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Ciclesonide in wheezy preschool children with a positive asthma predictive index or atopy[☆]

Paul L.P. Brand^{a,*}, María Luz García-García^b, Adrian Morison^c,
Jan H. Vermeulen^d, Heinrich C. Weber^e

^a Princess Amalia Children's Clinic, Isala klinieken, PO Box 10400, 8000 GK Zwolle, The Netherlands

^b Pediatrics Department, Hospital Universitario Severo Ochoa, Leganés, Madrid, Spain

^c Paediatric Department, Victoria Hospital, Cape Town, South Africa

^d Panorama Medi-Clinic, Cape Town, South Africa

^e Jan S Marais Hospital, Cape Town, South Africa

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KEYWORDS

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Summary

Background: Few large-scale studies have examined inhaled corticosteroid treatment in preschool children with recurrent wheeze. We assessed the effects of ciclesonide in preschool children with recurrent wheeze.

Methods: We included children 2–6 yrs with recurrent wheeze and a positive asthma predictive index or aeroallergen sensitization to, excluding patients with episodic viral wheezing. After a 2–4-week baseline period, patients with ongoing symptoms or rescue medication use were randomised to once-daily ciclesonide 40, 80, 160 µg or placebo for 24 weeks.

Results: The number of wheeze exacerbations requiring systemic corticosteroids was unexpectedly low in all groups: 25 (10.2%) in placebo group, as compared to 11 (4.4%), 18 (7.3%), and 17 (6.7%) in ciclesonide 40, 80, and 160 µg, respectively. The difference in time to first exacerbation was not significantly different between groups ($p = 0.786$), but the difference in exacerbation rates between placebo and the pooled ciclesonide groups was ($p = 0.03$). Large and significant ($p < 0.0001$) improvements in symptom scores and rescue medication use occurred in all groups, including placebo. Improvements in FEV₁ and FEF_{25–75} (measured in 284 4–6 yr olds) were larger in the ciclesonide than in the placebo group. No differences in safety parameters (adverse events, height growth, serum and urinary cortisol levels) between ciclesonide and placebo were observed.

Conclusions: In preschool children with recurrent wheeze and a positive asthma predictive index, ciclesonide modestly reduces wheeze exacerbation rates and improves lung function.

[☆] This study was registered online (www.clinicaltrials.gov) under no. NCT00163449.

* Corresponding author. Tel.: +31 384244165; fax: +31 384247660.

E-mail address: p.l.p.brand@isala.nl (P.L.P. Brand).

A large placebo response and unexpected selection of patients with mild disease may have affected outcomes, highlighting the heterogeneity of preschool wheezing disorders.

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Introduction

Although recurrent wheeze is very common in preschool children,^{1,2} the evidence on its treatment is limited.³ Inhaled corticosteroids (ICS) appear to be effective,⁴ but their effects are smaller than in older children and adolescents.³ The scant available evidence suggests that ICS effects in preschool children may depend on wheezing phenotype, severity, and atopic sensitization.^{3,5} Wheeze both during viral colds and in response to other stimuli (multiple trigger wheeze) improves during ICS maintenance therapy.^{3,5,6} Although no studies have shown ICS efficacy in patients with episodic viral wheeze, interpretation of these data is limited by the small number of subjects studied.^{3,5,7} A recent large study showed that ICS are effective in reducing wheeze in preschool children with a positive asthma predictive index,⁸ which indicates a high risk of symptoms persisting beyond the 6th birthday.⁹ In this study, children were more likely to respond to ICS if they were male, had more severe symptoms and were atopic,¹⁰ confirming results from smaller studies.^{6,11,12} Although the evidence on ICS effects in preschool children and the factors associated with a favourable ICS response in this age group is accumulating, there is an ongoing need of large-scale clinical trials of maintenance treatment for preschool wheezing disorders,³ in particular studies assessing more objective parameters of treatment effect, such as lung function.

