Patient characteristics associated with improved outcomes with use of an inhaled corticosteroid in preschool children at risk for asthma

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Background: Maintenance inhaled corticosteroid (ICS) therapy in preschool children with recurrent wheezing at high-risk for development of asthma produces multiple clinical benefits. However, determination of baseline features associated with ICS responsiveness may identify children most likely to benefit from ICS treatment.

Objective: To determine if demographic and atopic features predict response to ICS in preschool children at high risk for asthma.

Methods: Two years of treatment with an ICS, fluticasone propionate (88 μg twice daily), was compared with matching placebo in a double-masked, randomized, multicenter study of 285 children 2 and 3 years old at high risk for asthma development. Baseline demographic and atopic features were related to clinical outcomes in a post hoc subgroup analysis.

Results: Multivariate analysis demonstrated significantly greater improvement with fluticasone than placebo in terms of episode-free days among boys, white subjects, participants with an emergency department (ED) visit or hospitalization within the past year, and those who experienced more symptomatic days at baseline. Children with aeroallergen sensitization experienced greater benefits in terms of oral corticosteroid use, urgent care and ED visits, and use of supplemental controller medications.

Conclusions: More favorable responses to ICS than placebo in high-risk preschool children over a 2-year period were more likely in those with a ED visit or hospitalization for asthma within the past year, children with aeroallergen sensitization, boys, and white subjects. (J Allergy Clin Immunol 2009;123:1077-82.)

Key words: *Childhood asthma, inhaled corticosteroids, response*

In school-age children with persistent asthma, treatment with inhaled corticosteroids (ICSs) is associated with significant improvements in lung function, bronchial hyperresponsiveness, and clinical and humanistic outcomes in established mild to moderate persistent asthma.[1] There is conflicting evidence on the effectiveness of ICSs in reducing illness burden in preschool children.[2,3] Potential reasons for the varying study findings may derive from the different phenotypes of participants studied and the frequency and duration of medication administration.

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For a listing of the members of the Childhood Asthma Research and Education Network of the National Heart, Lung, and Blood Institute, please see Appendix E1 in this article's Online Repository at www.jacionline.org

Supported by grants 5U10HL064287, 5U10HL064288, 5U10HL064295, 5U10HL064307, 5U10HL064305, and 5U10HL064313 from the National Heart, Lung, and Blood Institute. This study was carried out in part in the General Clinical Research Centers at Washington University School of Medicine (M01 RR00036) and National Jewish Medical and Research Center (M01 RR00051).

Disclosure of potential conflict of interest: L. B. Bacharier has received honoraria from AstraZeneca, Genentech, GlaxoSmithKline, Merck, and Aerocrine and has served on the advisory board for Schering-Plough. T. W. Guilbert has received honoraria from GlaxoSmithKline, AstraZeneca, PeerPoint Medical Education Institute, Merck, and Antidote; has received research support from Altus Pharmaceuticals, Inspire Pharmaceuticals, and the National Institutes of Health; and is a member of the American Lung Association, the American Thoracic Society, and the American Academy of Pediatrics. R. S. Zeiger has served as a consultant for Aerocrine, AstraZeneca, Dynavax, Genentech, GlaxoSmithKline, Merck, Novartis, and Schering-Plough and has received research support from AstraZeneca, GlaxoSmithKline, Genentech, Merck, the National Heart, Lung, and Blood Institute, Sanofi-aventis, and TEVA Pharmaceuticals. W. J. Morgan has served as a consultant for the Cystic Fibrosis Foundation and Genentech and has received research support from the National Institutes of Health/University of Wisconsin. R. F. Lemanske, Jr, has received honoraria as a speaker for Merck, has served as a consultant for GlaxoSmithKline, and has received research support from the National Heart, Lung, and Blood Institute. M. Moss served as the president of the Wisconsin Allergy Society from 2005 to 2007. S. J. Szefler has served as a consultant for AstraZeneca, GlaxoSmithKline, Aventis, Genentech, Merck and has received research support from the National Institutes of Health/National Heart, Lung, and Blood Institute Childhood Asthma Management Program, the National Heart, Lung, and Blood Institute Childhood Asthma Research and Education, the National Institutes of Health/National Heart, Lung, and Blood Institute Asthma Clinical Research Network, the National Institutes of Health/National Institute of Allergy and Infectious Diseases Inner City Asthma Consortium, and Ross Pharmaceuticals. M. Krawiec has served on the speakers' bureau for Merck and GlaxoSmithKline and as a consultant for Novartis, has received research support from the American Lung Association, and has served as an expert witness for Parexel. F. D. Martinez has served on the advisory board for Merck, has received lecture fees from Merck and Pfizer, and has served as a consultant for GlaxoSmithKline and MedImmune. The rest of the authors have declared that they have no conflict of interest.

Received for publication July 22, 2008; revised October 29, 2008; accepted for publication December 11, 2008.

