



Long-term asthma treatment guided by airway hyperresponsiveness in children: a randomised controlled trial

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ABSTRACT: Management plans for childhood asthma show limited success in optimising asthma control. The aim of the present study was to assess whether a treatment strategy guided by airway hyperresponsiveness (AHR) increased the number of symptom-free days and improved lung function in asthmatic children, compared with a symptom-driven reference strategy.

In a multicentre, double-blind, parallel-group, randomised, 2-yr intervention trial, 210 children (aged 6–16 yrs) with moderate atopic asthma, selected on the basis of symptom scores and/or the presence of AHR, were studied. At 3-monthly visits, symptom scores, forced expiratory volume in one second (FEV₁) and methacholine challenge results were obtained, and medication (five levels of fluticasone with or without salmeterol) adjusted according to algorithms based on symptom score (reference strategy, n=104) or AHR and symptom score (AHR strategy, n=102).

After 2 yrs, no difference was found in the percentage of symptom-free days between treatment strategies. Pre-bronchodilator FEV₁ was higher in the AHR strategy (2.3% predicted). This was entirely explained by a gradual worsening of FEV₁ in a subgroup of 91 hyperresponsive children enrolled with low symptom scores (final difference between study arms was 6%).

Asthma treatment guided by airway hyperresponsiveness showed no benefits in terms of number of symptom-free days, but produced a better outcome in terms of pre-bronchodilator forced expiratory volume in one second in allergic asthmatic children, especially those characterised by low symptom scores despite airway hyperresponsiveness.

KEYWORDS: Airway hyperresponsiveness, childhood asthma, inhaled corticosteroids, lung function in disease, salmeterol, symptom evaluation and management

The long-term outcome of asthma depends upon the severity of the disease in early life; persistence into adulthood is more likely in children with more severe airway obstruction and airway hyperresponsiveness (AHR) [1]. It has recently been shown that childhood asthma is associated with reduced lung function in young adults [2]. Therefore, treatment strategies that preserve lung function in addition to controlling symptoms in childhood may offer substantial long-term benefits. Despite effective therapies, asthma control appears far from optimal in a large proportion of asthmatics worldwide [3]. One explanation is inadequate suppression of airway inflammation. Inhaled corticosteroids (ICS) are the first-choice anti-inflammatory treatment for asthma, suppress airway inflammation and improve symptoms and lung function [4]. According to the Global Initiative for Asthma (GINA), ICS dosing is

guided by symptoms and lung function [5]. However, the relationship between these parameters and severity of airway inflammation is weak or absent [6]. Moreover, several studies have shown persisting inflammation in the airways of well-controlled asthmatic patients despite treatment with ICS, and in patients showing clinical remission of asthma [7, 8]. These data indicate that not only symptoms or lung function but also inflammation should be considered when treating asthma with ICS. The validity of this concept is supported by a number of studies using different approaches.

In adult asthmatics, a treatment strategy focusing on the suppression of sputum eosinophilia resulted in a reduction in asthma exacerbations [9, 10]. SMITH *et al.* [11] found that titrating asthma therapy against exhaled nitric oxide fraction (FeNO), an indirect marker of eosinophilic airway

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inflammation, resulted in a substantial reduction in ICS dose without compromising asthma control in adults. In a recent paediatric study, PIJNENBURG *et al.* [12] showed that a significant improvement in AHR could be reached by titrating ICS against FeNO, and this effect was obtained without increasing the mean ICS dose. AHR to inhaled methacholine is associated with airway inflammation and remodelling [7, 13]. SONT *et al.* [14] showed that ICS dose titration guided by AHR reduced the asthma exacerbation rate 1.8-fold, improved lung function and reduced remodelling in airway biopsy specimens from adult asthmatics. AHR is a risk factor for rapid decline in lung function [1], and severe AHR is associated with inadequate symptom perception [15, 16]. Therefore, it could be reasoned that asthmatic children with AHR and inadequate symptom perception are especially at risk of a rapid decline in lung function and might, therefore, particularly benefit from titrating asthma therapy against AHR. The present study tested the hypothesis that a treatment strategy guided by AHR increases the number of asthma symptom-free days and provides better maintenance of lung function in children with moderately severe atopic asthma compared with a symptom-driven strategy.

METHODS

Patients

Clinically stable asthmatic children living in the Netherlands, aged 6–16 yrs and with a documented clinical history of moderate persistent asthma, according to GINA guidelines, were eligible and were enrolled from the 15 participating clinics, including seven university medical centres. All patients gave a positive, class ≥ 1 , radioallergosorbent test result for one or more airborne allergens and used $\geq 200 \mu\text{g}\cdot\text{day}^{-1}$ fluticasone or an equivalent dose of other ICS. The protocol allowed for inclusion of three different asthma phenotypes at randomisation were as follows. 1) Subgroup AHR ($n=91$ (44%)): children with a provocative dose of methacholine causing a 20% fall in forced expiratory volume in one second (FEV₁; PD₂₀) $<150 \mu\text{g}$ and a cumulative symptom score <14 . 2) Subgroup symptom (S; $n=46$ (22%)): children with a symptom score ≥ 14 and PD₂₀ $\geq 150 \mu\text{g}$. 3) Subgroup S+AHR

($n=69$ (34%)): children with a symptom score >14 and PD₂₀ $<150 \mu\text{g}$. By including these different phenotypes, the results were applicable to the disease spectrum in paediatric clinical practice. All parents and children aged >12 yrs signed their informed consent. The study was approved by the medical ethical committees of all the participating centres.