Ciclesonide is a once-daily ICS pro-drug that is converted to its active form, desisobutyl-ciclesonide, by esterases in the airways, and is delivered from a metered dose inhaler in a hydrofluoroalkane-based solution containing a high proportion of fine particles.¹³ Studies in children aged ≥ 6 yrs showed that ciclesonide had comparable efficacy and a similar to superior safety profile when compared to fluticasone or budesonide.^{14,15} Long-term safety studies of ciclesonide in school-aged children showed no adverse effects on adrenal function or height growth.^{16,17}

The aim of this study was to assess the effects of three doses of ciclesonide, *versus* placebo, for 24 weeks, on wheeze exacerbations, symptom scores, and lung function in preschool children with recurrent wheeze.

Patients and methods

This randomised, double-blind, placebo-controlled, parallel-group study was conducted in 77 centres (Brazil, Germany, Hungary, India, the Netherlands, Poland, South Africa, Spain and Switzerland). The study was registered with <http://clinicaltrials.gov> under number NCT00163449.

Patients

Children aged 2–6 yrs were eligible for inclusion if they had a documented clinical history of asthma (defined as 3 or

more episodes of wheezing, or troublesome recurrent symptoms and/or episodes wheezing, as reported by parents) for ≥ 6 months, plus a positive stringent asthma predictive index⁹ or a positive screening test for atopy (Phadiatop^{®18}).

Exclusion criteria included a parental report or documentation in the medical chart of one or more of the following: previous use of systemic steroids; a respiratory tract infection in the month before the study; a history of exclusive episodic viral wheezing; concomitant severe diseases; diseases impairing lung function or precluding ICS use; >2 hospitalisations for wheezing in the past year; history of life-threatening wheeze or mechanical ventilation; premature birth; and abnormal height.

Methods: study design

Baseline period

Current ICS and non-steroidal controller (e.g., montelukast) therapy was withdrawn before study entry, and during the 2–4 wk baseline period patients only used inhaled salbutamol (100 μ g/puff, inhaled by valved holding chamber, Aerochamber[®] Plus) on demand. All children had to demonstrate the use of inhaler and spacer to the study staff until these were satisfied that drug administration and inhalation technique were correct; children aged 2–3 yrs were equipped with a facemask (medium size Comfort Seal[®] facemask fitted to the Aerochamber[®] Plus by the manufacturer) if unable to use the inhaler with a spacer and mouthpiece. Throughout the study, parents kept a daily symptom diary of rescue medication use and both daytime and nighttime symptoms on a scale ranging from 0 (no symptoms) to 4 (very bad symptoms: awake most of the night, or unable to carry out daily activities as usual). The total daily symptom score, therefore, ranged from 0 to 8.

Eligibility to enter the treatment period was assessed during the last week of the baseline period. In the week before randomisation, patients had to have a total daily symptom score of ≥ 1 on ≥ 4 days, or used rescue medication on ≥ 4 days, indicating ongoing symptoms during baseline.

Treatment period

When patients fulfilled the eligibility criteria at the end of the baseline period, they were randomised to 24-wk study treatment with placebo or ciclesonide 40 μ g, 80 μ g or 160 μ g using a computer-generated randomisation list following age-stratified block randomisation (2–3 yrs and 4–6 yrs). Allocation of treatment was performed by an independent telephone centre, and was blinded to study investigators enrolling the patients.

Study medication was dispensed via a hydrofluoroalkane-metered-dose inhaler, one puff daily in the evening, administered with a spacer (AeroChamber Plus[®]). Placebo

and ciclesonide inhalers were identical in appearance. Salbutamol 100 µg/puff could be used as reliever therapy throughout the study. If a patient experienced insufficient control of symptoms, montelukast was allowed as additional medication until study end, in a once daily dose of 4 mg chewing tablet for 2–5 year olds, and 5 mg chewing tablet for 6 year olds. During the first 12 weeks of treatment, such insufficient control was determined by the physician of each patient; in the final 12 weeks, montelukast treatment was added if, within the last week, the cumulative daily symptom score was ≥ 8 or rescue medication had been used ≥ 8 times.