Available online February 23, 2009.

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0091-6749/$36.00

doi:10.1016/j.jaci.2008.12.1120

Abbreviations used
API: Asthma predictive index
ED: Emergency department
EFD: Episode-free day
ICS: Inhaled corticosteroid
PEAK: Prevention of Early Asthma in Kids

One study in preschool children with recurrent wheeze reported that age ≥2 years, greater baseline symptom frequency, and family history of asthma were associated with an improvement in symptom-free days during ICS therapy.[4] This report highlights the concept that not all patients respond equally well to a given therapy, with certain patient characteristics influencing the degree of response.

The Prevention of Early Asthma in Kids (PEAK) trial was performed to determine whether early intervention with ICS in preschool children with recurrent wheezing and positive asthma predictive index (API) would alter the development of asthma symptoms after ICS discontinuation.[5] In the PEAK trial, ICS therapy for 2 years did not appear to modify the natural history of asthma during the year after ICS discontinuation.[2] However, group mean response measures during the 2-year treatment phase clearly demonstrated the efficacy of ICS in reducing illness symptom burden in this high-risk cohort. Furthermore, there may be patient characteristics other than the presence of a positive API, or components of the API itself, that were associated with the magnitude of response to ICS relative to placebo. We examine multiple demographic and atopic characteristics of participants in the PEAK trial in an attempt to identify further participant factors associated with greater response to ICS therapy to facilitate selection of appropriate high-risk recurrent wheezing preschool children for maintenance ICS therapy.

METHODS

A detailed description of the recruitment, design, and statistical analysis for the PEAK trial has been reported in detail elsewhere.[2,5]

Overview of the PEAK Trial

The PEAK trial was a multicenter, double-blind, randomized, placebo-controlled, parallel-group comparison trial of ICS (fluticasone propionate [Flovent], 44 μg/puff, 2 puffs twice daily, via metered-dose inhaler, provided by GlaxoSmithKline, Research Triangle Park, NC) or matching placebo, involving 285 children 2 and 3 years of age at high-risk for the development of asthma. Both ICS and placebo were delivered using an AeroChamber with mask (Monaghan Medical, Plattsburgh, NY). Assignments were made with permuted blocks randomization with stratification according to clinic and age groups. Two years of continuous treatment was followed by a 1-year observation year off study medication. For this post hoc analysis, the primary focus was on the 2-year treatment phase to examine the baseline demographic and atopic features associated with ICS responses.

Adherence was promoted by an educational program and measured by using an electronic meter (Dose, Meditrack, S. Easton, Pa). The average percentage of days on which a child took the prescribed dose of study medication was similar in the 2 study groups (74% in the fluticasone group and 69% in the placebo group; $P = .10$).[2] Rescue therapy in the form of 2 puffs of albuterol metered-dose inhaler (90 μg/puff) or albuterol nebulization (2.5 mg; both provided by Schering-Plough Corp, Kenilworth, NJ) was used per written action plan. Four-day courses of oral prednisolone (provided by Muro Pharmaceutical, Inc, Tewksbury, Mass) were prescribed by protocol for exacerbations as detailed previously.[5] Specific algorithms were used to treat participants who developed persistent symptoms.[2,5] Additional details on the protocols for the addition and stopping of supplementary medications and the criteria for assignment of treatment failure status are detailed elsewhere.[5]

Inclusion criteria for PEAK included children 2 to 3 years of age with a positive, modified API consisting of frequent wheezing (at least 4 episodes in the previous year) and either 1 major risk factor (parental history of asthma, personal history of atopic dermatitis, or aeroallergen sensitization) or 2 of 3 minor risk factors (peripheral blood eosinophilia ≥4%, wheezing without colds, or allergic sensitization to food). Children were eligible if they were healthy with no clinically significant medical disorders apart from wheezing or allergy and were excluded if they had received more than 4 months of inhaled corticosteroid use before enrollment or if they required controller medication during the run-in month.[2,5]

Skin prick testing with a core battery of 10 allergens in all clinical centers was performed at enrollment along with total serum IgE levels and peripheral blood eosinophil percentage.[5,6]

Follow-up visits occurred every 4 months after randomization, and data were collected on medical and environmental history, medication use, physical examination findings, and lung function testing. Telephone assessments were conducted every 2 months during the 24-month treatment phase. These assessments collected parent-reported data on asthmalike symptoms (cough and wheeze), asthma medication use, and health care use for respiratory symptoms during the 2 weeks before to the call.[2,5]

The PEAK study was reviewed by the Childhood Asthma Research and Education (CARE) Network Protocol Review Committee; approved by the National Heart, Lung, and Blood Institute, the Childhood Asthma Research and Education Network Steering Committee, and the Institutional Review Boards at all participating centers; and monitored by the CARE Network Data and Safety Monitoring Board. Parents provided written informed consent.