Study design

The present study was performed as a multicentre, parallel-group, randomised, 2-yr intervention trial. Children were randomised after a run-in period of 1 month. In children treated with $500 \mu\text{g}\cdot\text{day}^{-1}$ fluticasone who did not meet the criteria for randomisation after 1 month, the dose of ICS was tapered down to $200 \mu\text{g}\cdot\text{day}^{-1}$ fluticasone for a further 2 months before randomisation. After run-in, children were randomised into one of two treatment strategy arms if they showed a cumulative symptom score ≥ 14 during the last 2 weeks of the run-in period and/or a PD₂₀ $<150 \mu\text{g}$ (fig. 1). The subjects were allocated in consecutive order. Randomisation was performed centrally using a minimisation programme. Both treatment strategy groups were stratified for centre, baseline PD₂₀ at the end of the run-in period (PD₂₀ ≥ 150 or $<150 \mu\text{g}$), cumulative symptom score at the end of the run-in (symptom score ≥ 14 or <14), starting dose of fluticasone (100 or $250 \mu\text{g}$ *b.i.d.*) and age (<9 or ≥ 9 yrs).

In the reference strategy arm, adjustment of treatment was based upon the cumulative symptom score alone. In the AHR strategy arm, treatment was adjusted on the basis of PD₂₀ and symptom score, according to the algorithm shown in table 1, with PD₂₀ cut-off levels of 100 and $300 \mu\text{g}$, corresponding to more severe and mild AHR, arbitrarily defined on the basis of current practice in the participating centres. During the run-in phase, patients were put on 100 or $250 \mu\text{g}$ fluticasone *b.i.d.* depending on their equivalent treatment before run-in. After randomisation, the children received treatment according to level 3 or 4 of the algorithm. Every 3 months, the cumulative symptom score, lung function (FEV₁ and forced vital capacity (FVC)) and AHR were assessed by a lung function technician. Data were transmitted to a central computing facility that immediately produced dosing advice according to the study

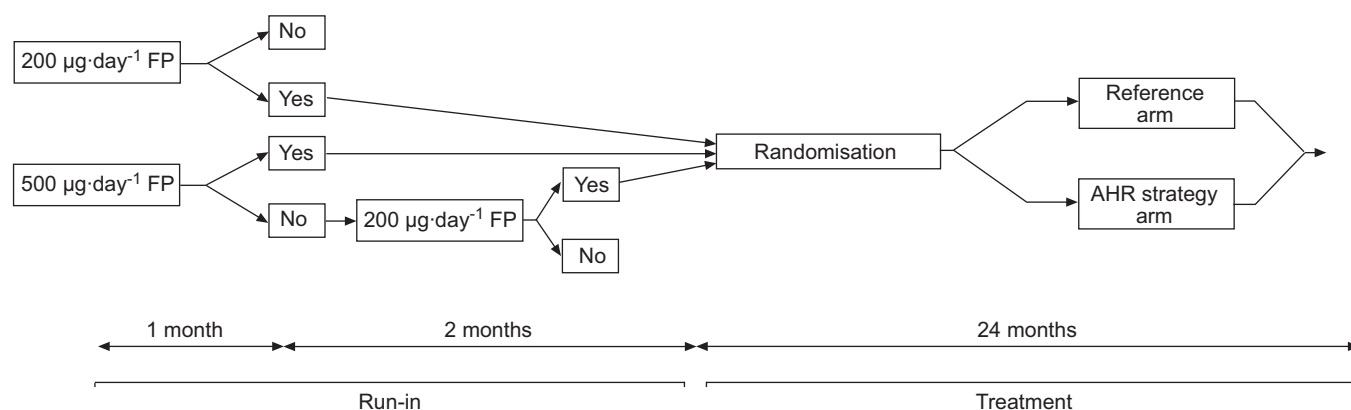


FIGURE 1. Study design. The criteria for randomisation were a provocative dose of methacholine causing a 20% fall in forced expiratory volume in one second (PD₂₀) $<150 \mu\text{g}$ at the end of the run-in and/or a cumulative symptom score ≥ 14 during the last 14 days of run-in. In the reference strategy arm, adjustment of treatment was based on the cumulative symptom score alone. In the airway hyperresponsiveness (AHR) strategy arm, treatment was adjusted according to PD₂₀ and symptom score. FP: fluticasone propionate. 'yes' and 'no' refer to either meeting the criteria for randomisation or not.

TABLE 1 Study algorithm

Medication level	Reference strategy	AHR strategy
Increase by 1	SS ≥ 14	PD ₂₀ < 100 µg and SS < 14 or PD ₂₀ < 300 µg and SS ≥ 14
No change	0 < SS < 14	PD ₂₀ 100–300 µg and SS < 14 or PD ₂₀ ≥ 300 µg and SS ≥ 14
Decrease by 1	SS = 0	PD ₂₀ > 300 µg and SS < 14

AHR: airway hyperresponsiveness; SS: cumulative symptom score during the 14 days before the clinic visit; PD₂₀: provocative dose of methacholine causing a 20% fall in forced expiratory volume in one second.

algorithm. This advice was communicated to the physician who was blinded to outcomes and study arm allocation.

During the treatment period, subjects used a fluticasone dry powder inhaler (Flixotide Diskus®; GlaxoSmithKline, Brentford, UK), 100 or 200 µg·day⁻¹ (levels 1 and 2, respectively), or fluticasone/salmeterol multidose dry powder inhaler (Seretide Diskus®; GlaxoSmithKline), 200/100, 500/100 or 1,000/100 µg·day⁻¹ (levels 3, 4 and 5, respectively; table 2). Medication levels were not blinded. For rapid relief of symptoms, 200 µg salbutamol (Ventolin Diskus®; GlaxoSmithKline) could be used. Subjects were asked to return all study medication at every visit and the remaining doses were counted. Compliance was defined as the number of doses used divided by the number of prescribed doses.