Study endpoints and assessments

The primary efficacy endpoint was (time to) severe wheeze exacerbation, defined as a worsening of asthma/wheeze symptoms requiring treatment with systemic steroids as judged by the treating physician. Patients experiencing severe wheeze exacerbation were withdrawn from the study.

Secondary efficacy endpoints were: percentage of wheeze-controlled days (days without wheeze and without use of rescue medication); daily symptom scores and use of rescue medication. In addition, lung function was assessed in children aged 4–6 yrs able to provide reliable and reproducible spirometry measurements following published recommendations for this age group.¹⁹ Individual spirometry measurements were checked for acceptability and reproducibility by study investigators, and were filed for verification purposes. Forced expiratory volume in 1 s (FEV₁), peak expiratory flow (PEF) and forced expiratory flow during the middle half of the forced vital capacity (FEF_{25–75}) were recorded from

reproducible expiratory flow-volume loops. Rescue medication was withheld for ≥ 4 h before spirometry.¹²

Adverse events were recorded at each study visit. If oropharyngeal fungal infection was suspected, a throat swab was cultured at a central laboratory. Patient height was measured by stadiometry at the start of treatment period, after 12 weeks' treatment, and at study end. To assess potential suppression of the hypothalamic-pituitary-adrenal axis, serum and urinary cortisol levels were measured at baseline, after 12 weeks' treatment (urine levels only) and study end.

Ethical and quality considerations

The study was approved by the ethical review boards of all participating centres and was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki. Caregivers provided written informed consent. Study centres, documents and the clinical study report were audited by the Quality Assurance Department of the study sponsor (then ALTANA Pharma, now Nycomed).

Statistical analysis

In order to be able to detect the difference in estimated severe wheeze exacerbation rate between 25% (placebo) and 14% (ciclesonide) with 90% power (log-rank test), and assuming a withdrawal rate of 10% for reasons other than severe wheeze exacerbation, 250 patients were needed in each group. The following efficacy analyses were planned a priori to be conducted in the intent-to-treat population. First, the Tarone trend test examined the probability of

