

Secondary prevention of asthma by the use of Inhaled Fluticasone propionate in Wheezy INfants (IFWIN): double-blind, randomised, controlled study

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Summary

Background Wheezing and asthma often begins in early childhood, but it is difficult to predict whether or not a wheezy infant will develop asthma. Some researchers suggest that treatment with inhaled corticosteroids at the first signs of wheezing in childhood could prevent the development of asthma later in life. However, other investigators have reported that although such treatment could help control symptoms, the benefits can disappear within months of stopping treatment. We tested our hypothesis that to prevent loss of lung function and worsening asthma later in childhood, anti-inflammatory treatment needs to be started early in life.

Methods We did a randomised, double-blind, controlled study of inhaled fluticasone propionate 100 µg twice daily in young children who were followed prospectively and randomised after either one prolonged (>1 month) or two medically confirmed wheezy episodes. The dose of study drug was reduced every 3 months to the minimum needed. If the symptoms were not under control by 3 months, open-label fluticasone propionate 100 µg twice daily was added to the treatment. Children were followed-up to 5 years of age, at which point we gave their parents or guardians questionnaires, and measured the children's lung function (specific airways resistance [sR_{aw}], forced expiratory volume in 1s [FEV_{1s}] and airway reactivity (eucapnic voluntary hyperventilation [EVH] challenge). This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN86717853.

Findings We followed 1073 children prospectively, of whom 333 were eligible, and 200 of these began treatment (130 male, median age 1.2 years [range 0.5–4.9]; 101 placebo, 99 treatment); 173 (85 treatment, 88 placebo) completed the follow-up at age five years. The groups did not differ significantly in the proportion of children with current wheeze, physician-diagnosed asthma or use of asthma medication, lung function, or airway reactivity (percentage change in FEV_{1s} , adjusted mean for placebo 5.5% [95% CI –2.5 to 13.4]) vs for treatment 5.0% [–2.2 to 12.2], $p=0.87$). There were no differences in the results after adjustment for open-label fluticasone propionate, nor between the two groups in the time before the open-label drug was added (estimated hazard ratio 1.12 [95% CI 0.73–1.73], $p=0.60$), or the proportion needing the open-label drug (43 [42.57%] placebo, 41 [41.41%] treatment).

Interpretation The early use of inhaled fluticasone propionate for wheezing in preschool children had no effect on the natural history of asthma or wheeze later in childhood, and did not prevent lung function decline or reduce airway reactivity.

Introduction

Most cases of persistent wheezing and asthma begin in early childhood,¹ and these can determine respiratory health throughout life.^{2,3} Although wheeze is common in pre-school children, it can result from several different conditions,⁴ and it is difficult to predict whether or not a wheezy infant will develop asthma. Cohort studies suggest that around half of children who wheeze early in life become asymptomatic by school age.¹ Lung function in these children tends to be diminished in infancy, and improved (but still lower than normal) by age 6 years.¹ By contrast, lung function in children with persistent wheeze is normal in infancy, but reduced by age 6 years.¹ Asthmatics with significant airway obstruction in mid-adult life (aged 30–40) already have reduced lung function by the age of 10 years.⁵ This evidence suggests that most asthmatic children have normal lung function at birth, but that an ongoing chronic inflammatory

process could be associated with airway changes resulting in loss of lung function by early childhood, which then extends into adulthood.

Some researchers have suggested that treatment with inhaled corticosteroids (ICS) early in childhood asthma could improve long-term outcomes.⁶ However, others have reported that although such treatment of school-aged children with asthma improves symptom control, the benefits can disappear within months of stopping treatment.⁷ We postulated that to stop the progression of childhood wheezing and prevent loss of lung function, anti-inflammatory treatment needs to be started early in life. Thus, in the IFWIN study (Inhaled Fluticasone in Wheezy INfants), we investigated whether the use of ICS early in the natural history of wheezing at the minimum dose required to control symptoms alters the progression of disease, prevents lung function decline, or reduces the incidence of asthma in later childhood.

Lancet 2006; 368: 754–62

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The authors dedicate this paper in fond memory of our friend and colleague, Stephen Langley.

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Methods

Participants

Potential participants at risk of asthma (one parent atopic) were identified prenatally during recruitment for a birth cohort study in South Manchester, UK⁸ and followed prospectively from birth. A further group of young children with one atopic parent was referred by local doctors after the first confirmed episode of wheeze. All participants were followed-up through monthly telephone calls. In addition, parents were asked to contact the study team immediately if the child developed wheeze.

Children were eligible for randomisation if they had either two episodes of wheeze lasting more than 24 h confirmed by either the primary-care doctor or study team doctor, or one prolonged physician-confirmed wheezy episode lasting more than 1 month.

Children were excluded from the trial if: they had wheeze due to bronchiolitis; they were preterm (<34 weeks' gestation); had other chronic lung disease or chronic illness; had previous ICS use; or were unable to use the inhaler.

The sponsor provided treatment supplies; treatment and placebo inhalers were indistinguishable in appearance (masking was done at source). To ensure the groups were equivalent, stratification for passive smoking, pet ownership, maternal asthma, and age of onset of wheeze, was done with a computer randomisation programme. Participants, those administering the intervention, and those assessing outcomes were all masked to group assignment. The study was approved by the local research ethics committee; written informed consent was obtained from all parents.