Outcome measures

Several factors reflective of response to ICS compared with placebo during the 2-year double-blind treatment phase were analyzed, including episode-free days (EFDs; primary study outcome), the number of systemic corticosteroid courses, urgent care visits, and use of any supplementary controller medication. EFDs were defined as those days during which there were no asthmalike symptoms, no unscheduled medical visits for respiratory symptoms, and no use of any supplementary asthma medications including pre-exercise albuterol. EFDs were reported by the parents during interviews based on 2-week recalls.

Statistical analyses

Episode-free days, exacerbations, and use of supplementary asthma medication were determined from the self-reported data corrected by the coordinator record in cases in which the family did not self-report previously prescribed supplementary controller medication that was recorded and dispensed by the coordinators. The proportion of EFDs for each participant was calculated as the number of EFDs divided by the number of days observed. Data from all participants were used in the analysis regardless of how many days were observed.

Episode-free days were analyzed on the logit scale within the linear regression framework, whereas supplementary controller medication use (guided per protocol[5]), prednisone use, and urgent care/emergency department (ED) visits were analyzed within the Poisson regression framework. The following general analysis approach was used for each of the outcome measures in this post hoc analysis. The predictive value of each subgrouping factor under consideration was screened by examining the subgroup by treatment interaction term in a multivariable model that also included the following 10 covariate factors: age at randomization (age 2 vs 3 years), sex, race (white vs all others), aeroallergen skin test reactivity (at least 1 positive skin test vs 0 positive tests), peripheral blood eosinophils (≥4% vs <4% based on the asthma predictive index[2]), total serum IgE levels (below the median [45 kU/L] vs ≥45 kU/L), eczema (presence vs absence), proportion of EFDs during the run-in phase (≥80% vs <80%), ED visit or hospitalization during the preceding 12 months (yes vs no), duration of asthmalike symptoms before randomization (<2 years vs ≥2 years), and parental history of asthma (positive vs negative). Adherence

to treatment, both ICS and placebo, was recorded during the study and was included as an additional covariate in these models. These analyses were performed under the intent-to-treat principle, so the inclusion of this covariate is intended to reflect participant behavior across both treatment groups as opposed to the absolute dose of fluticasone received (μg/kg) in the ICS group, which would be confounded by body weight in this age group.

Those covariates that demonstrated significant (at the .10 level) interaction with the treatment effect were then examined simultaneously in a multivariable model including all of those interaction terms and the covariates listed. The treatment effect within each subgroup was assessed by examining linear contrasts from this model. All analyses were performed by using the SAS statistical software system version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

Study population

The 2 study groups were similar with respect to all baseline characteristics except that the ICS group had a higher percentage of peripheral blood eosinophils (Table I).

TABLE I. Characteristics of the participants at baseline*

Characteristic	Baseline	
	Fluticasone (n = 143)	Placebo (n = 142)
Age (y)	3 (0.6)	3 (0.6)
Race or ethnic group, n (%)†		
Non-Hispanic white	76 (53.2)	76 (53.5)
Non-Hispanic black	17 (11.9)	21 (14.8)
Hispanic	29 (20.3)	26 (18.3)
Other	21 (14.7)	19 (13.4)
Sex, n (%)		
Female	55 (38.5)	53 (37.3)
Male	88 (61.5)	89 (62.7)
Age of onset of asthma symptoms (y)	0.97 (0.7)	0.93 (0.6)
Age of first asthma diagnosis by a doctor (y)	1.46 (0.9)	1.28 (0.8)
Parental history of asthma, n (%)	94 (65.7)	90 (63.4)
Parental history of atopy, n (%)	86 (60.1)	78 (54.9)
Cigarette exposure first 2 years of life, n (%)	39 (27.3)	43 (30.3)
Children with pets in house, n (%)	66 (46.2)	63 (44.4)
Symptoms during month before randomization		
Symptom-free days (%)‡	72.6 ± 24.2	74.4 ± 24.3
Albuterol use, average days per week	1.0 ± 1.1	1.1 ± 1.5
Night awakenings because of asthmalike symptoms, average days per month	2.2 ± 2.9	2.2 ± 3.8
At least 1 ED visit for an asthma exacerbation in year before enrollment, n (%)	67 (46.9)	66 (46.5)
At least 1 hospitalization for an asthma exacerbations in year before enrollment, n (%)	10 (7.0)	10 (7.0)
Height (cm)	94.9 ± 6.1	94.7 ± 5.4
Eczema, n (%)	83 (58.0)	70 (49.3)
≥1 Positive aeroallergen skin test, n (%)	88 (61.5)	81 (57.0)
IgE (IU/mL)§	42.5 (5.4)	37.7 (5.1)
Peripheral blood eosinophils (%)‖	4.5 ± 3.3	3.6 ± 2.7

*Plus-minus values are means ± SDs. Not all percentages add to 100, because of rounding.
†Race was determined by family self-report on questionnaire.
‡A symptom-free day was defined by diary card during run-in as a day with no nocturnal awakenings, no use of albuterol for symptoms or other asthma medications, no need for unscheduled physician visits, and no cold or cold symptoms or any asthma symptoms.
§Values are geometric means (geometric SDs).
‖*P* value at baseline visit = .01.