Symptom scores

During the study, patients filled in a diary card daily for 2 weeks before each visit, and for 3 months before the last visit [17]. Cough, shortness of breath and wheezing during night and day were recorded on a 4-point (0–3: no symptoms–severe symptoms interfering with activity or sleep) scale. The maximum 14-day cumulative score was 252. For each diary card period, the percentage of symptom-free days (defined as a score of 0 for cough, wheeze and shortness of breath) was determined.

Lung function and AHR

The study medication was stopped 36 h before lung function and AHR testing. During each visit, FEV₁ and FVC were measured [18]. AHR was tested by methacholine challenge using a dosimeter method [19]. Nebulised methacholine bromide was given in doubling oral doses of 1.52–1,570 µg via a DeVilbiss 646 nebuliser (DeVilbiss Health Care Inc., Somerset, PA, USA) attached to a Rosenthal–French or KoKo dosimeter (Laboratory for Applied Immunology, Fairfax, VA, USA). The PD₂₀ was calculated from a log dose–response plot by linear interpolation of the data points. At the end of the challenge test, 400 µg salbutamol was administered after a 20-min pause and the FEV₁ was measured again.

Asthma exacerbations

An exacerbation was defined as a deterioration of asthma requiring treatment with oral corticosteroids, as judged by the physician [20].

Safety measures

Standing height was measured every 3 months using a wall-mounted Holtain stadiometer (Holtain, Crymmych, UK). If a

child showed a decrease in height of 0.125 × SDS (standard deviation score) in 6 months on two subsequent visits, the data were reviewed by an independent paediatric endocrinologist (W.J.M. Gerver, Dept of Paediatrics, Maastricht University Hospital, Maastricht, the Netherlands), and further evaluation could take place, including Tanner staging of puberty and radiological assessment of bone age. If serious growth problems were suspected, the patient could be withdrawn from the study.

Statistical analysis

Diary card data were aggregated per patient for each of the nine periods in the study (run-in and seven subsequent periods of 14 days each prior to the clinic visit, followed by a final period of 3 months at the end of the study). Changes in the mean percentage of symptom-free days were compared between treatment strategies using repeated measures ANOVA (rMANOVA; with unstructured covariance matrix), with adjustment for baseline percentage during run-in. In the various rMANOVA models, time of assessment was included as a discrete factor. The mean percentage of symptom-free days during the final 3 months was the primary end-point. Power calculation was based on data from a previous study [17]. With a two-sided α of 0.05, 100 patients were needed in each group in order to detect a 15% difference in symptom-free days at the end of the study with a power of 80%. Lung function (FEV₁ (% predicted) and FEV₁/FVC × 100 (%)) was also analysed using rMANOVA, and the value measured at randomisation was used as a covariate. PD₂₀ outcomes at the various visits were compared between study arms after logarithmic transformation. If, at a given visit, a patient did not reach the PD₂₀ at the highest methacholine dose, this dose was considered a right-censored observation in the analysis. The risk of exacerbation was compared between treatment strategies using the log-rank test. Cumulative doses of ICS were compared between treatment strategies using the Mann–Whitney U-test. At baseline, a possibly relevant difference between the treatment strategies was found in the proportion of patients who had experienced exacerbations requiring

TABLE 2 Study medication levels

Level 1	100 µg fluticasone o.d.
Level 2	100 µg fluticasone b.i.d.
Level 3	100 µg fluticasone/50 µg salmeterol b.i.d.
Level 4	250 µg fluticasone/50 µg salmeterol b.i.d.
Level 5	500 µg fluticasone/50 µg salmeterol b.i.d.

prednisone treatment in the year before the study. Thus, all analyses were performed with an additional adjustment for this imbalance. Pre-planned subgroup analyses were performed for the three subgroups (AHR, S and S+AHR). Adjusted differences of means between treatment strategies cited in the present study always refer to the outcome in the AHR strategy arm minus the outcome in the reference strategy arm. All analyses were performed according to the intention-to-treat principle. A p-value of 0.05 (two-sided) was considered the limit of significance.

RESULTS

Between December 1999 and November 2003, 288 children entered the run-in period, of whom 210 fulfilled the criteria for randomisation. As four patients withdrew within the first 3 months after randomisation and no follow-up data were available, 206 could be evaluated (fig. 2). The characteristics of the children in both treatment strategy arms and in the three subgroups are summarised in table 3. At baseline, the patients in both arms were similar, except for a higher number of children in the AHR strategy arm who had experienced one or more asthma exacerbations in the year prior to the study.

Symptom-free days

The number of patients with an evaluable diary decreased from baseline to the end of the study from 104 to 90 for the reference strategy, and from 102 to 85 for the AHR strategy. Within each treatment strategy arm, the percentage of symptom-free days increased similarly. The mean \pm SEM percentage of symptom-free days within the reference and AHR strategy arms rose from 50 ± 4 to 71 ± 3 and from 47 ± 3 to 69 ± 3 , respectively (both $p < 0.001$; fig. 3a). The adjusted difference in the mean percentage of symptom-free days between the strategy arms during the last 3 months was -1.1 (95% confidence interval (CI) -10.1 – 7.9 ; $p = 0.84$). Within the three subgroups, this difference was also nonsignificant (3.1% ($p = 0.63$), -11.9% ($p = 0.26$) and -3.2% ($p = 0.72$) for subgroups AHR, S and S+AHR, respectively; fig. 3b–d).