Procedures

Participants were reviewed monthly in the first 3 months of the study, and, if symptoms were controlled, every 3 months thereafter until their fifth birthday. The initial dose of 100 µg fluticasone propionate twice daily was reduced every 3 months to the minimum needed to control symptoms. In addition participants could take β agonists as needed. If symptom were not under control by 3 months, open-label fluticasone propionate 100 µg twice daily was added, and follow-up was done once a month.

Open-label treatment was reduced every 2 months to the minimum needed (figure 1). Children who failed to respond to additional open-label treatment were withdrawn from the treatment protocol and referred to the local paediatric service; they continued to be followed as an observational group. We weighed inhaler canisters before administration and on their return to estimate adherence to treatment. The importance of compliance with treatment was emphasised at each visit.

Parents were asked to keep daily diaries recording symptom scores, reliever use, and unscheduled visits to the doctor. Regular follow-up visits involved assessment

of symptoms, recording of height (Harpender's stadiometer), adverse events, physical examination, and collection of urine sample (creatinine to cortisol ratio).

The children were reviewed at age 5 years (±4 weeks) when we obtained information on symptoms, lung function, airway reactivity, and post-bronchodilator lung function. We used a standard interviewer-administered respiratory questionnaire⁹ to obtain information on symptoms, physician-diagnosed illnesses, and treatments received. To ascertain lung function, specific airway resistance (sRaw) was measured through plethysmography.¹⁰ Dynamic lung volumes and expiratory flow were measured with incentive animation software using spirometry program. The test was repeated at 30-s intervals until three technically acceptable traces were obtained (two highest measurements being within 5%); the highest forced expiratory volume in 1 s (FEV₁) was recorded. We measured lung function only in children who were asymptomatic and had not used β₂ agonists within the previous 24 h. We assessed airway reactivity with eucapnic voluntary hyperventilation (EVH) challenge.¹¹ Subjects hyperventilated gas containing 21% O₂, 5% CO₂, remainder N₂ with a water content of less than 10 mg/l for 6 minutes at a ventilation rate of 75% of maximum voluntary ventilation. Lung function was measured 2, 5, and 10 min after challenge and the response expressed as percentage change. We measured post-bronchodilator lung function 15 min after

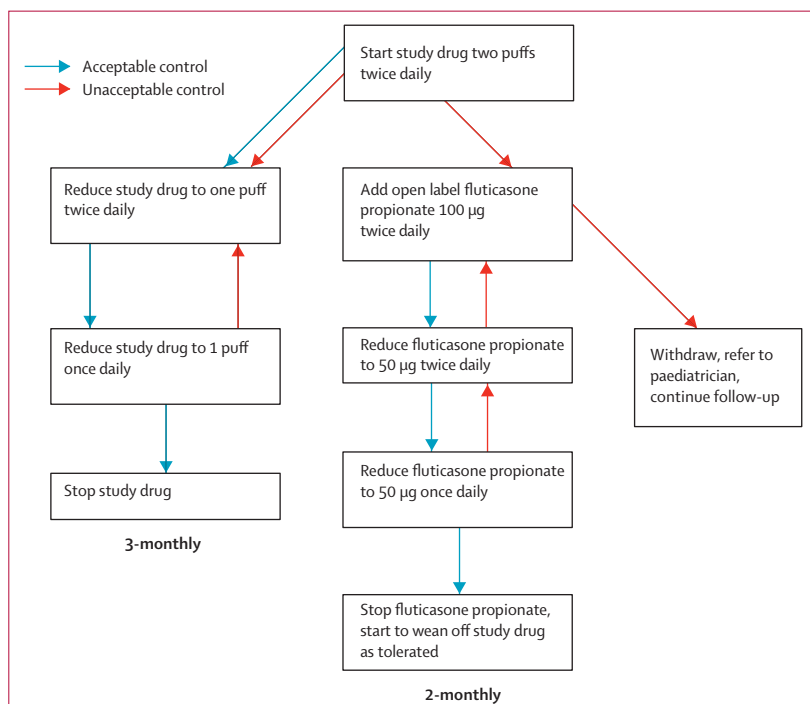


Figure 1: The treatment decision-making algorithm

Unacceptable control was defined by two or more of the following: use of reliever medication three or more times per day; woken by wheeze three or more times per week; two or more unscheduled visits to the family doctor or hospital since the last visit; parent's overall assessment of the child having frequent wheeze or wheeze and cough most of the time.