Factors associated with greater improvement in EFDs

Characteristics of participants with significantly higher percentage of EFDs with ICS therapy relative to those receiving placebo were as follows: male sex ($P < .001$), white race ($P < .001$), history of an ED visit or hospitalization for asthma within the year preceding the trial ($P < .001$), sensitization to aeroallergen ($P < .05$), and having fewer than 80% EFDs during the run-in period ($P = .02$; Table II). Response to ICS therapy in terms of EFDs varied by ethnicity, with most favorable responses noted among non-Hispanic white participants and less favorable responses amongst other ethnicities, predominantly non-Hispanic black participants (data not shown). Age, duration of asthma, eczema status, peripheral blood eosinophil and IgE levels, and parental asthma did not influence EFD response. We found no difference in the results between the first and second years of therapy (data not shown).

In the multivariable analysis (see Table II), comparisons for effects of treatment on EFD between the 2 components of each subgroup revealed significant interactions indicating significantly greater ICS therapy benefits for boys than girls ($P = .04$), white than nonwhite subjects ($P = .003$), those with an ED visit or hospitalization for asthma within the year preceding the trial than those without such visits ($P = .004$), and participants with <80% EFD during run-in than those with ≥80% EFDs ($P = .02$) These differences in EFDs were a result of differing percent of EFD over the 2-year treatment period within the placebo group across the 2 strata. For example, among placebo-treated participants, boys experienced 86% EFDs, whereas girls experienced 92% EFDs. In contrast, boys and girls receiving ICS experienced a comparable percentage of EFDs (93% and 92%, respectively; Table III).

Factors associated with secondary trial outcomes

Several secondary trial outcomes were examined, and the factors identified associated with ICS response in terms of EFDs were consistent with those identified in the multivariable analyses for these additional outcomes: white subjects and those with a previous ED visit or hospitalization also had significantly greater likelihood of demonstrating favorable responses with respect to oral corticosteroid use, ED and urgent care visits, and supplementary controller use (see Table II; see this article's Tables E1, E2, and E3 in the Online Repository at www.jacionline.org). Aeroallergen sensitization was associated with greater ICS response in terms of oral corticosteroid use, ED and urgent care visits, and supplementary controller use (see Table II), but not EFDs. In addition, boys receiving ICS therapy were less likely to receive oral corticosteroids ($P = .004$), and participants with <80% EFDs during run-in who received ICS were less likely to require ED or urgent care during the trial ($P = .005$). Multiple subgroups experienced significantly greater ICS therapy benefit in multivariable analysis in terms of supplementary controller medication use, including boys ($P < .001$), 3-year-olds ($P = .04$), participants without eczema ($P < .001$), and IgE ≥45 kU/L ($P = .02$).

Treatment response and observation year outcomes

As previously reported,[2] children in the ICS group who experienced a response during the 2-year treatment period (proportion

