

Pilot Study: The Effect of Reducing Treatment on Exercise Induced Bronchoconstriction

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Summary. Rationale: Asthma therapy should be stepped up or stepped down in response to changes in asthma control. However, there is little evidence available on the optimal timing, sequence, and degree of medication reductions. In this study we analyzed clinically stable asthmatic children who underwent a medication reduction from a combination preparation consisting of an inhaled corticosteroid (ICS) and long acting beta2-agonist (LABA) to monotherapy with the same dose of the ICS. We hypothesized that the extent of exercise-induced bronchoconstriction (EIB) would not increase after the cessation of the LABA. Methods: Nineteen children, aged 8–16 years, with clinically stable asthma, receiving LABA/ICS combination therapy, were analyzed in this open-label pilot study. Children performed an exercise challenge at baseline and 3 weeks after the medication reduction. Best values of spirometric measurements of the forced expiratory volume in 1 sec (FEV₁) were used for statistical calculations. Results: Maximum percent fall in FEV₁ was significantly lower after 3 weeks of ICS monotherapy ($P = 0.03$). Eight of 19 children had a $\geq 15\%$ fall in FEV₁ after exercise at the initial exercise challenge. In this subgroup, maximum percent fall in FEV₁ after the medication reduction was significantly lower ($P < 0.01$), and in six children it decreased to $< 15\%$, indicating they no longer had EIB. Conclusion: In clinically stable asthmatic children on LABA/ICS combination therapy, the cessation of the LABA can reduce and in most cases abolish EIB. **Pediatr Pulmonol.** 2010; 00:1–7. © 2010 Wiley-Liss, Inc.

Key words: asthma; children; long acting bronchodilator agent; inhaled corticosteroid.

INTRODUCTION

According to international guidelines, asthma therapy should be stepped up or stepped down in response to changes in asthma control.^{1,2} Combination therapy with an inhaled corticosteroid (ICS) and long acting beta2-agonist (LABA) is often prescribed as the third step in treatment regimens.^{1,2} There are many arguments in favor of this combination.³ A meta-analysis reviewing LABA treatment for childhood asthma concluded that the addition of a LABA to an ICS improved pulmonary function measures, reduced the use of rescue medications and improved quality of life measures.⁴ LABAs are also effectively used as prophylaxis for exercise-induced bronchoconstriction (EIB).^{5–7} EIB occurs in the majority of asthmatic children and is an index of airway hyper-responsiveness (AHR). However, regular use of LABAs can lead to downregulation of the beta2-adrenoreceptor (β 2AR), resulting in the development of tolerance.⁸ This implies that the duration of the bronchoprotective effect of a LABA against EIB is reduced.^{6,7,9,10} Furthermore, the recovery time from EIB to pre-exercise lung function after rescue therapy with a short-acting beta2-agonist (SABA) is prolonged.^{11,12} Regular treatment with SABAs can even enhance the severity of EIB.^{11,13}

By reviewing the medical records of asthmatic adults, Yawn et al.¹⁴ found that only 13% of medication changes were step-down changes. Reductions of the dosage were

about twice as common as steps down in the class of medication prescribed. There is little evidence available on the optimal timing, sequence, and degree of treatment reductions. When asthma is controlled with LABA/ICS combination therapy, the suggested step-down approach for adult asthmatics is to reduce the dose of the ICS.^{15–17} An alternative that is recommended by the FDA¹⁸ is to discontinue the LABA and continue ICS monotherapy at the same dose.^{1,2} The effect of stepping down treatment from LABA/ICS combination therapy to ICS monotherapy on EIB has not yet been studied.

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In this study, we analyzed this medication reduction in clinically stable asthmatic children. Because the development of tolerance has an impact on the severity of EIB, we hypothesized that the extent of EIB would not increase after the cessation of the LABA.

MATERIALS AND METHODS

Subjects

Children were recruited from the outpatient clinic of the Medisch Spectrum Twente in Enschede. Fifty-two children with clinically stable asthma for >3 months receiving treatment with LABA/ICS combination therapy, who underwent a medication reduction according to treatment guidelines,^{1,2} were selected. Twenty-four otherwise healthy children, aged 8–16 years, with a history of allergy (confirmed by a positive RAST test on ≥ 1 allergen) and EIB (confirmed by a previous exercise challenge) were asked to participate in this study. Twenty children signed an informed consent form and were included in the study. Children had to be able to run on a treadmill and perform reproducible spirometry (i.e., variation of percentage of the predicted value in three of five consecutive measurements <5%). Their forced expiratory volume in 1 sec (FEV₁) had to be at least 70% of predicted normal value. Children were required to withhold the use of leukotriene receptor antagonists (LTRAs), intranasal steroids, LABAs and ICSs for 24 hr and SABAs for 8 hr before both exercise challenges. No vigorous exercise was permitted for 4 hr before an exercise challenge.

