EIA, and they may be useful in selected children, i.e. in some patients where the β_2-adrenoceptor agonists cause significant adverse effects or are contraindicated,[82] such as in the case of the sport restrictions described in section 4.3.[12] The efficacy of ipratropium bromide as an EIB inhibitor has been shown in some studies in children.[82-85] However, in children, the degree of protection against EIA may not correlate with the bronchodilation caused by ipratropium bromide, which suggests that muscarinic mechanisms are only partly responsible for the pathogenesis of EIA (EL:1).[84] Their importance varies among individuals and may also vary in the same individual,[84] possibly because the therapeutic effect of ipratropium bromide on EIA in children may be related to vagal

activity[83] and, thus, be beneficial only for those with the increased vagal activity.

5. Studies Comparing the Efficacy of Various Novel Therapies in the Prevention of EIB in Asthmatic Children

5.1 Therapy with LABAs versus LTRAs

The study of Villaran et al.[79] was the first to compare an LTRA (montelukast) with an LABA (salmeterol) in a group of 197 mainly adult patients (aged 14–54 years), with subgroups of only eight patients in each group aged <18 years (EL:1+). This was an 8-week, open-label, intent-to-treat study. Up to 25% of patients already taking ICSs were allowed to continue (doses of 200–500 μg). Montelukast was superior to salmeterol in protecting against EIB without inducing tolerance, which occurred in the salmeterol group (figure 6). More respiratory clinical adverse events and discontinuations because of clinical adverse events were reported in the salmeterol group. This study showed for the first time that an LTRA, montelukast, could be a better alternative than a LABA agent, salmeterol, for the long-term treatment of EIB. However, the trial was performed mainly in adults.[79] Similar results were achieved in an 8-week study in adolescents and adults with asthma and EIB.[86]

One trial compared the effects of the addition of montelukast or salmeterol to an ICS on the response to rescue β_2-adrenoceptor agonist use after EIB (EL:1+).[87] The participants were adolescent and adult patients (aged 15–58 years) with asthma experiencing uncontrolled symptoms while taking low-dose inhaled fluticasone and with a history of EIB worsening of asthma. The patients were treated with montelukast, salmeterol or placebo for 4 weeks. Patients treated with montelukast had significantly greater response to salbutamol compared with patients taking salmeterol at 1 and 4 weeks of therapy, which was the result of a decrease in the level and rapidity of rescue bronchodilation in patients taking salmeterol. In addition, patients receiving montelukast had a significantly greater attenuation of EIB compared with the placebo group, in contrast to the patients from the salmeterol group, who did not. In summary, the authors underlined that in patients with asthma and EIB, the advantage of montelukast add-on therapy with a LABA lies in providing the persistent attenuation of EIB and possessing an additional effect with rescue SABA therapy.[87]