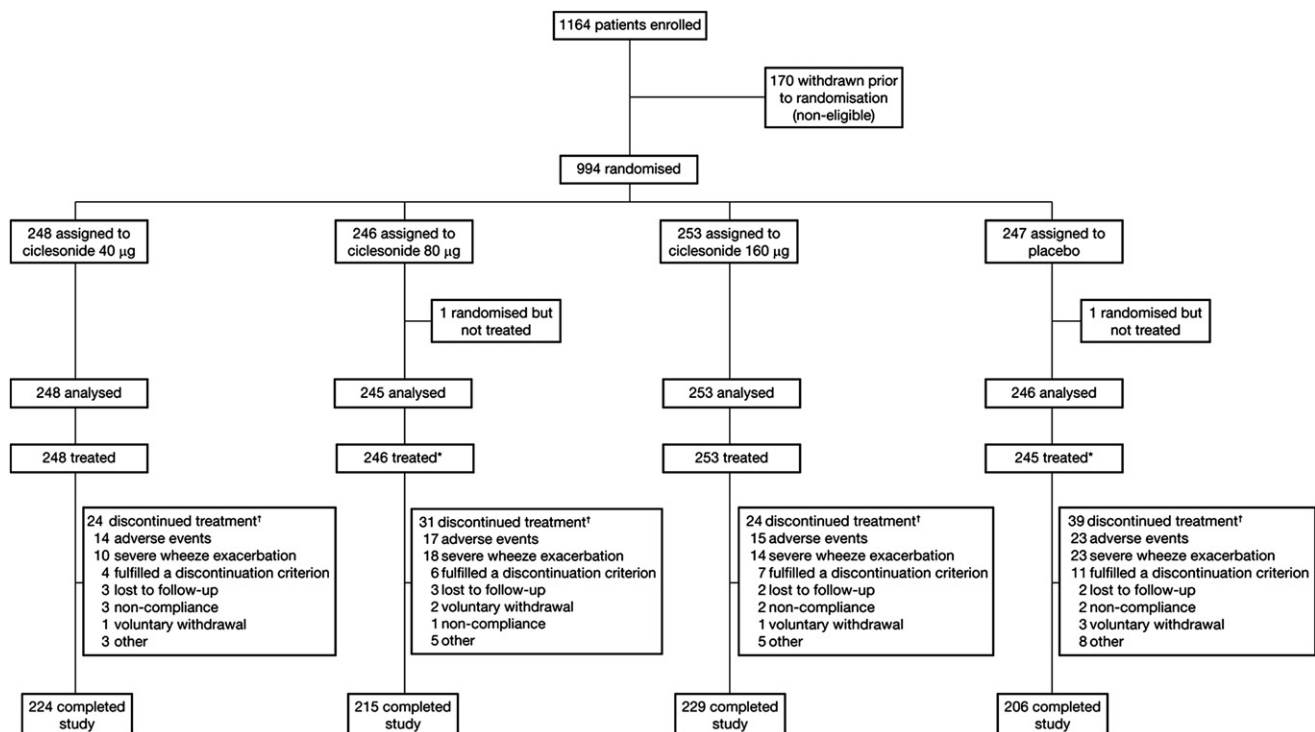


Figure 1 Patient disposition. *: one patient was assigned to placebo but received ciclesonide 80 µg instead; †: multiple reasons for discontinuation may have been provided for a single patient.

Table 1 Demographic and clinical baseline characteristics.

	Placebo (n = 246)	Ciclesonide 40 µg (n = 248)	Ciclesonide 80 µg (n = 245)	Ciclesonide 160 µg (n = 253)
Median age yrs (range)	4.0 (2.0–6.0)	4.0 (2.0–6.0)	4.0 (2.0–6.0)	4.0 (2.0–6.0)
Mean height cm (SD)	103.8 (9.8)	103.7 (10.4)	103.9 (10.4)	104.6 (10.4)
Sex n (%)				
Female	86 (35.0)	84 (33.9)	85 (34.7)	116 (45.8)
Race n (%)				
White	159 (64.6)	159 (64.1)	148 (60.4)	149 (58.9)
Black	8 (3.3)	7 (2.8)	11 (4.5)	14 (5.5)
Asian	43 (17.5)	44 (17.7)	44 (18.0)	45 (17.8)
Other	36 (14.6)	38 (15.3)	42 (17.1)	45 (17.8)
Median disease duration months (range)	21.3 (4.2–70.2)	21.6 (3.8–81.1)	22.5 (5.9–79.8)	23.5 (5.9–77.1)
ICS pretreatment n (%)				
Yes	140 (56.9)	143 (57.7)	138 (56.3)	135 (53.4)
Mean baseline ICS daily dose µg (SD) ^a	332.0 (136.9)	353.0 (141.6)	339.7 (143.0)	335.8 (142.2)
Mean baseline FEV ₁ L (SD)	0.94 (0.27)	0.97 (0.30)	1.05 (0.23)	1.01 (0.28)

FEV₁: forced expiratory volume in 1 s; ICS: inhaled corticosteroids; SD: standard deviation.

^a Beclomethasone dipropionate equivalent.

a patient experiencing severe wheeze exacerbation before study end in patients using ciclesonide 160 µg *versus* placebo, and in the other ciclesonide groups *vs* placebo. Subsequently, the proportion of patients experiencing severe wheeze exacerbation were compared between the pooled ciclesonide groups and the placebo group using Fisher's exact test. Diary data were analysed using non-parametric methods, and lung function and stadiometry data with analysis of covariance. A two-sided *p* value of <0.05 was considered statistically significant (referred to as "significant" in results and discussion).