Study Design

This was an open-label pilot study. Children and their parents were contacted twice, 4 and 2 weeks prior to the first visit, to inform them about the importance of medication adherence. During the initial visit all children were asked to fill out Juniper's asthma control questionnaire (ACQ) and pediatric asthma quality of life questionnaire (PAQLQ). They performed an exercise challenge, with pulmonary function tests before and after the challenge, at the local ice rink, Euregio Kunstijsbaan, Enschede. Standard pulmonary function test in this study consisted of a duplicated expiratory flow-volume loop.

After the initial visit treatment was reduced from LABA/ICS combination therapy to monotherapy with the same dose of the ICS. The second visit was scheduled at the local ice rink 3 weeks after the first visit. During the second visit children were again asked to fill out both questionnaires and performed a second exercise challenge. This study was conducted with permission from the local Medical Ethics Committee.

Questionnaires

The ACQ has seven questions, scoring five symptoms, baseline FEV₁ % predicted and daily rescue bronchodi-

lator use. Children can respond to these questions on a 7-point scale (0 = no impairment, 6 = maximum impairment). Baseline FEV₁ % predicted is also scored on a 7-point scale. The questions are equally weighted and the ACQ score is the mean of the seven questions and therefore between 0 (totally controlled) and 6 (severely uncontrolled).

The PAQLQ has 23 questions in three domains; symptoms, activity limitation, and emotional function. Children can respond on a 7-point scale (1 = maximum impairment, 7 = no impairment). The total PAQLQ score is the mean of all 23 questions and therefore between 1 (impaired quality of life) and 7 (no impairment in quality of life). Domain scores are the means of the items in those domains.

Fraction of Exhaled Nitric Oxide

FE_{NO} was measured before any forced expiratory maneuvers according to current guidelines¹⁹ at an exhaled flow rate of 50 ml/sec. The single-breath online measurement method was used to measure FE_{NO}. Children were asked to exhale to residual volume and then inhale gas with a low NO concentration through a hand-held nitric oxide analyzer (Niox Mino[®], Aerocrine, Stockholm, Sweden). Children inhaled to near to total lung capacity and immediately exhaled at a constant flow rate.

Pulmonary Function Test

A MicroLoop MK8 Spirometer (ML3535)[®], with Spida5[®] software, was used to measure pulmonary volumes and flow-volume loops. The calibration of this spirometer was checked before testing. The expiratory flow-volume loop was recorded by instructing the children to perform a maximal expiratory effort from inspiratory vital capacity to residual volume. All measurements were performed in duplicate using a standard protocol.²⁰ Pulmonary function was calculated from the best curve.²¹

Exercise Challenge

Exercise challenge testing was performed by running with nose clipped on a treadmill (Reebok[®], TR1 premium run) using the standardized ATS protocol.²² A constant temperature of 10°C and absolute humidity of 4.2 g/kg (relative humidity of 56%) was obtained by testing in the local ice rink. Baseline spirometry was performed and the pre-challenge FEV₁ documented as the best FEV₁ of two measurements. The test started with running at low speed on the treadmill with an incline of 10%. During the test, heart rate was continuously monitored by a radiographic device (Inventum SH 40[®]). The running speed of the treadmill was increased, raising the heart rate to ~90% of the predicted maximum ((220 – age) × 0.9). This speed was maintained for 6 min. After the exercise challenge,

flow volumes were measured at $t = 1, 3, 6, 9, 12, 15$, and 20 min. Maximum percent fall in FEV_1 was used for further analysis. A fall of $\geq 15\%$ in FEV_1 from baseline was considered a positive response.

Statistical Analysis

Best values of spirometric measurements of FEV_1 were used for statistical calculations with SPSS[®] Statistics Version 17.0 for Windows[®]. Data were split into two groups: children with EIB during the initial visit (defined as a $\geq 15\%$ fall in FEV_1 after exercise) and children without EIB. Further calculations were performed on both groups separately and together. The same analysis was performed on children with a $\geq 10\%$ fall in FEV_1 after the initial exercise challenge.