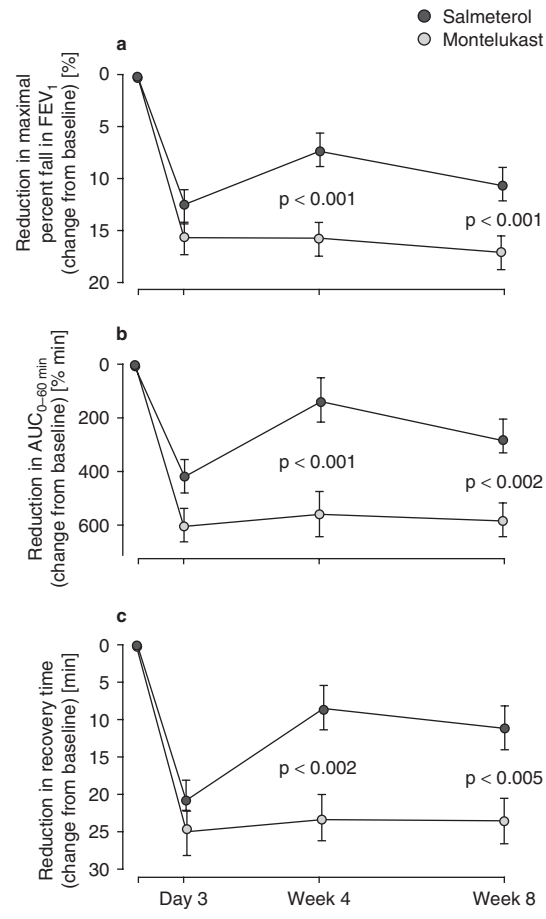

Fig. 6. Comparison of the efficacy of montelukast and salmeterol in preventing exercise-induced bronchoconstriction in asthmatic children. Treatment with montelukast (n = 97–98) caused a significant reduction compared with salmeterol (n = 83–88) in change from baseline in (**a**) maximum percentage fall in forced expiratory volume in 1 second (FEV_1) after exercise; (**b**) area under the curve from 0 to 60 minutes ($AUC_{0\text{-}60min}$); and (**c**) time to recovery to within 5% of pre-exercise FEV_1 at weeks 4 and 8 of treatment. Values are means ± SEM (reproduced from Villaran et al.,[79] with permission from Elsevier).

Both drugs have also been compared as a short-term prophylactic treatment of EIB in

47 adolescent and adult patients.[88] Spirometric indexes of EIB were reduced significantly when assessed from 2 to 24 hours after a single dose of montelukast 10 mg; its efficacy was similar in magnitude to that of a single dose of inhaled salmeterol 50 μg, but was longer than that of salmeterol (EL:1). However, both drugs possessed similar efficacy up to 8.5 hours after a single dose.[88]

5.2 Therapy with SABAs versus LTRAs

Recently, two studies have compared the protective efficacy against EIB of SABAs with LTRAs in paediatric populations.[45,89] The first study was performed in 11 children, aged 7–17 years with mild-to-moderate asthma and compared pretreatment with salbutamol versus montelukast added to the current asthma regimen (EL:1).[45] This trial showed significant differences in favour of two doses of salbutamol compared with 3–7 days of montelukast as measured by exercise challenge spirometric indexes 1 hour after exercise. 100% of patients receiving salbutamol were completely protected against EIB compared with only 55% of patients receiving montelukast.[45] The second study compared the protective effects against EIB of a single inhalation of the combination of reproterol/sodium cromoglycate with montelukast in 24 asthmatic children, aged 6–18 years (EL:-1).[89] Reproterol is known to be a dual-acting β_2-adrenoceptor agonist and phosphodiesterase inhibitor.[90] Both treatment methods clearly provided protection against EIB; however, the protection provided by one dose of reproterol/sodium cromoglycate was more pronounced than that of montelukast after 3 days of treatment.[89]

5.3 Comparison between Therapies with Two Different LABAs

We were able to find only one study directly comparing the protective effect against EIB of single doses of formoterol and salmeterol administered via a pMDI in 11 adolescents and adults with asthma (EL:1).[60] Immediately after drug administration, formoterol provided significantly better protection against EIB than salmeterol, and 4 hours later, the protection was similar with both drugs in all measured parameters. This comparative study clearly revealed that formoterol inhaled via a pMDI is effective in preventing EIB within a few minutes of administration, which is not characteristic for all LABAs, namely salmeterol.[60] This study also confirmed the results of previous studies regarding differences between these LABAs in children,[91,92] and underlined that both the rapid and long-lasting protective effect of formoterol gives it an advantage over salmeterol in the management of asthmatic adolescents and adults with EIB.[60]

The results of this study were confirmed by Richter et al.,[93] although in adults only. The baseline of the differences in action between these LABAs is that salmeterol is known to be a partial β_2-adrenoreceptor agonist,[94] while formoterol is almost a full agonist;[95] this is the reason why it acts more rapidly than salmeterol.

5.4 ICSs/LABAs Combination versus ICSs Monotherapy

Studies performed in recent years have shown that ICSs/LABAs administered via single devices improved asthma control in paediatric patients as well as adults. However, all the trials examined standard measures of asthma and did not include EIB tests.[96] We were able to find only one more recent trial that evaluated the protective effects of fluticasone/salmeterol (250/50 μg twice daily) against EIB compared with the effect of fluticasone alone (250 μg twice daily) via Diskus® for 4 weeks (EL:1+); that was the trial by Weiler et al.,[97] performed in a group of 192 adolescent and adult patients with asthma (aged 12–50 years). Each subject in this study was receiving moderate-dose ICSs for the treatment of persistent asthma at least 30 days before screening. Improvements in the mean values of the maximal percentage decline in FEV_1 1 hour after drug administration were both in favour of a combined treatment schedule on day 1 and in week 4; interestingly, at 8.5 hours after drug administration on day 1 (after the first doses), the maximal percentage decline in FEV_1 did not differ between the two studied groups. However, after four consecutive weeks there was a difference observed in favour of fluticasone/salmeterol therapy. This study showed that fluticasone/salmeterol 250/50 μg taken regularly