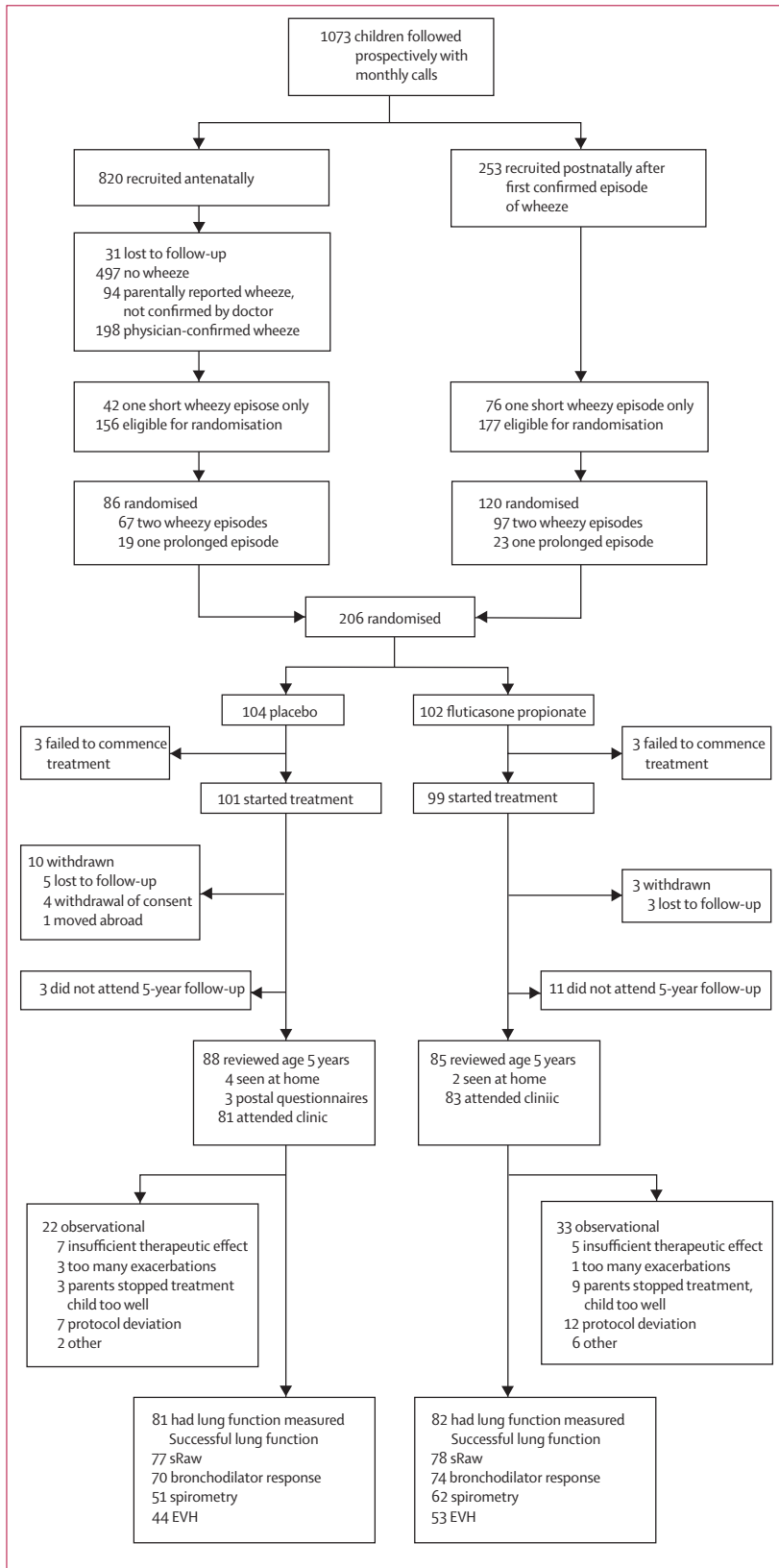


Figure 2: Trial profile

administration of 400 µg salbutamol via a spacer. Of children who had undergone EVH challenge, only those in whom lung function had returned to within 5% of the baseline value had been included.

Primary outcomes were the prevalence of asthma (diagnosed by a doctor other than the one in the study) and wheeze (at the previous 12 months); lung function; airway reactivity; and total dose of open-label fluticasone propionate. Secondary outcomes were symptom scores, reliever medication use, and unscheduled visits to the family doctor in the first 3 months of the study; exacerbation rate; length or height; creatinine to cortisol ratios measured after 1, 2, 3, 6, and 9 months of treatment; and adverse events.

We estimated the risk of subsequent asthma in children who had wheezed twice and had one atopic parent to be 70%. To detect a relative reduction in asthma prevalence of 33% with a power of 80% and a two-sided significance level of 0.05 would require 67 patients per group.

Statistical analysis

We analysed the data using SAS (version 8.02) and SPSS (version 11.0). The height standard deviation scores (Z score) was calculated from the UK 1990 reference curves.¹²

Analysis was on an intention-to-treat basis, using logistic regression and analysis of covariance. Included in the model were the stratification variables, age at randomisation, and sex. A further model included the addition of the open-label drug. We did not adjust for multiple comparisons. Time to addition of the open-label drug and the first exacerbation were analysed between treatment groups using Cox's proportional hazards. The number of open-label doses and the number of exacerbations by age 5 years was compared with Poisson regression. Data obtained from the diary cards were not normally distributed and were analysed using the Mann-Whitney U test.

Further post-hoc subgroup analysis was then done between the four groups derived according to whether open-label fluticasone propionate was needed (ie, placebo only, masked treatment only, placebo+open-label drug, masked treatment+open-label drug). These analyses must be treated with caution, since the groups are no longer truly randomised (addition of the open-label drug might have been affected by the response to randomised treatment), and should be considered as hypothesis-generating rather than hypothesis-testing.

This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN86717853.

Role of the funding source

The study was funded by an unconditional grant from GlaxoSmithKline; the sponsor undertook data monitoring and provided assistance with statistical analysis and data interpretation. The authors were responsible for the study design; data collection, analysis, and interpretation

of data and in the writing of the report. The authors had complete independence over the conduct, integrity and publication of the study.