TABLE II. Multivariate analyses for predictors of response to ICS

	Percent EFDs		Oral corticosteroid use		ED and urgent care visits		Supplementary controller medication use	
Stratifying variable	**Absolute difference: ICS vs placebo (95% CI)**	***P* value: treatment by subgroup interaction (R^2)**	**Relative rate: ICS vs placebo (95% CI)**	***P* value: treatment by subgroup interaction (R^2)**	**Relative rate: ICS vs placebo (95% CI)**	***P* value: treatment by subgroup interaction (R^2)**	**Relative rate: ICS vs placebo (95% CI)**	***P* value: treatment by subgroup interaction (R^2)**
Male	7.3 (3.9, 11.1)‡		0.62 (0.47, 0.82)‡				0.27 (0.20, 0.38)‡	
Female	0.1 (−3.4, 3.5)	.04 (15%)	1.15 (0.82, 1.62)	.004 (16%)			0.61 (0.41, 0.92)*	<.001 (8%)
White	9.1 (4.8, 13.9)‡		0.60 (0.46, 0.80)‡		0.67 (0.51, 0.87)*		0.26 (0.19, 0.37)‡	
Nonwhite	−1.0 (–3.9, 1.7)	.003 (31%)	1.18 (0.84, 1.67)	.002 (18%)	1.44 (1.05, 1.98)	<.001 (23%)	0.63 (0.43, 0.94)*	<.001 (10%)
2 y of age							0.51 (0.36, 0.71)‡	
3 y of age							0.33 (0.22, 0.49)‡	.04 (3%)
ED/hospitalization history	7.7 (3.9, 11.6)‡		0.54 (0.40, 0.73)‡		0.57 (0.42, 0.78)‡		0.20 (0.14, 0.29)‡	
No ED/hospitalization history	−1.1 (−4.4, 2.1)	.004 (29%)	1.33 (0.97, 1.82)	<0.001 (36%)	1.69 (1.27, 2.24)‡	<0.001 (44%)	0.82 (0.56, 1.20)	<0.001 (23%)
≥1 Positive aeroallergen skin test	6.5 (3.2, 10.0)†		0.61 (0.47, 0.80)‡		0.75 (0.58, 0.98)*		0.26 (0.18, 0.36)‡	
Negative aeroallergen skin tests	0.9 (−2.5, 4.4)	0.11 (9%)	1.17 (0.82, 1.66)	0.004 (16%)	1.28 (0.93, 1.76)	0.009 (11%)	0.66 (0.45, 0.95)*	<0.001 (12%)
IgE ≥45 kU/L			0.97 (0.70, 1.34)		0.92 (0.67, 1.25)		0.31 (0.21, 0.47)‡	
IgE <45 kU/L			0.74 (0.54, 1.02)	0.25 (3%)	1.05 (0.80, 1.38)	0.52 (1%)	0.54 (0.38, 0.76)‡	0.02 (3%)
Eosinophils ≥4%			0.82 (0.58,1.16)				0.41 (0.28, 0.61)‡	
Eosinophils <4%			0.88 (0.66, 1.16)	0.76 (1%)			0.41 (0.29, 0.58)‡	0.97 (1%)
Eczema					1.14 (0.88, 1.48)		0.68 (0.52, 0.88)†	
No eczema					0.85 (0.62, 1.16)	0.14 (3%)	0.25 (0.15, 0.41)‡	<0.001 (9%)
Asthma duration <2 y			0.77 (0.56, 1.05)		1.04 (0.77, 1.41)			
Asthma duration ≥2 y			0.93 (0.70, 1.25)	0.34 (2%)	0.93 (0.71, 1.21)	0.55 (1%)		
Run-in EFD <80%	8.6 (4.2, 13.2)†				0.74 (0.57, 0.96)*		0.35 (0.24, 0.49)‡	
Run-in EFD ≥80%	0.0 (−2.5, 2.5)	0.02 (18%)			1.30 (0.95, 1.78)	0.005 (13%)	0.48 (0.34, 0.70)‡	0.10 (2%)

*$P < .05$.
†$P < .01$.
‡$P < .001$.
Empty cells denote factors that were not included in the final multivariate model because of lack of a significant interaction with treatment effect (at the .10 level) in univariate analysis.

of EFD >92%) had more asthmalike symptoms during the observation year than did those in the placebo group. Thus, we examined the outcome of EFDs during the observation period on the basis of the subgroups described. Similar to the findings for the entire cohort, none of the subgroups experienced a significant disease-modifying (ie, greater proportion of EFDs by treatment group) effect during the observation year. Furthermore, the subgroups that demonstrated significantly better response during the treatment period also demonstrated a significant decrease in the proportion of EFDs after ICS therapy was discontinued

TABLE III. Percent EFDs

Stratifying variable	ICS mean (95% CI)	Placebo mean (95% CI)	Difference (95% CI)	*P* value (ICS vs placebo)
Male	93 (92, 95)	86 (83, 89)	7.3 (3.9, 11.1)	.0005
Female	92 (89, 94)	92 (89, 94)	0.1 (-3.4, 3.5)	.9493
White	93 (91, 95)	84 (80, 88)	9.1 (4.8, 13.9)	.0001
Nonwhite	92 (89, 94)	93 (91, 94)	−1.0 (−3.9, 1.7)	.6028
Run-in EFD <80%	92 (90, 94)	84 (79, 87)	8.6 (4.2, 13.2)	.0009
Run-in EFD ≥80%	93 (91, 95)	93 (91, 95)	0.0 (−2.5, 2.5)	.9856
ED/hospitalization history	95 (93, 96)	87 (83, 90)	7.7 (3.9, 11.6	.0004
No ED/hospitalization history	90 (87, 92)	91 (89, 93)	−1.1 (−4.4, 2.1)	.6218
≥1 Positive aeroallergen skin test	93 (91, 94)	86 (83, 89)	6.5 (3.2, 10.0)	.0027
Negative aeroallergen skin test	93 (90, 95)	92 (89, 94)	0.9 (−2.5, 4.4)	.6809

(boys [$P < .01$], white subjects [$P < .05$], positive aeroallergen skin test [$P < .01$], previous ED visit or hospitalization [$P < .05$]).