twice daily protects against EIB in patients already receiving moderate-dose ICSs. Furthermore, in this study, the protective effect of fluticasone/salmeterol was maintained with long-term administration.[97] Initial data from studies in adults regarding general efficacy of some combinations with extra-fine particles, such as beclomethasone/formoterol, suggests caution in any future assessment of efficacy in preventing EIB in children with asthma.[98] The extra-fine combination of beclomethasone/formoterol, although allowing a decrease in the dose of ICSs, still maintains the same dose of LABAs.[98]

6. Studies Comparing/Combining Available Treatment Options in Children with Asthma and EIB

In a recent study, we compared the ability of different combinations of anti-asthmatic treatment recommended in childhood asthma to protect paediatric patients from EIB.[99] Ninety-one children aged 6–18 years with atopic asthma were randomized to a 4-week trial. We compared treatment with ICS/LABA (budesonide/formoterol), ICS alone (budesonide), LTRA alone (montelukast) or LTRA/ICS (montelukast plus budesonide) to placebo for the prevention of EIB in five groups of subjects. All active treatment groups were effective for EIB, as evidenced by an increase in AUC for the FEV_1 values with exercise over a 20-minute period ($AUC_{0–20min}$) and by reduction in the maximum percentage fall in FEV_1 (figure 7). The protective effect of monotherapy with montelukast and combined therapy of montelukast with budesonide on EIB was significantly greater than that in two other active treatment groups.[99] In the opinion of current referees, the most valuable information in our study is that the protective effect of montelukast or the combination of montelukast with budesonide on EIB was found to be greater than that of budesonide or budesonide/formoterol.[100]

Furthermore, our findings provide additional evidence that cysteinyl leukotrienes play a key role in the pathogenesis of EIB and suggest that treatment with LTRAs should be preferred over other options in individuals with normal baseline lung function but indirect airway hyperresponsiveness manifested by EIB.[101] With these results, it may seem reasonable to develop a combined and complete anti-asthma treatment in order to prevent EIB symptoms in children. Therefore, we need to perform further studies in children with persistent asthma and EIB that will define more precisely the balance of the benefit-risk ratio of such a complex combined treatment.

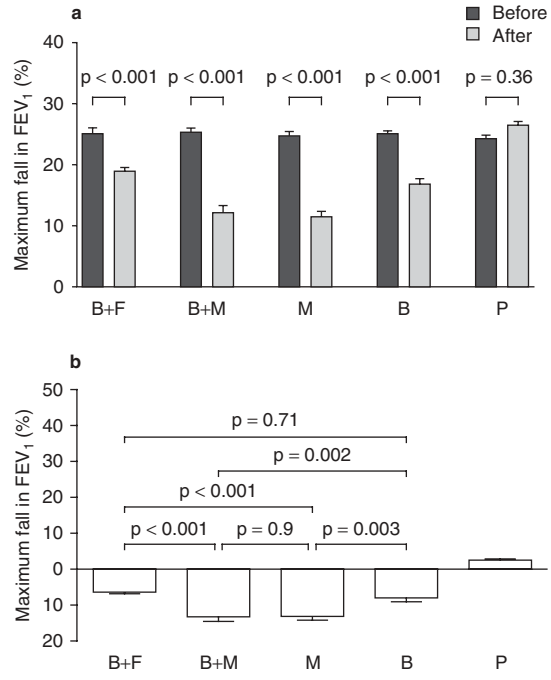

Fig. 7. The ability of different combinations of anti-asthmatic treatments recommended in childhood asthma to protect paediatric patients from exercise-induced bronchoconstriction, based on maximum percentage fall in forced expiratory volume in 1 second (FEV_1). Data are presented as (**a**) means with SEMs before and after treatment and (**b**) change in maximum percentage fall in FEV_1 presented as means with SEMs. All treatments significant ($p < 0.001$) compared with placebo (reproduced from Stelmach et al.,[99] with permission from Elsevier). **B** = budesonide; **F** = formoterol; **M** = montelukast; **P** = placebo.