Results

The study profile is shown in figure 2. 1073 children were followed (820 from birth and 253 from their first wheezy episode). Of the 333 eligible for randomisation, 206 were randomised and 200 commenced treatment (median age 1.2 yrs, 130 male; 101 placebo, 99 study drug). By their fifth birthday, 13 children had been withdrawn, 55 moved into the observational group, and 43 children in the placebo group and 41 in the treatment group had received open-label fluticasone propionate. 173 (86.5%) children attended follow-up at age 5 years; the 27 (13 withdrawn, 14 failed to attend) who did not attend the follow-up did not differ significantly from those who attended in terms of age of onset of symptoms, age at randomisation, sex, passive smoking, pet exposure, maternal asthma, number randomised to treatment or placebo, or number needing the open-label drug. Characteristics of the study groups are shown in table 1.

There was no significant difference between the two groups in the proportion of children with current wheeze (wheeze in the previous 12 months), physician-diagnosed asthma, use of asthma medications, or current wheezers using asthma medication (table 2). There were no differences in the results when the analysis was adjusted for the addition of the open-label drug. The two groups did not differ significantly in lung function (baseline [ie, pre-challenge and pre-bronchodilator], post-challenge or post-bronchodilator; table 3). Adjusting the analysis for the addition of the open-label drug made no difference to the results.

Only four children in the treatment group had a fall in FEV₁ of 10% or greater after EVH challenge compared with three in the placebo group. There was no significant difference in the percentage change in FEV₁ from baseline to post-challenge in the placebo group (adjusted mean 5.5% [95% CI -2.5 to 13.4]) compared with the treatment group (5.0% [-2.2 to 12.2]) (p=0.87). Similarly, there was no significant difference between the groups in the percentage change in sRaw from baseline to post-challenge (placebo 26.4% [13.9–38.9] vs treatment 22.7% [11.8–33.6], p=0.42). Further adjustment for open-label fluticasone propionate made no difference to the results.

The number of children needing the open-label drug was similar in the two groups (43 of 101 placebo, 41 of 99 treatment). The odds for having open-label treatment in the placebo group was 1.08 times (95% CI 0.61–1.94, p=0.79) greater than for the treatment group, after adjustment for the stratification variables, age at randomisation, and sex. There was little difference between the two groups in the time to adding open-label treatment (estimated hazard ratio 1.12 [0.73–1.73],

p=0.60). There was no significant difference in the mean number of doses of the open-label treatment up to age 5 years in the placebo (105.4) compared with the treatment group (88.5), from the Poisson model.

	Placebo n=101	Treatment n=99
Male	67 (66%)	63 (64%)
Age (years) at randomisation*	1.79 (1.12)	1.71 (1.12)
Passive smoking	45 (45%)	42 (42%)
Maternal asthma	31 (31%)	31 (31%)
Pet exposure	46 (46%)	47 (47%)
Onset of wheeze		
0–12 months	70 (69%)	69 (69%)
13–24 months	15 (15%)	15 (15%)
25–36 months	10 (10%)	11 (11%)
≥37 months	6 (6%)	5 (5%)

*Mean (SD).

Table 1: Characteristics of participants

	Placebo n=88	Treatment n=85	Odds ratio (95% CI)	p
Current wheeze*	41 (47)	44 (52)	1.18 (0.63–2.21)	0.61
Further adjusted current wheeze†			1.23 (0.64–2.38)	0.53
Doctor diagnosis of asthma*	56 (64)	52 (61)	0.88 (0.46–1.66)	0.68
Further adjusted doctor diagnosis of asthma†			0.92 (0.48–1.76)	0.80
Current asthma medications*	58 (66)	56 (66)	1.00 (0.51–1.93)	0.99
Further adjusted current asthma medication†			1.07 (0.54–2.12)	0.85
Current asthma and asthma medication*	40 (45)	43 (51)	1.18 (0.63–2.22)	0.61
Further adjusted current asthma and asthma medication†			1.23 (0.64–2.37)	0.53

*Adjusted for age of onset of wheeze, passive smoking, maternal asthma, pet exposure, sex and age at randomisation.
†Additionally adjusted for addition of open label fluticasone propionate.

Table 2: Wheeze, asthma, and medication use at age 5 years in the treatment group compared with the placebo group

	Placebo (mean [95% CI])	Treatment (mean [95% CI])	p
Baseline FEV ₁ (L/s)*	1.04 (0.96–1.12)	1.03 (0.96–1.10)	0.79
Further adjusted baseline FEV ₁ †	1.04 (0.96–1.11)	1.03 (0.95–1.10)	0.72
Post challenge FEV ₁ (L/s)*	1.06 (0.96–1.16)	1.05 (0.96–1.14)	0.77
Further adjusted post challenge FEV ₁ †	1.06 (0.96–1.16)	1.04 (0.95–1.14)	0.66
Post-bronchodilator FEV ₁ (L/s)	1.13 (1.05–1.20)	1.12 (1.05–1.19)	0.82
Further adjusted post-bronchodilator FEV ₁ †	1.12 (1.05–1.20)	1.11 (1.04–1.18)	0.73
Baseline sRaw (kPa/s)*‡	1.28 (1.17–1.39)	1.32 (1.22–1.43)	0.34
Further adjusted baseline sRaw†	1.28 (1.17–1.40)	1.33 (1.22–1.44)	0.32
Post-challenge sRaw (kPa/s)*‡	1.50 (1.32–1.70)	1.50 (1.35–1.67)	0.97
Further adjusted post-challenge sRaw†	1.51 (1.34–1.71)	1.53 (1.37–1.71)	0.77
Post-bronchodilator sRaw (kPa/s)*‡	1.02 (0.95–1.09)	1.05 (0.98–1.12)	0.24
Further adjusted post-bronchodilator sRaw†	1.02 (0.95–1.09)	1.05 (0.99–1.12)	0.19