Lung function and AHR

During the study, the number of patients with valid lung function results decreased from 101 to 92 in the reference strategy, and from 99 to 93 in the AHR strategy. Overall, the adjusted mean FEV₁ (95% CI) at the eight visits after randomisation was 2.3 (0.05 – 4.6) percentage points higher in the AHR strategy arm ($p = 0.046$; fig. 4a). Children with AHR and well-controlled symptoms at randomisation (subgroup AHR) exhibited a significantly higher FEV₁ in the AHR strategy arm than in the reference strategy arm ($p = 0.024$). The adjusted difference in FEV₁ between the two treatment strategies in the AHR subgroup after 2 yrs of treatment was 6.0 (1.2 – 10.8)% pred in favour of the AHR strategy arm ($p = 0.017$; fig. 4b). This difference was explained by a gradual decrease in the reference strategy arm from $97 \pm 2\%$ pred at randomisation to $93 \pm 2\%$ pred after 2 yrs ($p = 0.027$), whereas FEV₁ did not change within the AHR strategy arm (97 ± 2 to $98 \pm 2\%$ pred; $p = 0.23$). In subgroups S and S+AHR, there were no significant changes in FEV₁ between treatment strategies after 2 yrs (-2.0 ($p = 0.55$) and -0.15% pred ($p = 0.98$), respectively). Of the two results, the first was borderline significantly different ($p = 0.052$) from the corresponding difference of 6.0% pred in

the AHR subgroup. In the AHR subgroup, the mean FEV₁/FVC at the end of the study was 1.6 (0.3 – 2.9) percentage points higher in the AHR strategy arm ($p = 0.015$). In the other two subgroups (S and S+AHR), differences were nonsignificant (both $p > 0.17$). The PD₂₀ increased significantly during the treatment period. No difference was found between reference and AHR strategies (the change from baseline at 2 yrs was 2.6 and 2.8 doubling doses, respectively).

Treatment strategies and ICS dose

In the AHR strategy arm, 47% of decisions would have been different had patients been treated according to the reference strategy; it would have led to a higher medication level in 24% and to a lower level in 23%. The mean \pm SEM daily ICS dose was 478 ± 27 μ g fluticasone in the reference strategy arm and 562 ± 26 μ g in the AHR arm ($p = 0.025$). However, at the end of the study, the difference between the treatment strategy arms was nonsignificant (505 μ g·day⁻¹ in reference strategy and 557 μ g·day⁻¹ in AHR strategy; $p = 0.428$; fig. 5a). The largest difference between strategies was seen after 6 months in the AHR subgroup (fig. 5b). The mean \pm SD compliance with treatment was excellent, $89 \pm 9\%$ in the reference strategy arm and $88 \pm 8\%$ in the AHR strategy arm. Compliance was equally good in children with and without symptoms (subgroups S and S+AHR *versus* subgroup AHR).

Asthma exacerbations

During the study, 17 out of 104 subjects in the reference strategy arm experienced at least one asthma exacerbation, *versus* 16 out of 102 in the AHR strategy arm ($p = 0.69$). During the year before the study, these figures were 12 and 25, respectively.

Side-effects

At the end of the study, no significant difference in change in growth rate was found between the treatment strategies (baseline adjusted difference of $-0.1 \times$ SDS (95% CI -0.2 – 0.04); $p = 0.18$). However, in the AHR subgroup, a significant height difference was found between the treatment strategies at the end of the study (adjusted difference of $-0.4 \times$ SDS (95% CI -0.6 – -0.2); $p < 0.001$). Growth data were not a reason for discontinuing the study in any subject.

DISCUSSION

It has been shown that, in allergic asthmatic children, 2 yrs of AHR-driven treatment did not improve the percentage of symptom-free days, but resulted in better pre-bronchodilator FEV₁, especially in a large subgroup whose asthma was characterised by AHR and low symptom scores. Adjusting maintenance treatment solely based on symptoms in this subgroup produced a gradual deterioration in pre-bronchodilator FEV₁ during the treatment period of 2 yrs.

Inflammation is associated with structural changes in the airways, and one of the major functional consequences of airway inflammation and remodelling is considered to be AHR [13]. Remodelling has been found in early stages of childhood asthma, and it is not known whether remodelling is responsible for long-term changes in lung function in childhood asthma [21]. However, prolonged ICS treatment results in progressive improvement in AHR [22]. This might be an important therapeutic objective, since AHR correlates with the