Baseline percent predicted FEV_1 before both challenges were expressed as mean $\pm$ SD and compared using Student's paired t -test. Symptom scores on the ACQ and PAQLQ before both challenges were compared using Wilcoxon's rank test. Maximum percent fall in FEV_1 after both exercise challenges were compared using Student's paired t -test.

Spearman's rank order correlation coefficient was calculated for the correlation between ACQ and PAQLQ scores and % fall in FEV_1 after exercise.

RESULTS

Research population consisted of 20 children. One child was excluded from analysis because he was not able to perform reproducible spirometry. Data from 19 children

were used for analysis (Table 1). Among them were 13 boys and 6 girls. Mean age ($\pm$ SD) was 11.2 ± 2.8 years. Fifteen children were using the combination preparation fluticasone/salmeterol (median dose 400 μ g) before the first visit and stepped down to fluticasone monotherapy and four children were using the combination preparation budesonide/formoterol (median dose 400 μ g) before the first visit and stepped down to budesonide monotherapy. Six children were on a LTRA and six on an intranasal steroid.

Baseline FEV_1 before the initial exercise challenge had a normal distribution with a mean ($\pm$ SD) of $94.1 \pm 13.6\%$ predicted value, which was not significantly different from baseline FEV_1 3 weeks after the medication reduction ($94.6 \pm 15.1\%$ predicted value).

Mean maximum heart rate during the first exercise challenge was $87.6 \pm 4.2\%$ of maximum heart rate, which was not significantly different from mean maximum heart rate during the second challenge ($87.2 \pm 3.9\%$). SABA use was monitored by the ACQ (question 6). Before the first exercise challenge (before LABAs were stopped) children reported an average use of 3.4 puffs of SABA per week (including pre-exercise use). After the medication reduction children reported an average use of 4.2 puffs per week.

Mean maximum percent fall in FEV_1 after the first exercise challenge was $14.5 \pm 10.4\%$. Maximum percent fall in FEV_1 after the second exercise challenge was significantly lower ($P = 0.03$), with a mean of $9.0 \pm 6.5\%$ (Figs. 1 and 2). In 14 children the response to an exercise challenge, measured by the maximum percent fall in

TABLE 1—Baseline Characteristics of Research Population (N = 19)

	Gender	Age	Medication	Dose (μ g/day)	LTRA	Baseline FEV_1 % pred.		Postexercise % fall in FEV_1	
						ICS/LABA	ICS	ICS/LABA	ICS
1	F	10	FP/SAL	500	+	87	84	5.1	9.5
2	M	8	FP/SAL	300	—	93	101	5.4	3.3
3	M	15	BUD/F	400	+	123	125	17.9	16.5
4	M	15	FP/SAL	200	—	90	92	27.0	4.0
5	M	10	FP/SAL	500	—	95	85	17.8	6.3
6	M	11	FP/SAL	200	—	81	86	26.0	6.6
7	F	8	FP/SAL	200	—	94	111	2.2	9.1
8	F	8	FP/SAL	500	—	96	98	9.0	4.4
9	F	8	BUD/F	600	+	78	74	5.7	12.2
10	M	8	FP/SAL	500	+	72	73	25.2	13.3
11	M	8	FP/SAL	500	—	101	105	6.7	3.7
12	F	9	FP/SAL	200	—	99	99	7.9	2.1
13	M	12	BUD/F	400	—	111	113	20.4	8.6
14	M	12	FP/SAL	300	+	99	97	11.2	6.5
15	F	13	FP/SAL	500	—	101	96	5.1	7.1
16	M	14	FP/SAL	500	—	90	85	33.4	29.0
17	M	8	FP/SAL	250	—	94	97	33.3	8.1
18	M	10	FP/SAL	400	+	70	66	3.3	17.1
19	M	16	BUD/F	400	—	115	111	12.4	3.1

FP/SAL, fluticasone propionate/salmeterol; BUD/F, budesonide/formoterol; LTRA, leukotriene receptor antagonist; ICS, inhaled corticosteroid; LABA, long acting beta2-agonist.