Results

Of the 1164 patients enrolled, 994 patients were randomised to study treatment (Fig. 1). Two patients (one placebo, one ciclesonide 80 µg) did not receive study medication and were excluded from the analysis (Fig. 1). Demographics and baseline clinical characteristics were comparable between groups (Table 1). Mean (standard deviation) duration of exposure to study medication was comparable in patients receiving placebo (153.2 ± 41.3 days), ciclesonide 40 µg (159.1 ± 32.9), ciclesonide 80 µg (155.3 ± 39.2), and ciclesonide 160 µg (159.5 ± 31.5).

Efficacy

Exacerbations

The proportion of patients experiencing severe wheeze exacerbation in the four study groups is presented in Fig. 2. In all groups, the occurrence of severe wheeze exacerbation was considerably lower than estimated before the study: 25 (10.2%) in placebo group, as compared to 11 (4.4%), 18 (7.3%), and 17 (6.7%) in ciclesonide 40, 80, and 160 µg, respectively. The Tarone trend test showed no significant difference in the probability of experiencing

severe wheeze exacerbation between ciclesonide 160 µg and placebo (*p* = 0.786), nor between the other ciclesonide groups and placebo (*p* > 0.4). The difference in exacerbation rates between the placebo (10.2%) and the pooled ciclesonide groups (6.2%, relative risk 1.65, 95% CI 1.04–2.63), however, was significant (*p* = 0.030).

Symptom scores

Highly significant increases in the percentage of wheeze-controlled days, symptom scores and rescue medication use were observed in all groups, including placebo (*p* < 0.0001), with no significant differences between groups (Table 2).

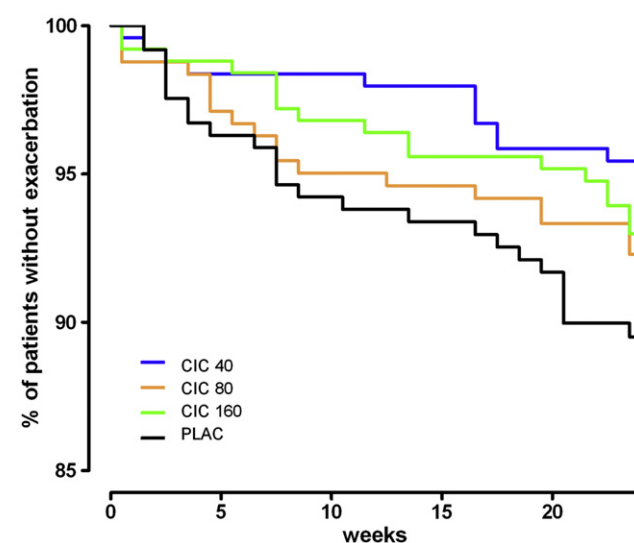


Figure 2 Proportion of patients not experiencing a severe wheeze exacerbation throughout the study period. CIC = ciclesonide; PLAC = placebo.

Table 2 Changes in secondary efficacy endpoints during the study.

	Placebo	Ciclesonide 40 µg	Ciclesonide 80 µg	Ciclesonide 160 µg
<i>Percentage of wheeze-controlled days</i>				
<i>Within-group changes (median)</i>				
Baseline median (IQR)	23.1 (0.0–50.0)	25.0 (0.0–50.0)	23.1 (0.0–50.0)	23.1 (0.0–50.0)
Study end median (IQR)	69.2 (3.6–100.0)	67.9 (3.7–100)	71.4 (15.4–100)	64.3 (10.7–100)
	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
<i>Median (95% CI) difference (versus placebo), p</i>	–	0.0 (–6.4, 7.1) $p = 0.827$	3.1 (–3.6, 10.4) $p = 0.363$	0.0 (–7.1, 7.1) $p = 0.986$
<i>Symptom scores</i>				
<i>Within-group changes (median)</i>				
Baseline median (IQR)	1.57 (0.71–2.86)	1.29 (0.71–2.57)	1.50 (0.71–3.00)	1.43 (0.71–2.86)
Study end median (IQR)	0.71 (0.00–2.57)	0.57 (0.00–2.29)	0.57 (0.00–2.43)	0.71 (0.00–2.29)
p	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
<i>Median (95% CI) difference (versus placebo), p</i>	–	0.00 (–0.29, 0.14) $p = 0.893$	–0.10 (–0.29, 0.14) $p = 0.373$	–0.01 (–0.29, 0.14) $p = 0.544$
<i>Rescue medication use (puffs per day)</i>				
<i>Within-group changes (median)</i>				
Baseline median (IQR)	1.00 (0.29–2.57)	1.00 (0.14–2.43)	1.14 (0.14–2.86)	1.00 (0.14–2.71)
Study end median (IQR)	0.29 (0.00–2.00)	0.14 (0.00–2.00)	0.14 (0.00–2.71)	0.29 (0.00–2.14)
p -value	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
<i>Median (95% CI) difference (versus placebo), p</i>	–	0.00 (–0.14, 0.29) $p = 0.889$	–0.14 (–0.29, 0.14) $p = 0.394$	0.00 (–0.29, 0.14) $p = 0.923$