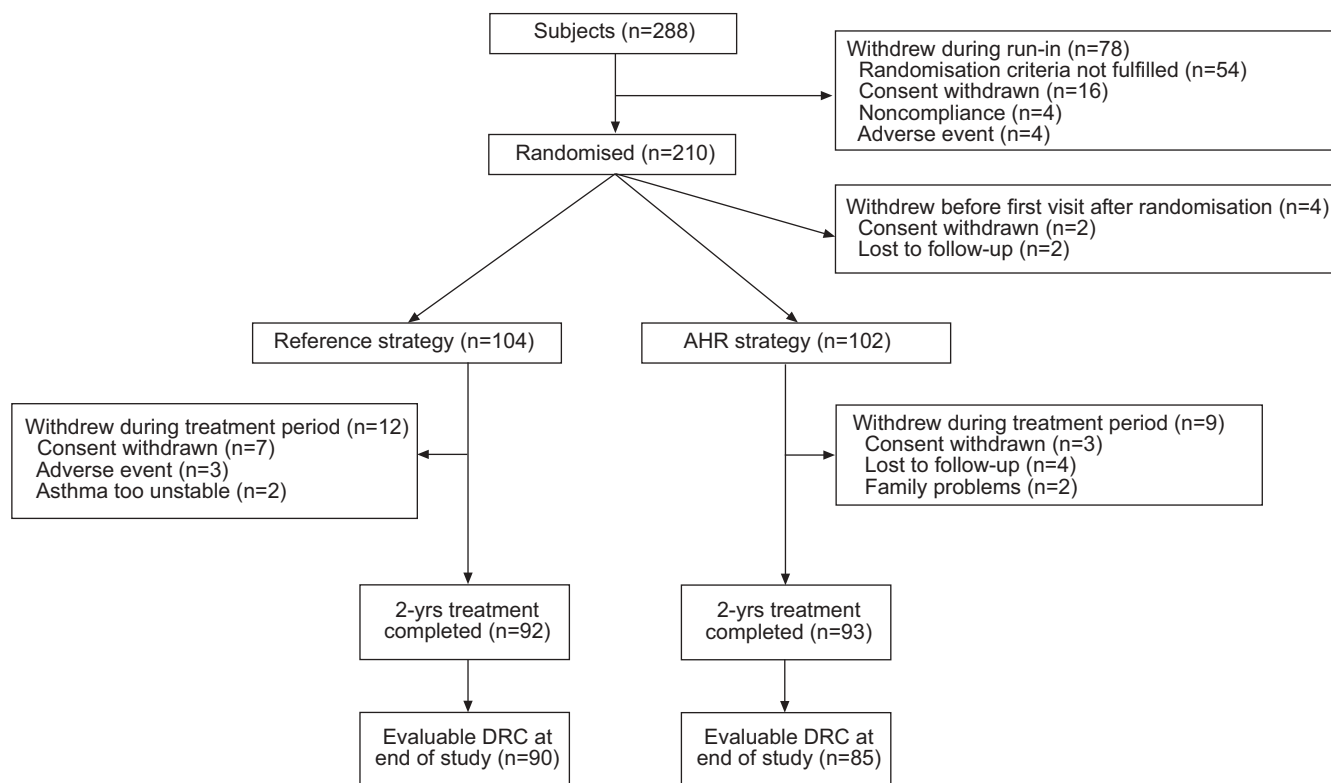


FIGURE 2. Trial profile. AHR: airway hyperresponsiveness; DRC: daily record card.

long-term prognosis of lung function development and with the risk of persistence of disease into adulthood [23–25]. Indeed, young adult asthmatics already show loss of lung function in comparison with controls [2]. Late introduction of ICS or inadequate dosing may well promote such lung function impairment [23].

Several studies have examined the long-term effects of ICS in children with asthma. The Childhood Asthma Management Program (CAMP) study [26] found that ICS improved pre- but not post-bronchodilator FEV₁ compared with placebo, suggesting an effect of treatment on smooth muscle tone, rather than airway structure, and no loss of lung function.

TABLE 3 Anthropometric data of subjects in two treatment strategies and three subgroups

	Strategy		Subgroup		
	Reference	AHR	AHR [#]	S [†]	S+AHR ⁺
Subjects n	104	102	91	46	69
Males/females n	54/50	63/39	54/37	30/16	33/36
Age yrs	10.9±2.5	10.8±2.4	10.7±2.5	11.0±2.1	11.0±2.5
Duration of asthma yrs	7.1±3.0	7.3±3.1	7.3±3.0	7.0±3.3	7.3±3.0
Duration of ICS usage yrs	5.2±2.7	5.8±2.7	5.4±2.9	5.4±3.0	5.7±2.4
Asthma exacerbations in year prior to study n	12	25	20	5	12
FEV ₁ % pred	98±14	96±14	97±15	100±12	94±14
FEV ₁ /FVC %	83±8	81±9	81±9	86±6	81±8
PEF variability %	7±4	7±4	6±3	7±5	8±5
PD ₂₀ µg	73 (0.8–>1570)	68 (0.8–>1570)	47 (3–148)	553 (154–>1570)	42 (0.8–144)
Run-in SS	17 (0–87)	17 (0–152)	2 (0–13)	28 (14–100)	31 (15–152)

Data are presented as mean±SD or median (range), unless otherwise stated. AHR: airway hyperresponsiveness; S: symptom; ICS: inhaled corticosteroid; FEV₁: forced expiratory volume in one second; % pred: % predicted; FVC: forced vital capacity; PEF: peak expiratory flow; PD₂₀: provocative dose of methacholine causing a 20% fall in FEV₁; SS: cumulative symptom score during the last 14 days before the clinic visit. [#]: well-controlled symptoms and AHR during run-in; [†]: manifest symptoms without AHR during run-in; ⁺: manifest symptoms and AHR during run-in.