*Adjusted for age of onset of wheeze, passive smoking, maternal asthma, pet exposure, sex, and age at randomisation.
†Further adjusted for the addition of open-label fluticasone propionate. ‡Geometric mean (95% CI).

Table 3: Lung function in placebo and treatment groups at age 5 years

	Placebo (median [range]) n=92	Treatment (median [range]) n=89	p
Daily symptom score	Median (range)	Median (range)	
Month 1	3.2 (0-10.9)	2.0 (0-12.3)	0.52
Month 2	1.7 (0-8.1)	1.3 (0-9.4)	0.57
Month 3	1.6 (0.4-4.1)	0.6 (0-2.4)	0.02
Daily reliever use			
Month 1	0.37 (0-5.1)	0.46 (0-6.8)	0.84
Month 2	0.34 (0-7.8)	0.31 (0-5.5)	0.76
Month 3	0.32 (0-6.5)	0.11 (0-5.0)	0.15
Children with unscheduled visits for wheeze	Number (%)	Number (%)	
Month 1	26 (28.3%)*	25 (28.1%)*	0.98
Month 2	11 (12%)*	8 (9%)*	0.52
Month 3	10 (10.9%)*	3 (3.4%)*	0.05

*Data are n (%)

Table 4: Results from diary cards in the first 3 months of the study

Parents of 181 children (89 treatment, 92 placebo) returned correctly completed diary cards for the first 3 months after randomisation (five withdrawn, 11 failed to return cards, and three returned incorrectly completed cards) (table 4). There was no significant difference between the groups in median daily symptom scores for months 1 and 2. However, by the third month, children in the treatment group had significantly lower median daily symptom scores compared with those receiving placebo. The groups did not differ significantly in median daily reliever medication usage for months 1 and 2; by the third month, there was a trend towards less use in the treatment group. There was no significant difference between the groups in the number of unscheduled visits to the family doctor for wheeze in months 1 and 2. However, by the third month, children in the treatment group had significantly fewer unscheduled visits than those in the placebo group.

The number of exacerbations for the duration of the study was low (median for placebo 0 [range 0–12] vs for

treatment 0 [0–11]). There was no significant difference in the number of exacerbations per year in study between the groups (mean for placebo 0.4 vs 0.5 for treatment), nor any difference in time to first exacerbation (hazard ratio 0.93 [95% CI 0.56–1.55], p=0.78).

There were no significant differences in actual height or height Z scores at randomisation between placebo (mean actual height 82.7 cm [95% CI 80.4–85.0]; height Z score -0.041 [-0.25 to -0.17]; p=0.78) and treatment (82.3 cm [79.9–84.6]; 0.15 [-0.068 to -0.37]; p=0.22). Similarly, no significant differences between the groups were seen for actual height and height Z scores at age 5 years. However, the analysis of change in height Z score from randomisation to 3 months, 6 months, 12 months, 24 months post-randomisation and age 5 years showed a significantly greater reduction in height Z score in the treatment group after 6 months of treatment and a similar trend at 12 months (table 5). Age at randomisation was significant within the model at 3, 6, and 12 months. Addition of the open-label drug was either significant or showed a trend towards significance at all time points. There were no significant differences in the ratio of urinary cortisol to urinary creatinine between the groups, even after adjusting for open-label treatment (data available from authors on request).

There were 44 serious adverse events in 31 children in the treatment group (including 16 asthma exacerbations), compared with 36 in 23 children on placebo (14 exacerbations). Over the course of the study, five cases of oral candidosis were detected—four in the treatment group and one in the placebo group.

The results of the subgroup analysis in placebo only (n=58), masked treatment only (n=58), placebo+open label treatment (n=43), masked treatment+open label treatment (n=41) are shown in table 6. We found no differences between these groups in passive smoking, pet exposure, or sex.