DISCUSSION

When evaluating the results of a clinical trial, emphasis has been traditionally placed on a comparison of mean responses between the treatment groups. A treatment is considered effective if a statistically significant difference exists between the average responses among those receiving the treatment of interest relative to the comparator treatments. The present post hoc subgroup analysis of the PEAK trial examined patient characteristics associated with favorable responses to ICS therapy. We found several factors, including male sex, white race, baseline EFD frequency, and ED visit or hospitalization for asthma within the preceding year, that were independently related to favorable responses with ICS in terms of EFDs, as well as several secondary outcome domains. Among these factors, an asthma-related ED visit or hospitalization in the preceding year was identified as a strong predictor of ICS response as reflected by the large R^2 values for all 4 outcome measures, because patients with such events experienced more than twice the relative rates of EFDs, as well as lower oral corticosteroid use, ED visits, and supplementary medication use during the trial than did participants without a pretrial ED visit or hospitalization. This is consistent with findings that previous indicators of substantial asthma morbidity, including recent severe exacerbations[7,8] or hospitalization,[9] are significant predictors of subsequent morbidity. In this study, the response to ICS therapy varied by ethnicity, with most favorable responses noted among non-Hispanic white participants and less favorable responses among other ethnicities, predominantly non-Hispanic black participants.

The API was developed as a tool to identify children at increased risk for persistence of asthma symptoms after recurrent wheezing in early life.[10] The PEAK trial enrolled children identified by a positive API and demonstrated that, on average, children who received ICS for 2 years experienced more EFDs and lower rates of asthma exacerbations requiring oral corticosteroids and supplementary controller medication use than children who received placebo.[5] On the basis of these findings, the most recent National Asthma Education and Prevention Program Guidelines[11] recommend consideration of daily controller therapy in young children with positive APIs. However, despite the substantial symptomatic benefits noted during the treatment phase of PEAK, once ICS therapy was discontinued, participants who received ICS therapy for 2 years did not have an advantage in terms of asthma symptoms during the third year of the study, indicating an absence of a disease-modifying effect of ICS in this population. The post hoc analyses reported here was performed in an effort to determine whether additional patient factors may help identify children who derive the greatest benefits from continuous ICS therapy. We have demonstrated that there are indeed significant heterogeneity and variability among API positive children in response to ICS, and we have identified several factors beyond the API itself that are associated with favorable responses to ICS therapy. Factors associated with greater ICS responsiveness reflect greater disease severity, either in terms of morbidity (EFDs during run-in, previous ED visit/hospitalization) or atopy (IgE levels and aeroallergen sensitization). Although global aeroallergen sensitivity was predictive of ICS benefit, we found no consistent patterns of specific sensitivity (pet vs other aeroallergen) that differentially predicted ICS benefit (data not shown). Because not all children with positive APIs have or will go on to have asthma,[10] the presence of aeroallergen sensitization as a marker of atopic disposition appears to identify further a subgroup of API-positive children who are most likely to have more favorable response to anti-inflammatory therapy with ICS than placebo in terms of oral corticosteroid use, acute care visits, and need for supplementary controller medication use during the PEAK trial.

Participants with indicators of greater pretrial disease severity experienced the greatest improvement in EFDs, as well as other secondary outcome measures, with ICS therapy relative to placebo. However, ICS treatment brought the outcomes in these subgroups of children to the same level as the children in the less severe stratum who received either ICS or placebo, because children in the strata which did not experience a differential response in EFDs to ICS relative to placebo had very little room to improve with treatment, as evidenced by 90% to 93% EFDs during the trial in both treatment arms. In contrast, the children in the strata that experienced differential responses in EFDs had greater potential room to improve (84% to 87% EFDs during the trial in the placebo group; see Table III). These results thus suggest that the main effect of ICS in this population is to attenuate indicators of disease burden in children in whom the presence of certain risk factors is associated with increased severity of symptoms.

This subgroup analysis of the PEAK trial provides an extensive report of factors that are associated with ICS response among preschool children at high risk for asthma. Roorda et al[4] examined subgroups of preschool children (12-47 months) with symptoms of wheeze, cough, or shortness of breath or who needed albuterol on at least 7 of the last 14 days of a 4-week run-in period, from

pooled data of two 12-week studies that compared maintenance ICS at varying doses to placebo. They reported that only the subgroups with frequent symptoms during run-in (>3 days per week and >75% of days) and a family history of asthma (a component of the API) achieved the beneficial response to ICS compared with placebo.[4] Similar to our findings for the outcome of EFDs, a personal history of eczema did not influence ICS responsivity as measured by days or nights without asthma symptoms in the analyses by Roorda et al.[4] The current study extends considerably these types of analyses because it was based on multiple predictors, several different outcomes, and longer-term therapy (2-year treatment period), and examines the interrelationships of these findings using multivariate analysis methods.

Limitations to these findings are largely related to the post hoc nature of these subgroup analyses. Subgroup analyses may be limited by diminished power to detect differences between groups and/or by a potential loss of comparability of groups. Furthermore, multiple comparisons increase the likelihood of a false finding that achieves a prespecified level of statistical significance (ie, $P < .05$). However, given the large overall sample size of the cohort, the consistency of the findings, the high levels of statistical significance seen for most of our findings, and the adjustment for multiple baseline characteristics, it seems likely the findings are valid; still, we cannot totally dismiss inadequate power to determine some relationships.