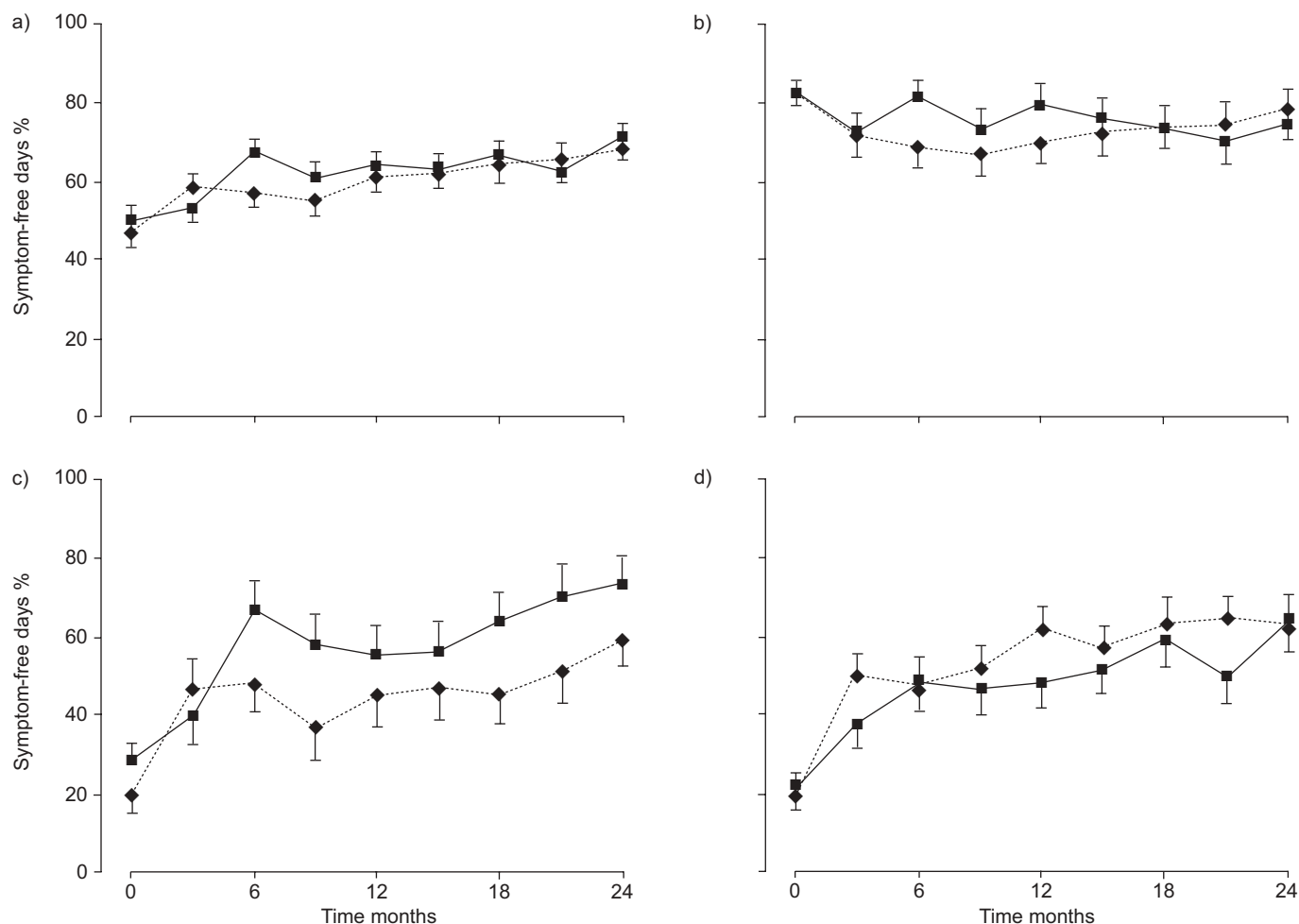


FIGURE 3. Symptom-free days as a function of time during follow-up (■: reference strategy; ◆: airway hyperresponsiveness (AHR) strategy) in: a) total study population (n=206); b) AHR subgroup (AHR and well-controlled symptoms during run-in; n=91); c) symptom (S) subgroup (manifest symptoms without AHR during run-in; n=46); and d) S+AHR subgroup (manifest symptoms and AHR during run-in; n=69). Error bars represent SEM at each visit. The adjusted difference in the mean percentage of symptom-free days during the last 3 months did not differ between the strategy arms.

The pre-bronchodilator FEV₁/FVC ratio was also significantly higher in steroid-treated children compared with the placebo group, consistent with less airway obstruction. Indeed, the large inhaled Steroid Treatment As Regular Therapy (START) in early asthma study [27] showed a small increase in pre-bronchodilator FEV₁ as a result of steroid treatment when comparing ICS and placebo. Both studies were essentially different from the present one, in which the focus was not on ICS *versus* placebo but on treatment strategies. In addition, the participating children were already being treated with ICS in specialist practices prior to the study, and used higher inhaled steroid doses than in the CAMP or START studies. It is remarkable that there was no reduction in FEV₁ with placebo treatment in both studies; indeed, a small increase was observed. The present authors speculate that this may be related to initial asthma severity. MERKUS *et al.* [28] examined the effect of ICS on the progression of FEV₁ in children aged >3 yrs, and showed preservation of lung function compared with placebo. In children receiving placebo, pre- and post-bronchodilator values ran largely in parallel, whereas a ceiling effect towards a submaximal level was seen with ICS.

How can the beneficial effect on lung function of treatment guided by AHR be explained? Conflicting data on the effects of medium- and long-term treatment with ICS on airway remodelling have been published [14, 29, 30]. AHR is a risk factor for a rapid decline in lung function in asthma, and, moreover, the decline in lung function with age in asthmatics correlates with the severity of AHR [1, 22, 31]. Several studies have shown that AHR is inversely associated with growth of airway calibre [32]; therefore, it is possible that airway growth benefits from the AHR strategy. The present authors speculate that the gradual and consistent effects on FEV₁ of the AHR strategy represent a preventive and, perhaps, therapeutic effect of ICS on airway remodelling.

Using both treatment strategies, the percentage of symptom-free days increased. Possible reasons include an effect of medication, increased compliance with treatment or spontaneous improvement of disease. An effect of treatment seems plausible and could be caused by ICS or long-acting β_2 -agonists (LABAs). Most of the time, LABAs were used by most children according to GINA guidelines and could have