At age 5 years, children in both of the two open-label drug groups had a significantly greater risk of current wheeze, current use of asthma medications, and current

	Placebo (mean [95% CI])	FP (mean [95% CI])	P
Randomisation to 3 months*	-0.063 (-0.24 to 0.12)	-0.11 (-0.28 to 0.056)	0.507
Further adjusted randomisation to 3 months†	-0.078 (-0.26 to 0.10)	-0.13 (-0.29 to 0.040)	0.497
Randomisation to 6 months*	-0.12 (-0.33 to 0.093)	-0.31 (-0.51 to -0.11)	0.024
Further adjusted randomisation to 6 months†	-0.13 (-0.33 to 0.082)	-0.34 (-0.53 to -0.14)	0.015
Randomisation to 12 months*	-0.050 (-0.29 to 0.19)	-0.21 (-0.43 to 0.0067)	0.079
Further adjusted randomisation to 12 months†	-0.047 (-0.28 to 0.19)	-0.22 (-0.44 to 0.0047)	0.057
Randomisation to 24 months*	0.057 (-0.21 to 0.33)	-0.099 (-0.35 to 0.16)	0.123
Further adjusted randomisation to 24 months†	0.050 (-0.22 to 0.32)	-0.12 (-0.37 to 0.14)	0.102
Randomisation to fifth birthday*	-0.002 (-0.23 to 0.22)	-0.066 (-0.28 to 0.15)	0.501
Further adjusted randomisation to fifth birthday†	-0.0071 (-0.23 to 0.22)	-0.089 (-0.30 to 0.13)	0.385

*Adjusted for age of onset of wheeze, passive smoking, maternal asthma, pet exposure, sex, and age at randomisation. †Further adjusted for the addition of open-label fluticasone propionate.

Table 5: Change in height Z score after randomisation

wheeze with asthma medication use compared with placebo. There were no significant differences between the groups in baseline, post-challenge, or post-bronchodilator FEV₁. There were no significant differences between the four groups in baseline or post-challenge sRaw. However, post-bronchodilator sRaw was significantly higher (ie, reduced lung function) in the groups receiving treatment compared with the placebo group. None of the other covariates were significant within the model.

Change in height Z score from randomisation to 3, 6, 12, and 24 months post-randomisation and age 5 years showed a significantly greater reduction in height Z score for all children who had received treatment after 6 months of treatment compared with the placebo group. However, at all time points, the change in height Z score was significantly reduced in the masked treatment+open-label treatment group (ie, the highest dose group) compared with the placebo group. Age at randomisation was also significant within the model at 3, 6, and 12 months.

Discussion

Our results suggest that in very young children at risk of asthma, the use of ICS when they first start to wheeze has no significant effect on the natural history of wheezing, at least until age 5 years. In addition, there was no effect of this early intervention on lung function

or airway reactivity by this age. We saw a small, but significant improvement in symptom scores and the number of unscheduled physician visits for wheeze in children in the treatment group, but only during the third month of the study.

We randomised children over a large age range, although over two-thirds were younger than 2 years. Thus, most children were followed-up for more than 3 years post-randomisation—a major strength of our study. Only 6.5% of children were withdrawn, and we were able to follow-up 86.5% of children to their fifth birthday. Although over the course of the study, 55 children came off the treatment protocol, they continued to be followed-up on an observational basis, and data continued to be obtained for any other asthma treatments that they were prescribed.

Taking into account any other treatments used in children under observation did not alter the results.

Another strength of our study was the prospective method of follow-up until randomisation. We followed the children until they started wheezing, and then confirmed the wheezing (either immediately by the general practitioner or by the study doctor visiting the child at home after a parental report of wheezing). Thus, children were truly randomised early in the natural history of wheezing, and they had definite wheeze rather than other respiratory problems often confused with wheezing by parents.^{13,14} That is, the study design was

	Placebo only (n=47)	Masked fluticasone propionate only (n=51)	Placebo+open label fluticasone propionate (n=41)	Masked fluticasone propionate+open label fluticasone propionate (n=34)	p
Current wheeze; n (%)	16 (34%)	23 (45%)	25 (61%)	21 (62%)	0.03
Current wheeze; OR (95% CI)	1.0	1.56 (0.63–3.86)	4.17 (1.56–11.16)	3.87 (1.45–10.34)	
Doctor diagnosis of asthma; n (%)	26 (55%)	29 (57%)	30 (73%)	23 (68%)	0.25
Doctor diagnosis of asthma; OR (95% CI)	1.0	1.09 (0.46–2.55)	2.74 (1.03–7.24)	1.96 (0.74–5.21)	
Current asthma medications; n (%)	27 (57%)	30 (59%)	31 (76%)	26 (76%)	0.11
Current asthma medications; OR (95% CI)	1.0	1.11 (0.46–2.71)	3.45 (1.23–9.69)	3.44 (1.19–9.95)	
Current asthma and asthma medications; n (%)	16 (34%)	23 (45%)	24 (59%)	20 (59%)	0.06
Current asthma and asthma medications; OR (95% CI)	1.0	1.53 (0.62–3.79)	3.68 (1.38–9.79)	3.48 (1.31–9.25)	
Lung function at age 5 years					
Baseline FEV ₁ (L/s)	1.04 (0.96 to 1.13)	1.05 (0.97 to 1.12)	1.03 (0.94 to 1.12)	1.00 (0.92 to 1.09)	0.81
Post challenge FEV ₁ (L/s)	1.07 (0.97 to 1.18)	1.06 (1.96 to 1.16)	1.04 (0.92 to 1.16)	1.02 (0.91 to 1.14)	0.82
Post-bronchodilator FEV ₁ (L/s)	1.14 (1.06 to 1.22)	1.14 (1.06 to 1.22)	1.11 (1.02 to 1.19)	1.09 (1.00 to 1.17)	0.49
Baseline sRaw (kPa/s); GM (95% CI)	1.24 (1.12 to 1.38)	1.33 (1.21 to 1.45)	1.31 (1.19 to 1.45)	1.31 (1.18 to 1.46)	0.57
Post challenge sRaw (kPa/s); GM (95% CI)	1.45 (1.27 to 1.66)	1.47 (1.31 to 1.65)	1.58 (1.36 to 1.83)	1.60 (1.39 to 1.84)	0.36
Post-bronchodilator sRaw (kPa/s); GM (95% CI)	0.96 (0.89 to 1.04)	1.05 (0.98 to 1.13)	1.08 (1.00 to 1.17)	1.04 (0.96 to 1.13)	0.02
Change in height Z score*					
Randomisation to 3 months	-0.012 (0.22 to 0.20)	-0.039 (-0.22 to 0.15)	-0.15 (-0.36 to -0.06)	-0.22 (-0.44 to -0.008)	0.17
Randomisation to 6 months	-0.076 (-0.32 to -0.16)	-0.21 (-0.43 to 0.009)	-0.19 (-0.43 to 0.055)	-0.50 (-0.75 to -0.24)	0.01
Randomisation to 12 months	0.016 (-0.25 to 0.29)	-0.15 (-0.39 to 0.093)	-0.11 (-0.38 to 0.16)	-0.30 (-0.57 to -0.026)	0.15
Randomisation to 24 months	0.12 (-0.19 to 0.43)	-0.028 (-0.30 to 0.25)	-0.024 (-0.33 to 0.28)	-0.21 (-0.53 to 0.11)	0.19
Randomisation to fifth birthday	0.08 (-0.18 to 0.34)	0.018 (-0.22 to 0.26)	-0.096 (-0.36 to 0.17)	-0.20 (-0.48 to 0.076)	0.21