These analyses present a clinical dilemma. It is clear that certain patient phenotypes achieve greater benefit from ICS therapy, and they should remain the prime targets for therapy. Our findings suggest that among preschool children with a positive API, the following characteristics may predict children most likely to respond to ICS therapy with reduced illness burden: (1) more severe disease as reflected by ED visits or hospitalization within the past year or higher frequency of asthma symptoms, and (2) allergy features such as aeroallergen sensitization and elevated IgE levels. These findings also reinforce the recommendation that ICS therapy in children with positive APIs should be targeted at symptom control and improvement in quality of life rather than disease modification. Unfortunately, it is not clear what approach is most appropriate for the subgroups that did not demonstrate as favorable, albeit not necessarily poor, responses to ICS therapy. It could be argued that the strata not showing good responses (eg, girls, nonwhite subjects, subjects not aeroallergen sensitive, subjects with $\geq$80% EFDs during run-in, or subjects with absence of a previous ED visit or hospitalization) should not be treated with ICS. However, the fact that no differences were found between children treated with placebo and those treated with ICS within these strata does not infer that no child within these strata will respond to ICS. On the contrary, our results suggest that within girls, for example, those with a history of ED visit in the previous year or who are atopic are more likely to respond to ICS therapy than those with no such history. It is thus advisable that a trial of daily ICS be initiated in API-positive children with sufficiently severe or frequent symptoms to justify such treatment; such therapy may be discontinued after a reasonable period and clinical reassessment about the need to continue it should be made, taking into account, among other factors, the presence or absence of some of the risk factors we describe in this study. Furthermore, given the post hoc nature of these analyses and the potential for insufficient statistical power resulting in a type II error, it is premature to recommend avoidance of ICS therapy among any of the subgroups examined herein that did not demonstrate improvement with ICS unless confirmed in prospective comparative studies.

In summary, favorable responses to ICS compared with placebo in high-risk toddlers over a 2-year period were more likely in those with an ED visit or hospitalization within the past year, children with aeroallergen sensitization, boys, and white subjects. When contemplating prolonged treatment with ICS in high-risk preschool children, specific response profiles may be considered.

Clinical implications: Preschool children at high risk for asthma experience favorable responses to ICS therapy, particularly when indicators of greater disease severity and aeroallergen sensitization are present.

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APPENDIX I

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GlaxoSmithKline, Research Triangle Park, NC, donated fluticasone (Flovent) MDI and placebo; Schering-Plough Corporation, Kenilworth, NJ, donated Proventil metered-dose inhalers and Proventil nebules.

Equipment and materials support

Lincoln Diagnostics (Multi-Test II kits, donated), Decatur, Ill; Aerocrine, Inc, Chicago, Ill; VIASYS Healthcare GmbH, Hoechberg, Germany.

TABLE E1. Number of prednisone bursts*

Stratifying variable	ICS mean (95% CI)	Placebo mean (95% CI)	Relative rate	*P* value (ICS vs placebo)
Male	1.12 (0.9, 1.4)	1.81 (1.52, 2.15)	0.62 (0.47, 0.82)	.0009
Female	1.55 (1.23, 1.96)	1.35 (1.05, 1.72)	1.15 (0.82, 1.62)	.4090
White	1.35 (1.08, 1.7)	2.24 (1.88, 2.65)	0.6 (0.46, 0.8)	.0004
Nonwhite	1.29 (1.02, 1.63)	1.09 (0.85, 1.4)	1.18 (0.84, 1.67)	.3345
Duration <2 y	1.27 (1.01, 1.6)	1.66 (1.34, 2.05)	0.77 (0.56, 1.05)	.0982
Duration ≥2 y	1.37 (1.1, 1.7)	1.47 (1.21, 1.79)	0.93 (0.7, 1.25)	.6413
ER/hospitalization history	1.24 (0.98, 1.56)	2.29 (1.91, 2.75)	0.54 (0.4, 0.73)	<.0001
No ER/hospitalization history	1.41 (1.14, 1.75)	1.06 (0.84, 1.34)	1.33 (0.97, 1.82)	.0800
≥1 Positive aeroallergen skin test	1.26 (1.03, 1.54)	2.05 (1.72, 2.44)	0.61 (0.47, 0.8)	.0003
Negative aeroallergen skin test	1.39 (1.08, 1.77)	1.19 (0.92, 1.53)	1.17 (0.82, 1.66)	.3930
Eosinophils ≥4%	1.18 (0.91, 1.54)	1.44 (1.15, 1.82)	0.82 (0.58, 1.16)	.2622
Eosinophils <4%	1.48 (1.2, 1.82)	1.69 (1.4, 2.02)	0.88 (0.66, 1.16)	.3490
IgE ≥45 kU/L	1.4 (1.1, 1.77)	1.45 (1.15, 1.81)	0.97 (0.7, 1.34)	.8398
IgE <45 kU/L	1.25 (0.98, 1.59)	1.68 (1.37, 2.06)	0.74 (0.54, 1.02)	.0622

*The rightmost *P* value corresponds with the test of interaction between the stratifying variable and treatment—that is, is the treatment effect (ICS vs placebo) the same for each level of the stratifying variable? All models are adjusted for the baseline factors.