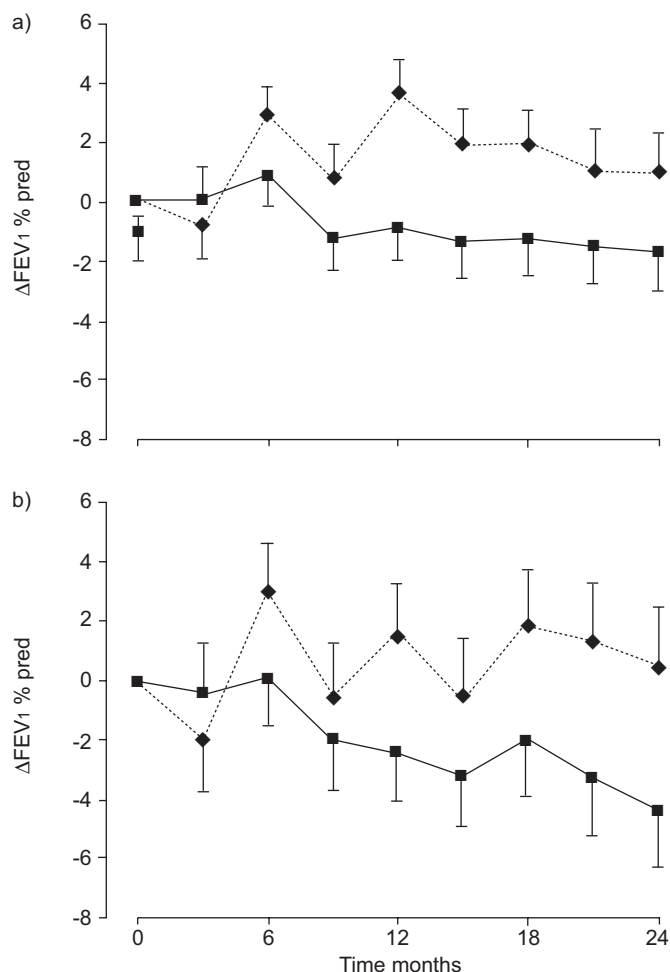


FIGURE 4. Change (Δ) from baseline in forced expiratory volume in one second (FEV₁) as a function of time during follow-up (■: reference strategy; ◆: airway hyperresponsiveness (AHR) strategy) in: a) total study population (n=206); and b) AHR subgroup (AHR and well-controlled symptoms during run-in; n=91). Error bars represent SEM. During the treatment period, the mean difference in change from baseline FEV₁ was 2.3% pred in the total study population (p=0.046). After 2 yrs of treatment, the adjusted difference in change from baseline of FEV₁ between the two treatment strategies was 6.0% pred in the AHR subgroup (p=0.017).

reduced symptoms. At baseline, symptom scores were unaffected by LABAs as these were not allowed during run-in. The study design did not allow for disentangling the effects of ICS and LABAs.

AHR was defined on the basis of fixed cut-off levels, and it may be argued that this is inappropriate for children of a wide age range. LeSouëf [33] reasoned that, merely as a result of different lung size, the same dose of methacholine would have a stronger effect in smaller children. In the absence of age-specific data for determining AHR, there is currently no means of solving this problem. The impact on the present study may be limited, as the treatment arms were stratified for age. However, it is probable that selection on the basis of a fixed level of AHR has favoured the inclusion of young patients with less severe AHR.

Of the present study population, 44% initially showed low symptom scores despite AHR, suggesting that this phenotype is common in the present secondary and tertiary care setting. Pre-planned analysis of this subgroup revealed that the AHR, but not the reference, strategy prevented worsening of pre-bronchodilator FEV₁ over 2 yrs of follow-up. In the remaining children, asthma outcome could not be improved by taking AHR into account. The present treatment algorithms predictably resulted in an increase in ICS dose in children with well-controlled symptoms treated according to the AHR strategy. A transient difference in ICS dose between the treatment strategies was seen over the course of the 2 yrs of treatment. This indicates that the AHR strategy was able to selectively improve the targeting of ICS to children in whom the reference strategy seems suboptimal. Overall, the increase in ICS dose was entirely explained by dose changes during the first two visits following randomisation. The cut-off symptom score at which the level of medication had to be increased was determined on the basis of a previous study using the same diary card [17]. The median symptom score at the start of the present study was higher than the pre-defined cut-off level, suggesting more severe disease in the present study than in the previous one. Studies published recently show that the dose-response relationship of inhaled fluticasone with symptoms and FEV₁ reaches a plateau at 200–400 $\mu\text{g}\cdot\text{day}^{-1}$ [34]. Based on these data, the present highest level of study medication could be questioned. However, not only dose but also inhaler technique and means of delivery of ICS determine their efficacy, and data from adults may not apply to children. More recently, systemic side-effects of fluticasone have been reported at doses of $\geq 500 \mu\text{g}\cdot\text{day}^{-1}$ [35]. At the onset of the present study, fluticasone doses of $\leq 1,000 \mu\text{g}\cdot\text{day}^{-1}$ were common practice in the participating clinics, and it was felt appropriate to continue this practice during the study. Whether similar long-term benefit could be derived from lower doses of ICS in children warrants further study.

In the present study, children were treated in line with GINA guidelines, often combining LABAs and an ICS. As LABAs improve symptoms but not inflammation, it could be argued that this affected assignment to subgroups and symptom scores. However, baseline symptom scores were obtained during the run-in period, when LABAs were not allowed. Furthermore, all lung function tests were performed ≥ 36 h after the last dose of study medication and, therefore, not influenced by LABAs. Finally, the cumulative proportion of children treated with LABAs did not differ between treatment strategies, and it seems likely that any effect of LABAs on symptoms will have been similar in both study arms. Consequently, the present authors are confident that the use of LABAs has not systematically biased the results of the present comparisons.

No adverse effects of ICS treatment on statural growth was found in the group as a whole, but a slight-but-significant reduction in growth velocity was observed in the AHR subgroup who were treated with relatively high ICS doses. Previous studies designed to evaluate growth in asthmatic children have shown that growth rates are commonly reduced during the first months of ICS treatment, but that this does not affect adult height [36]; thus, a negative effect on adult height is unlikely.