Data are mean (95% CI) unless otherwise indicated. *Adjusted for age of onset of wheeze, passive smoking, maternal asthma, pet exposure, sex and age at randomisation (general linear model). GM=geometric mean.

Table 6: Subgroup analysis

adequate to test the question whether secondary prevention of asthma is possible by the early introduction of anti-inflammatory treatment in wheezy infants.

A limitation of the study was that children did not undergo pre-randomisation lung function tests. This would have been difficult to undertake in view of the age spread and the number of the children followed (>1000). Very young children would have needed sedation and the use of the thoracic-abdominal compression technique. This technique would not have been appropriate or acceptable for the older children. Thus, different techniques would have been required, making comparisons difficult. In addition, 42 children were recruited after a prolonged wheezy episode (>1 month), and many of these had ongoing symptoms at the time of randomisation, making baseline lung function difficult to interpret.

Another limitation is the addition of open-label treatment in children who remained highly symptomatic despite the use of study drug. This clearly complicates the interpretation. However, it was deemed unethical to leave these children symptomatic, when the common practice was to treat children with persistent symptoms with an ICS. Despite this, participants, those administering the intervention, and those assessing outcomes remained masked to the study drug used, and children continued with the study drug in addition to the open-label treatment.

About one-third of children eligible for randomisation were not randomised for various reasons, such as parents being unable to commit to long-term follow-up, being concerned about the possibility of their child being given placebo, or holding the view that their child was too well to commence regular treatment. It is possible, but unlikely, that this non-recruitment of eligible children introduced bias into the study.

Our study is the third of a series of trials (the other two being the Prevention of Early Asthma in Kids—PEAK¹⁵ and Prevention of Asthma in Childhood—PAC¹⁶) assessing the potential role of ICS in the secondary prevention of asthma in young children. Of particular importance is the fact that the protocol for our trial differs in several crucial aspects from the other two recently published studies, and therefore, the negative results provide additional, non-overlapping evidence that ICS do not change the natural course of asthma.

Although the children enrolled in our IFWIN study were considered “at risk” for asthma, the definition of “at risk” was based solely on the children having one atopic parent. Compared with the PEAK study, the children we enrolled were younger and more likely to be transient wheezers. On the other hand, IFWIN children were older and probably less likely to be transient wheezers than those enrolled in the PAC study. The treatment strategies also differed in the three studies: short courses of ICS in PAC, 2 years of continuous ICS in PEAK, a step-up/step-down strategy in IFWIN. The fact that the long-term results of the three studies with respect to asthma

prevention were identical in spite of their disparate target populations and treatment strategies allows for reasonably definitive conclusions.

Several studies have investigated whether the use of ICS in very young wheezy children affects lung function^{17–20} but their results have been conflicting. Hofius and colleagues randomised 62 wheezy infants to fluticasone propionate 200 µg daily or placebo for 3 months and found no change from baseline maximal flow at functional residual capacity ($V_{max_{FRC}}$) in either treatment group.¹⁷ In a much smaller study of 26 wheezy children younger than 2 years, Teper and colleagues identified a significant improvement in $V_{max_{FRC}}$ after 6 months of treatment with fluticasone propionate 250 µg daily compared with placebo.¹⁸ A study of 38 infants randomised to beclomethasone 400 µg daily or placebo for 8 weeks reported that $V_{max_{FRC}}$ improved in both groups similarly.¹⁹ Bronchial hyper-responsiveness increased in the placebo group, and the authors concluded that beclomethasone use might have a beneficial effect on airway reactivity. However, all these previous studies have examined lung function at the end of a short course of ICS for wheeze symptoms. By contrast, our study has investigated long-term effect of ICS on lung function in children at a fixed future time point (child’s fifth birthday). Children in the study had treatment for varying periods depending on symptom control (minimum 9 months, but could continue on treatment up to fifth birthday). We found no significant difference in lung function at age five years between children who had received treatment or placebo. Similarly, both the PEAK¹⁵ and the PAC¹⁶ studies identified no difference in lung function, either by measuring reactance and resistance using impulse oscillometry at the end of the 12-month observation period (PEAK) or by measuring sRaw using plethysmography at age 3 years (PAC).