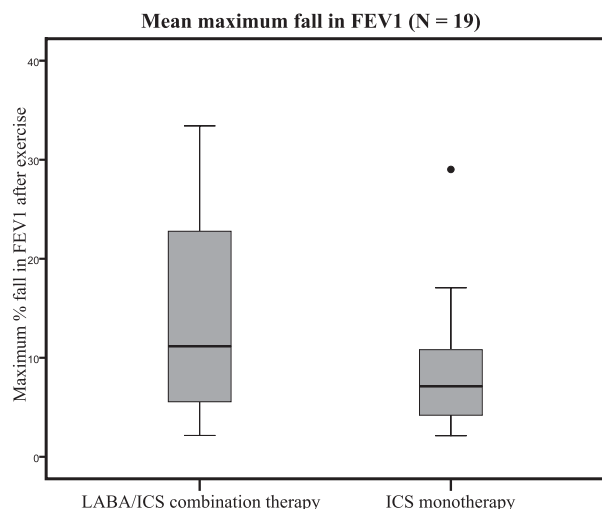


Fig. 1. Mean $\pm$ SD % fall in FEV₁ after exercise challenge after combination therapy and after 3 weeks of treatment with ICS monotherapy.

FEV₁, decreased after the medication reduction. In five children the response to an exercise challenge increased.

There were eight children on LABA/ICS combination therapy that experienced EIB; defined by a $\geq 15\%$ fall in FEV₁ after exercise. This subgroup had a mean maximum percent fall in FEV₁ after the first exercise challenge of $25.1 \pm 6.2\%$. Maximum percent fall in FEV₁ after the second exercise challenge was significantly lower ($P < 0.01$), with a mean of $11.6 \pm 8.1\%$ (Figs. 3 and 4). In all eight children, maximum percent fall in FEV₁ after exercise decreased after the medication reduction. In six children, maximum percent fall in FEV₁ was $< 15\%$, indicating they were no longer experiencing EIB.

There were 11 children on LABA/ICS combination therapy without EIB (fall in FEV₁ $< 15\%$). In this subgroup, there was no change in mean maximum percent fall in FEV₁ after the medication reduction (Fig. 5). Only one child developed a mild EIB (fall in FEV₁ 17.1%) after the medication reduction. Analysis using a cutoff of

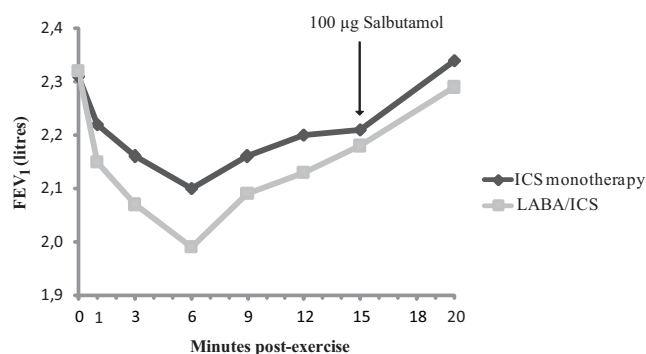


Fig. 2. FEV₁ changes after exercise and after 100 μ g salbutamol.

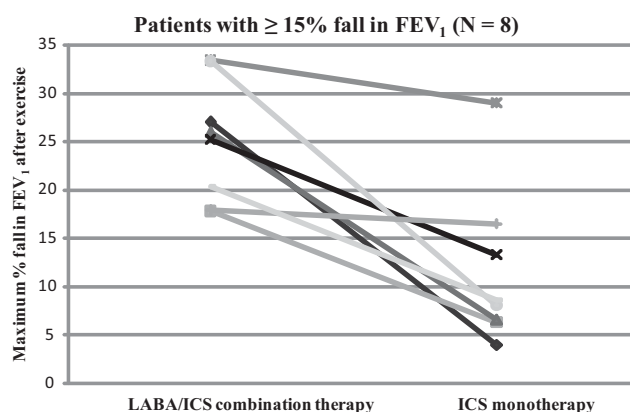


Fig. 3. Individual change in % fall in FEV₁ after exercise for those patients with a $\geq 15\%$ fall in FEV₁ at the first exercise challenge.

$\geq 10\%$ fall in FEV₁ provided similar statistically significant results.

At the initial visit asthma was generally well controlled with a median [range] score on the ACQ of 0.86 [3.00]. The children's quality of life was generally not impaired, with a total median [range] score on the PAQLQ at the initial visit of 5.8 [3.6] and a median score in the symptoms domain of 6.0 [2.7]. At the second visit median score on the ACQ was 0.71 [3.57], which was not significantly different from the initial score. Total and symptom scores on the PAQLQ were, respectively, 6.3 [3.8] and 6.1 [3.7], which were not significantly different from the initial scores.