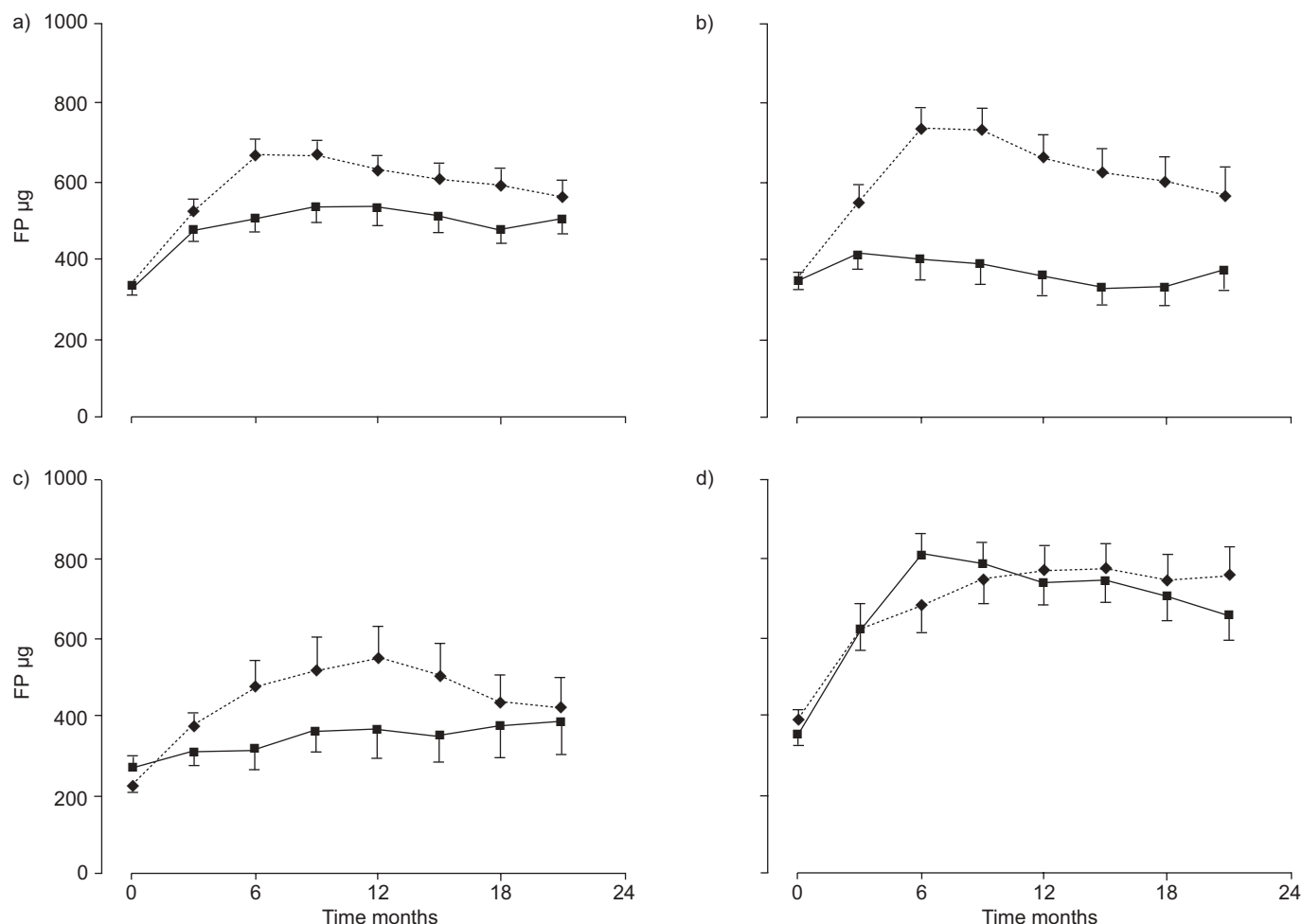


FIGURE 5. Daily fluticasone propionate (FP) dose during follow-up (■: reference strategy; ◆: airway hyperresponsiveness (AHR) strategy) in: a) total study population (n=206); b) AHR subgroup (AHR (provocative dose of methacholine causing a 20% fall in forced expiratory volume in one second (PD₂₀) <150 µg) and well-controlled symptoms (cumulative symptom score <14) during run-in; n=91 (44%)); c) symptom (S) subgroup (manifest symptoms (symptom score ≥14) without AHR (PD₂₀ ≥150 µg) during run in; n=46 (22%)); and d) S+AHR subgroup (manifest symptoms (symptom score ≥14) and AHR (PD₂₀ <150 µg) during run in; n=69). Error bars represent SEM. During the study, the mean daily FP dose in the total study population differed between the strategy arms (p=0.025); at the end of the study, this difference was no longer significant (p=0.428). During and at the end of the study, the mean daily FP dose in the AHR subgroup differed between the strategy arms (p<0.001).

What are the clinical implications of the present study? Asthmatic children characterised by AHR and well-controlled symptoms are obviously at risk of suboptimal treatment when treated according to the severity of their symptoms. However, measurement of AHR is currently rare in paediatric practice and is time consuming. The present authors would not advocate routine AHR measurements in all asthmatic children for that reason. However, AHR testing may be worthwhile in asthmatic children who report few symptoms in order to identify those at risk of lung function deterioration.

In conclusion, it was found that an airway hyperresponsiveness-driven asthma treatment, as compared with the conventional symptom-driven strategy, produced no improvement in the percentage of symptom-free days, but prevented long-term worsening of pre-bronchodilator forced expiratory volume in one second, specifically in a large subgroup of children who show airway hyperresponsiveness and low symptom scores.

This effect on lung function was achieved with higher doses of inhaled corticosteroids. The present authors speculate that phenotype-specific treatment strategies have the potential to improve the outcome of childhood asthma into adult life.

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