Notably, however, in this study’s subgroup analysis, all children who received the treatment had a higher post-bronchodilator sRaw (ie, reduced lung function) than those who received placebo only. We did not see any effect on FEV₁ (before or after bronchodilator use), but sRaw is one of the most sensitive measures of lung function in early childhood.²¹ We cannot rule out the possibility that children in the treatment groups had worse lung function before randomisation, or that the finding is due to children in treatment groups having more severe asthma at age 5 years. However, exclusion of children who required the open-label drug did not change this finding. In addition, the outcome was identical when we compared children who received only one 9-month cycle of treatment or placebo and were asymptomatic at age 5 years (data available from authors on request). We stress that these post-hoc analyses in small sub-groups must be treated cautiously. However, we detected a roughly 10% difference in post-bronchodilator sRaw at age 5 years in children who had received the treatment. Although the significance of this finding is unclear, there remains a possibility that

early use of ICS in very young children could be detrimental to lung development, which is thought to continue over the first few years of life.

This issue regarding immediate efficacy of ICS in young children is of major clinical importance. Although studies in older children have shown the efficacy of ICS even in mild persistent asthma,^{7,22,23} evidence for their efficacy in infants and very young children is conflicting. Although some studies show a significant, albeit modest improvement in symptom scores for very young children with wheeze,^{24–27} others have shown a lack of improvement.^{17,28} We identified a small but significant improvement in symptom scores and reduction in unscheduled physician visits for wheeze early in the course of treatment. Bronchodilator use also decreased but this failed to reach significance.

The efficacy of the therapeutic intervention with ICS can depend on the population studied and the nature of treatment. This is exemplified by the differences between the IFWIN, PEAK, and PAC studies. Whereas we saw marginal benefits in IFWIN, quite significant improvements were noted in PEAK¹⁵ and none in PAC.¹⁶ In the case of the PAC study, the lack of therapeutic effect may indicate both the study population (very young children, more likely to have transient wheeze) and the intermittent nature of the therapy. However, the argument of the intermittent nature of the therapy cannot be applied for IFWIN (minimum 9-month course of treatment), and it is plausible that the differences in efficacy between IFWIN and PEAK are due to the different populations: very high risk for asthma in PEAK, less so in IFWIN. Thus, ICS could be valuable to control active disease once a clear phenotype is established, but seems to be ineffective in intermittent early-life wheezing.

We found a transient reduction in growth velocity in children who received treatment. This effect was most evident in children who had been on treatment for 6–12 months, and gradually improved with time. Other studies in this age group have also shown an effect on growth velocity over the short to medium term, using both knemometry and stadiometry.^{6,29,30} A dose-response effect was also evident, in that in the four-group analysis at each time point, the children who had received both masked and open-label treatment (ie, up to 400 µg/day) had significantly slower growth velocity compared with the placebo group, whereas those who had only received only masked treatment or only open-label treatment (ie, up to 200 µg/day) did not.

This difference equated to about 1.4 cm at age 5 years. A previous study in toddlers comparing daily doses of budesonide of 200 µg and 800 µg showed a significant effect on growth velocity with the high-dose, but not with the low-dose treatment.³¹ To our knowledge this has not been shown in this age group with fluticasone propionate. We also found that age at randomisation had a significant effect, indicating that children who started treatment at a younger age were affected more. In contrast, Bisgaard and

others³⁰ studied growth velocity in young children taking fluticasone propionate 200 µg daily and reported the growth effect to be independent of age. However, this might have been because their population was considerably older, with approximately 25% of the participants younger than 2 years, and only 1% younger than 12 months (compared with 68% and 32%, respectively, in our study).

Since we saw no long-term benefit from the early use of inhaled steroids in very young children in our study, and the beneficial effect on symptoms was small, we believe that doctors should not rush into the treatment of intermittent infantile wheeze with ICS. Existing evidence suggests it would be better to wait until a clear phenotype is established (eg, such as the one described in PEAK study¹⁵) before commencing this treatment.

Contributors

A Custovic, S J Langley, and A Woodcock have contributed to the conception and design of the study, and the analysis and interpretation of data. S J Langley, A Custovic, and C Murray were principal investigators. C Murray and A Custovic drafted the article and revised it critically for intellectual content. C Murray, A Woodcock, J Morris, and A Custovic contributed to the analysis and interpretation of data. All authors gave final approval of the version to be published.

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Conflict of interest statement

AW and AC have received honoraria for advisory work, lecture fees and travel grants from GlaxoSmithKline. CM received travel grants from GlaxoSmithKline and holds company shares.

Acknowledgments

We thank all the parents and children who took part in the study, Leanne Rice and Richard Forth for the assistance with statistical analysis and data interpretation, and Paul Hedgeland for data monitoring (GlaxoSmithKline).

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