IQR: interquartile range.

Lung function

Reliable lung function measurements were obtained in 284/544 (52.2%) of the 4–6-yr-olds. There was a clear trend showing better lung function in ciclesonide-treated patients than in those receiving placebo, and this reached significance in a number of comparisons (Fig. 3).

Subgroup analysis: Asian and non-Asian patients

In an attempt to identify factors potentially explaining the unexpectedly low exacerbation rates and the pronounced placebo response, post hoc analyses were carried out, showing marked differences in baseline clinical characteristics between Asian and non-Asian patients (Table 3). Fewer Asian patients were pretreated with ICS, and the proportion of patients with personal or family history of asthma or atopy was lower among Asians than among non-Asians (Table 3). In addition, severe morbidity was less common in Asians (89/170, 52.3%) than in non-Asians (502/814, 61.7%).

Safety

Adverse event profiles with all ciclesonide doses were comparable with placebo. Culture-proven oral candidiasis was found in 9 patients (3 in placebo, and 3, 2, and 1 in ciclesonide 40, 80, and 160 µg, respectively), dysphonia in 4 (2, 1, 0, 1). Mean growth rates were higher with ciclesonide than placebo, but differences were not significant. No

clinically relevant changes in cortisol levels were detected, and differences between groups were not significant.

Discussion

In this large trial, ciclesonide modestly reduced wheeze exacerbation rates, and improved lung function in preschool children with recurrent wheeze and a positive API or atopy. The risk of severe wheeze exacerbation was lower in children using ciclesonide (10.4%) than in those on placebo (16.2%, $p = 0.017$, number needed to treat 16). No effects of ciclesonide on symptom scores and rescue medication use were found. Although we purposefully recruited a patient population with a high risk of wheeze persistence, and patients were suffering from ongoing symptoms when randomized to study treatment, the wheeze exacerbation rate in this study was considerably lower than estimated based on previous clinical trials in this age group,^{4,8} and an unexpectedly large placebo response was observed which may have obscured beneficial effects of ciclesonide therapy on symptom scores.

Previous studies have demonstrated the effectiveness of ciclesonide in older children (4–15 yrs) and adults with asthma, regardless of disease severity.^{14–16,20} It seems unlikely, therefore, that the limited influence of ciclesonide on symptoms in this study was due to lack of an anti-inflammatory effect of the drug. Although a recent meta-