7. Tolerability and Safety

7.1 LTRAs

7.1.1 Montelukast

Reported adverse events (AEs) in clinical trials with montelukast were not serious, and were transient and self-limited,[24,88] or were not observed.[26] No significant modification of lung

function was reported in another trial.[25] No patients were withdrawn from any study as a result of laboratory AEs measured.[24,26,88]

7.2 Inhaled β_2-Adrenoceptor Agonists

The latest data on genetic aspects of drug responsiveness deserve comment. The latest studies have supplied some evidence that single nucleic acid polymorphisms or DNA sequence variations in the β_2-adrenergic receptor coding gene may change the function of this receptor and are likely to modulate treatment response.[102] The results of the BARGE (Beta-Adrenergic Response by Genotype) trial, described in section 4.1, demonstrated that asthmatic patients with the Arg/Arg genotype at the amino acid position 16 should avoid regular treatment with salbutamol because of its possible lack of activity or resultant worsening of asthma symptoms and lung function.[53] While it is controversial whether we can extrapolate the results of this study to the use of LABAs or not, both studies investigating the longitudinal effectiveness and safety of salmeterol, i.e. the SMART (Salmeterol Multicenter Asthma Research Trial)[103] and the Serevent® Surveillance Study,[104] revealed an increased risk of very serious exacerbations of asthma, some of them leading to fatal or very severe asthma episodes, with especially high prevalence among African Americans. These results were probably the reason for a 'black box warning' for salmeterol and formoterol given by the US FDA.[105] One more recent study, performed in 546 children and adolescents with asthma, also showed that the Arg/Arg genotype in children increased the risk of asthma exacerbations if they had been taking salmeterol during the previous 6 months.[106]

7.2.1 SABAs

Salbutamol

Salbutamol was well tolerated in numerous studies in children. No drug-related AEs were reported and safety assessments were within normal limits after a single aerosol dose of 90 μg/inhalation,[42,49] a single aerosol dose of 180 μg/inhalation and a powder dose of 200 μg/inhalation.[44]

7.2.2 LABAs

Formoterol

The studies with single formoterol doses from 4.5 to 12 μg/inhalation did not report any adverse effects on blood pressure and resting heart rate in children with asthma and EIB.[57-60,67] In one study, 36.8% of both adolescent and adult patients who received formoterol 12 μg/inhalation, and 5.9% of patients who received formoterol 24 μg/inhalation reported mild or moderate AEs during the study.[42] The only AE reported by more than one patient during the study by Bronsky et al.[61] was nervousness in two patients after administration of formoterol 24 μg, which was considered serious. It should be noted that many studies in children and adults have shown favourable tolerability of formoterol at high doses.[107-110] Hermansen et al.[62] reported the observation that similar numbers of standard-dose inhalations of formoterol (4.5 μg) and terbutaline (0.5 mg) resulted in less systemic activity from formoterol.

Salmeterol

Many studies on salmeterol described no AEs after doses of 25 μg and 50 μg and no influence on heart rate after treatment.[68,73,75-77] In a single-dose study conducted in 24 children with asthma and EIB, 3 experienced AEs after salmeterol via Discus®; those were nasal congestion, headache and a rash. However, none were reported to be caused by the study medication.[74] Nevertheless, in longitudinal study of salmeterol aerosol 50 μg once-daily as a single morning dose in 14 adolescents, three subjects developed a headache during 28 days of salmeterol treatment.[78] Headaches and a previously described (section 4.2.2) tachyphylaxis phenomenon after long-term treatment with salmeterol[72,78] may limit the usefulness of this drug in the regular, maintenance treatment of EIB in children with asthma.

7.3 Combination Inhaled Therapy

7.3.1 Fluticasone/Salmeterol

No serious AEs were reported during 4 weeks of treatment with fluticasone/salmeterol administered via a single device.[97] Of the

patients receiving fluticasone/salmeterol, 7% reported AEs that were considered by the authors to be drug related, for example *candidiasis* (2%), headaches (3%) and one exacerbation of asthma due to a respiratory tract infection. One patient was withdrawn from this study because of 'fainting', which was considered by the authors as possibly related to the study medication.[97]

7.3.2 Budesonide/Formoterol

One paediatric trial conducted in children with asthma and a history of EIB has described the nature and quantity of safety issues of the budesonide/formoterol combination.[111] Serious AEs reported in 2 of 212 patients in the budesonide/formoterol DPI group were acute sinusitis and migraine; they were not considered to be related to treatment by the authors. Moreover, in this 12-week study, treatment with budesonide/formoterol DPI resulted in a significant decrease in urinary cortisol values compared with other treatment options studied. However, the authors concluded that this result could have been caused by lung tissue deposition and absorption of budesonide differences between the pMDI or DPI devices used, or this difference could have been due to the small sample size of the study.[111]