There was a correlation between scores on the ACQ and PAQLQ (Spearman's $\rho = 0.43$, $P = 0.01$). There was no correlation between scores on the ACQ or PAQLQ and maximum percent fall in FEV₁ after exercise.

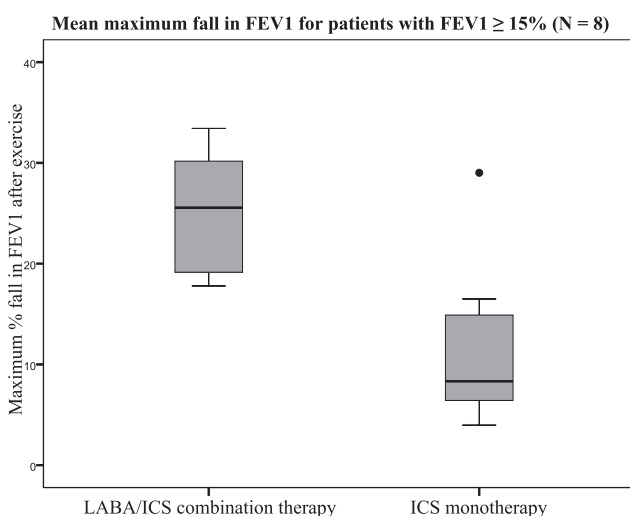


Fig. 4. Mean $\pm$ SD % fall in FEV₁ after exercise challenge after combination therapy and after 3 weeks of treatment with ICS monotherapy for those children with a $\geq 15\%$ fall in FEV₁ at the first exercise challenge.

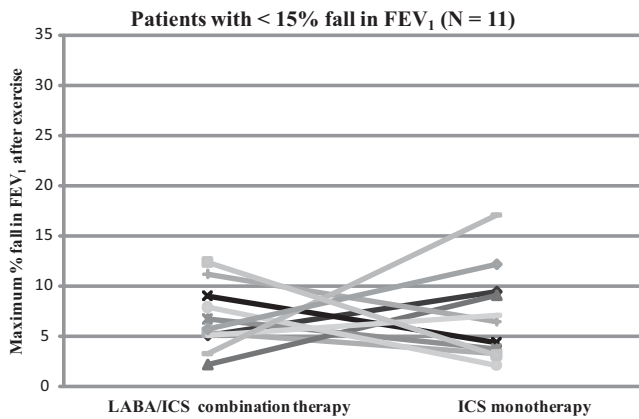


Fig. 5. Individual change in % fall in FEV₁ after exercise for those patients with a <15% fall in FEV₁ at the first exercise challenge.

FE_{NO} was measured at both visits in 14 patients. Mean $\pm$ SD was 16.6 ± 5.9 ppb after LABA/ICS combination therapy and 15.6 ± 8.6 ppb after ICS monotherapy. This was not significantly different.

DISCUSSION

In this study, we monitored a medication reduction from LABA/ICS combination therapy to monotherapy with the same dose of the ICS in clinically stable asthmatic children. Mean maximum percent fall in FEV₁ after an exercise challenge was significantly lower ($P = 0.03$) after the medication change. In a subgroup of eight children with a $\geq 15\%$ fall in FEV₁ after the first exercise challenge, maximum percent fall in FEV₁ reduced in all children after the medication change ($P < 0.01$). Of this subgroup, six children had a maximum percent fall in FEV₁ <15% after the second exercise challenge, indicating they were no longer experiencing EIB. This suggests that in asthmatic children on LABA/ICS combination therapy, the cessation of LABA can reduce and in most cases abolish EIB.

To our knowledge, the effect of reducing treatment from LABA/ICS combination therapy to ICS monotherapy on EIB has not yet been studied. According to international guidelines^{1,2} treatment choices should be guided by asthma control. Once asthma control is achieved and maintained for at least 3 months, a step down can be considered. When asthma is controlled with LABA/ICS combination therapy, the suggested approach for adults is to reduce the ICS by approximately 25–50% every 3 months to the lowest dose possible.^{1,2} An alternative that was recently recommended by the FDA¹⁸ is to discontinue the LABA and continue ICS monotherapy at the same dose.^{1,2} In adults, reducing the dose of the ICS is considered more effective than switching to an ICS alone.^{15–17} The cessation of the LABA could result in a

deterioration of asthma control.^{15–17} However, the benefits shown in these studies were largely a measure of the beta2-agonist effect, such as improved peak expiratory flow and reduced rescue use of SABAs. On the contrary, a report by Weinberger and Abu-Hasan²³ describes an example of two adolescent patients whose EIB improved after the replacement of salmeterol with slow-release theophylline.