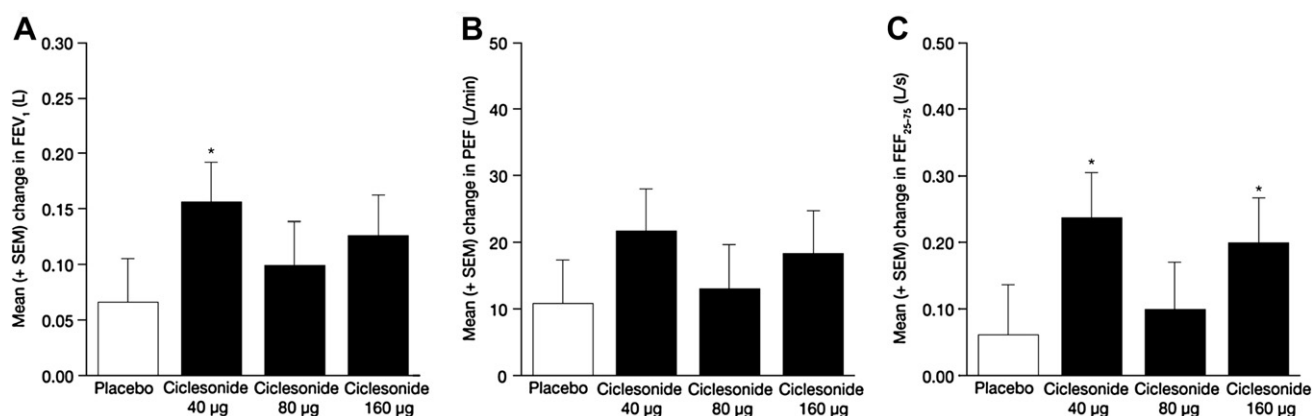


Figure 3 Change in lung function at study end compared with baseline. FEF₂₅₋₇₅: forced expiratory flow during the middle half of the forced vital capacity; FEV₁: forced expiratory volume in 1 s; PEF: peak expiratory flow; SEM: standard error of the mean; *: $p < 0.05$ versus placebo.

analysis of preschool wheezing studies showed superiority of ICS over placebo, there was a high degree of clinical and statistical heterogeneity between studies,⁴ illustrating that the interpretation and pooling of results from such studies are hampered by several methodological problems.³ In addition, the role of inflammation as a pathophysiological mechanism in preschool children with recurrent wheeze is poorly understood. Recent studies showed that acute viral-induced wheezing in preschool children did not respond to oral prednisolone,²¹ and that preschool children with transient wheeze had higher exhaled nitric oxide levels than children with persistent wheeze.²² Therefore, it remains unclear in what way and in which subgroups of preschool children with recurrent wheeze ICS may be beneficial.

To date, the lack of a uniformly accepted classification system for preschool wheeze has hampered comparison of

study results in this age group. The ERS task force guidelines recommendation to distinguish multiple trigger wheeze from episodic viral wheeze was largely based on a systematic review which concluded that ICS therapy improved symptoms in preschool children with multiple-trigger wheeze, but not in children with episodic viral wheeze.⁵ However, it was noted that this conclusion was based on a small number of studies with small sample sizes.³ Recently, it has been shown that patterns of wheeze may change over time in preschool children,²³ reducing the value of the distinction between episodic viral and multiple trigger wheeze. In addition, this distinction does not take severity or frequency of exacerbations into account.^{24,25}

This study was designed to include preschool children with recurrent wheeze with a high risk of wheeze persisting beyond the 6th birthday,⁹ and with relatively severe disease, expressed as ongoing symptoms during baseline.

Table 3 Baseline risk factors for asthma in Asian and non-Asian patients.

<i>n</i> (%) of patients with	Placebo (<i>n</i> = 246)	Ciclesonide 40 µg (<i>n</i> = 248)	Ciclesonide 80 µg (<i>n</i> = 245)	Ciclesonide 160 µg (<i>n</i> = 253)
History of allergies				
Asian	17 (39.5)*	16 (36.4)	21 (47.7)	21 (46.7)
Non-Asian	118 (58.1)	106 (52.0)	107 (53.2)	122 (58.7)
History of eczema				
Asian	3 (7.0)**	5 (11.4)**	2 (4.5)**	5 (11.1)**
Non-Asian	101 (49.8)	104 (51.0)	87 (43.3)	74 (35.6)
Nasal symptoms outside colds				
Asian	22 (51.2)	18 (40.9)*	14 (31.8)*	13 (28.9)**
Non-Asian	106 (52.2)	120 (58.8)	113 (56.2)	113 (54.3)
Family history of asthma				
Asian	39 (90.7)**	40 (90.9)*	36 (81.8)	38 (84.4)
Non-Asian	145 (71.4)	154 (75.5)	148 (73.6)	156 (75.0)
ICS pretreatment				
Asian	20 (46.5)	14 (31.8)**	22 (50.0)	15 (33.3)**
Non-Asian	120 (59.1)	129 (63.2)	116 (55.2)	120 (57.7)