7.4 Inhaled Ipratropium Bromide

Treatment with inhaled ipratropium bromide seems to be safe. In the studies reported to date, we have not found any important AEs after treatment with inhaled ipratropium bromide in children with asthma.[82-85]

8. Individualizing the Treatment of Exercise-Induced Asthma and EIB

In patients with chronic asthma, EIA may be a manifestation of poor asthma control and it is important to assess the overall treatment strategies to maximize therapy.[12] In contrast, for patients who primarily have EIA without other manifestations of chronic asthma, it is important to determine if there is no underlying chronic asthma.[12] That is why the most important recent guidelines underline the need for testing antiasthmatic drugs and their effect on different parameters of bronchial hyperresponsiveness, including testing for EIB.[11,12] This is also the case for children with EIB and EIA.

9. Conclusions

Recent important guidelines suggest that the principles of asthma management in general may also be applicable to EIA. Before starting treatment, there is a need to distinguish children with recurrent asthma symptoms in whom EIB is also present (patients with EIA) from asthmatic children whose symptoms appear only as a result of exercise (patients with EIB). This may indicate a requirement for further controller treatment in patients with EIA and reliever treatment in patients with EIB. The aim of treatment in every child with EIB is to maintain good physical activity with no symptoms. If the non-pharmacological treatment of EIB in children (advised as a first step in the management of EIB) fails, starting appropriate pharmacotherapy according to the current guidelines is strongly recommended.[1,2,5,6] ICSs are the first-choice controller drugs for EIA in children with persistent asthma (GR:A). In children with EIA without complete control with ICSs, SABAs (GR:A), LTRAs (GR:A) or LABAs (GR:A) may be added to gain control of the disease. Treatment with relievers such as SABAs (GR:A) [e.g. salbutamol], parasympatholytics (GR:B) [e.g. ipratropium bromide] or eventually LABAs (GR:A) [e.g. formoterol] administered 10–15 minutes before exercise is, and probably will remain, the most preferred method of preventing EIB symptoms in children; however, these should not be used as monotherapy in children with persistent asthma (EIA).

Clinicians need to be aware that over-reliance on bronchodilators, such as an inhaled β_2-adrenoceptor agonists when used on a regular basis can lead to a detrimental decrease of their effect, an increase in airway hyperresponsiveness and the underuse of ICSs, a group of drugs representing the mainstay of persistent asthma therapy in children. It should be remembered that according to international guideline recommendations, if any

patient requires treatment with a β_2-adrenoceptor agonist more than twice weekly, a low dose of ICSs should be administered.[41] On the basis of recent data, β_2-adrenoceptor agonists should never be used as monotherapy (i.e. without an ICS) in any patient with persistent asthma.[1,41]

Inhaled parasympatholytics may be effective as preventive relievers in some children with EIB or EIA, especially among those with increased vagal activity. Growing evidence regarding a well balanced efficacy-safety profile of the antileukotriene drugs in preventing the occurrence of EIB symptoms in children has led to widespread prescribing of this group of drugs in recent years, and to a hope that they can fill the gap between inhaled β_2-adrenoceptor agonists, parasympatholytics and ICSs. In patients with persistent asthma, the advantage of LTRAs over add-on therapy with LABAs lies in providing a persistent attenuation of EIB and producing an additional effect with rescue SABA therapy. On the other hand, an important disadvantage of this group of drugs may be a non-response phenomenon seen in some children, with a so far unknown pathophysiological and immunological origin.

Data concerning efficacy-safety profiles of fixed combination treatments in EIA in children are encouraging, but are still insufficient to make important conclusions, and further studies are needed to establish their role in this area. The safety profiles of inhaled SABAs and LABAs, anticholinergics and montelukast, when prescribed in the dosages approved for children and as demonstrated in the studies described in this article, seem to be sufficient to recommend use of these drugs in the prevention of EIB symptoms.

The need to individualize EIA treatment in children should always be remembered, together with the need to test prescribed drugs and assess their effect on different parameters of bronchial hyperresponsiveness, including testing for EIB.

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