We analyzed the effect of stepping down treatment on EIB because EIB occurs in the majority of asthmatic children and is considered to have a great impact on their quality of life²⁴ (although we found no correlation between the extent of EIB and PAQLQ scores). Measuring the airway response to exercise can be used as an indicator of AHR, which is indirectly associated with airway inflammation. Titrating treatment guided by AHR leads to fewer uncontrolled episodes in adults with asthma²⁵ and prevented a decline in lung function in children with asthma.²⁶ This suggests that AHR is an indirect marker of asthma control.

A possible limitation of this study is the lack of a control group in whom we did not change the medication regimen. In this pilot study, we decided to analyze regular medication reductions, based on clinical decisions. However, the lack of a control group makes this study susceptible to bias. The variability in fall in FEV₁ in standardized exercise challenges and regression to the mean may have influenced our results. However, children included in this study were clinically stable and their asthma was well controlled, as was confirmed by their baseline lung function, low FE_{NO} levels, and ACQ scores. To exclude a learning bias, only children who have performed an exercise challenge before were included. The consistent decrease in fall in FEV₁ shown in children with EIB (Fig. 3) cannot be solely contributed to regression to the mean, neither can the mean decrease in maximum percent fall in FEV₁ from 25.1% to 11.6%. In an epidemiological study by Haby et al. reproducibility of the % fall in FEV₁ to a standardized exercise challenge was assessed by the calculation of the single measurement 95% range. A 95% range of $\pm 12\%$ was calculated, meaning that there is a 95% probability that the true value for a subject is within the range of 12% fall in FEV₁ around the single measurement value.²⁷

Exercise challenge responses may be influenced by climatic and environmental factors such as circulating allergen. To exclude a seasonal bias, this study was performed outside the main pollen season. Second visits were planned 3 weeks after the first visit. There were no differences between baseline FEV₁ % predicted, FE_{NO} levels and scores on the ACQ and PAQLQ before both challenges.

To optimize adherence, children and their parents were informed about its importance 4 weeks prior to the first exercise challenge and again by a telephonic contact

2 weeks prior to the first exercise challenge. At the first visit to the ice rink, they reported an adherence of $86 \pm 12\%$.

A reversal of the previously developed tolerance due to regular use of LABAs could explain the reduction in EIB when LABAs were discontinued. Regular use of LABAs leads to downregulation of the β_2 AR.⁸ This results in a reduction of the duration of the bronchoprotective effect of a LABA against EIB^{6,7,9,10} and a prolonged recovery time from EIB after rescue therapy with a SABA.^{11,12} Although corticosteroids increase transcription of the β_2 AR-gene, which could theoretically compensate for the downregulation of the β_2 AR,³ tolerance is not prevented by the concomitant use of ICSs.^{9,12,28–30}

In addition to the development of tolerance to the bronchoprotective and bronchodilative effects, a growing body of evidence supports the hypothesis that regular use of beta2-agonists could increase AHR, especially to allergen.^{11,13,31–33} The increase in sputum inflammatory cells^{31,34} after regular use of beta2-agonists suggests they could paradoxically have a pro-inflammatory effect. Regular exposure to LABAs can cause functional desensitization of the β_2 AR in mast cells³⁵ and airway smooth muscle.³⁶ The complex signaling pathway underlying the relationship between AHR and the β_2 AR is still being explored. There appears to be a differentiation between downregulation of the β_2 AR (causing less effective bronchodilatation) and enhanced contractile signaling (causing enhanced AHR) due to chronic activation of the β_2 AR.³⁷ Both occur with regular use of beta2-agonists.

LABAs have been demonstrated to be useful for many patients whose symptoms are not adequately controlled with conventional doses of ICS alone.^{3,4} However, in this pilot study, we demonstrated that in clinically stable asthmatic children on LABA/ICS combination therapy, the cessation of the LABA can reduce and in most cases abolish EIB. Therefore, if EIB can still be demonstrated in children whose asthma is controlled with LABA/ICS combination therapy, changing therapy to ICS monotherapy should be considered. Further research is required to determine whether this applies to the general population or to a specific subgroup of patients.

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