Numbers of Asian and non-Asian patients in each group were: placebo, 43 and 203; ciclesonide 40 µg, 44 and 204; ciclesonide 80 µg, 44 and 210; ciclesonide 160 µg, 45 and 208.

* $p < 0.05$, ** $p < 0.01$ when comparing Asians to non-Asians.

The large improvements in symptom scores and rescue medication use seen in children treated with placebo, and the much lower rates of wheezing exacerbations than those found in earlier studies suggest however that the patients recruited had milder disease than expected. It is likely that caregivers are reluctant to allow young children to participate in placebo-controlled trials, especially when their child has severe disease, and that this caused the recruitment of patients with milder disease in our study.²⁶ This was particularly apparent in Asian patients, who differed from non-Asian patients in risk factors and disease severity (Table 3). This suggests that there are international variations in diagnosis and classification of preschool wheezing disorders. Taken together, these issues indicate that the current classification system for preschool wheezing requires improvement, preferably including objective criteria such as lung function or markers of atopy or inflammation.²⁶

Placebo responses like the one we found (Table 2) may occur both in objective and subjective measures of disease activity,²⁷ and tend to increase with a later date of study publication.²⁸ The latter effect is thought to be caused by increasing participation in clinical trials of individuals with milder disease.²⁸ This may also apply to ICS in preschool children because these drugs are increasingly prescribed to preschool children with non-specific recurrent respiratory symptoms.^{3,29,30} Because it is not always easy to distinguish wheeze associated with lower airway obstruction in young children from upper airway noises and other non-specific respiratory symptoms like cough and breathlessness,³ children with such non-specific symptoms may have been recruited into this study, and that spontaneous improvement of these symptoms over time (regression to the mean) may help to explain the limited effect of ciclesonide on symptoms in this study.

Ongoing concerns exist regard systemic side effects of ICS, particularly in young children.^{31,32} In this large and long-term study, we found no effects of any ciclesonide dose on height growth or adrenal function, confirming previous studies of ciclesonide in older children.^{17,33}

Few studies to date have used lung function as an outcome measure in preschool children. In agreement with previous smaller sample studies, more than half of the 4–6-yr-olds in this study were able to provide reproducible lung function measurements.^{34,35} Routine incorporation of spirometry measurements into future trials involving children ≥ 4 yrs old should be considered.

In conclusion, this large, randomised, placebo-controlled study showed modest effects of ciclesonide on exacerbation rates and lung function in preschool children with recurrent wheeze and a positive asthma predictive index or atopy. An unexpectedly large placebo response and unintended recruitment of patients with mild disease may have affected outcomes. This illustrates that preschool wheezing disorders are highly heterogeneous, and that their classification system requires improvement.

Conflict of interest statement

In the past five years, Paul Brand has received speaking fees, support to visit international conferences, and research

funding from Astra Zeneca, Glaxo Smith Kline, Merck, Boehringer Ingelheim and Nycomed.

Maria Luz Garcia Garcia has received speaking fees and support to visit international conferences from Astra Zeneca, Merck, and Glaxo Smith Kline.

The other authors declare no conflict of interest.

Contributions

PB was the principal investigator of this study, and was involved in the design of the study, recruitment and follow-up of patients, and analysis of the data. He also drafted and edited the manuscript. MLG, AM, JHV and HCW recruited and followed up patients for the study, commented on data analysis and interpretation, and edited the manuscript. All authors approve of the version submitted herewith.

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