TABLE E2. Number of ED and urgent care visits*

Stratifying variable	ICS mean (95% CI)	Placebo mean (95% CI)	Relative rate	*P* value (ICS vs placebo)
White	1.45 (1.18, 1.78)	2.17 (1.83, 2.57)	0.67 (0.51, 0.87)	.0027
Nonwhite	1.59 (1.29, 1.95)	1.1 (0.86, 1.41)	1.44 (1.05, 1.98)	.0237
Duration <2 y	1.49 (1.21, 1.84)	1.43 (1.15, 1.79)	1.04 (0.77, 1.41)	.7931
Duration ≥2 y	1.54 (1.27, 1.87)	1.66 (1.39, 1.99)	0.93 (0.71, 1.21)	.5724
Run-in EFD <80%	1.58 (1.3, 1.92)	2.12 (1.79, 2.52)	0.74 (0.57, 0.96)	.0245
Run-in EFD ≥80%	1.46 (1.18, 1.81)	1.12 (0.89, 1.41)	1.3 (0.95, 1.78)	.1040
ER/hospitalization history	1.13 (0.89, 1.44)	1.98 (1.63, 2.4)	0.57 (0.42, 0.78)	.0003
No ER/hospitalization history	2.03 (1.7, 2.43)	1.21 (0.97, 1.5)	1.69 (1.27, 2.24)	.0003
Eczema	1.93 (1.62, 2.29)	1.69 (1.38, 2.07)	1.14 (0.88, 1.48)	.3278
No eczema	1.19 (0.94, 1.52)	1.41 (1.15, 1.73)	0.85 (0.62, 1.16)	.2992
≥1 Positive aeroallergen skin test	1.35 (1.12, 1.64)	1.79 (1.51, 2.14)	0.75 (0.58, 0.98)	.0334
Negative aeroallergen skin test	1.7 (1.37, 2.11)	1.33 (1.05, 1.68)	1.28 (0.93, 1.76)	.1328
IgE ≥45 kU/L	1.35 (1.08, 1.68)	1.46 (1.18, 1.82)	0.92 (0.67, 1.25)	.5963
IgE <45 kU/L	1.71 (1.41, 2.07)	1.63 (1.33, 1.99)	1.05 (0.8, 1.38)	.7333

*The rightmost *P* value corresponds with the test of interaction between the stratifying variable and treatment—that is, is the treatment effect (ICS vs placebo) the same for the baseline factors?

TABLE E3. Use of supplementary controller medication (mo)*

Stratifying variable	ICS mean (95% CI)	Placebo mean (95% CI)	Relative rate	*P* value (ICS vs placebo)
Male	0.7 (0.53, 0.94)	2.57 (2.22, 2.98)	0.27 (0.2, 0.38)	<.0001
Female	0.73 (0.52, 1.01)	1.19 (0.93, 1.53)	0.61 (0.41, 0.92)	.0190
2-3 y of age	0.93 (0.7, 1.24)	1.83 (1.53, 2.2)	0.51 (0.36, 0.71)	<.0001
3-4 y of age	0.55 (0.39, 0.77)	1.66 (1.37, 2.02)	0.33 (0.22, 0.49)	<.0001
White	0.75 (0.56, 1.02)	2.84 (2.43, 3.33)	0.26 (0.19, 0.37)	<.0001
Nonwhite	0.68 (0.49, 0.94)	1.07 (0.85, 1.37)	0.63 (0.43, 0.94)	.0224
Eczema	1.66 (1.37, 2.02)	2.46 (2.07, 2.92)	0.68 (0.52, 0.88)	.0032
No eczema	0.31 (0.2, 0.48)	1.24 (1, 1.54)	0.25 (0.15, 0.41)	<.0001
Run-in EFD <80%	0.69 (0.51, 0.93)	2 (1.65, 2.42)	0.35 (0.24, 0.49)	<.0001
Run-In EFD ≥80%	0.74 (0.54, 1.01)	1.53 (1.26, 1.85)	0.48 (0.34, 0.7)	<.0001
ER/hospitalization history	0.63 (0.46, 0.87)	3.07 (2.6, 3.62)	0.2 (0.14, 0.29)	<.0001
No ER/hospitalization history	0.81 (0.6, 1.11)	0.99 (0.79, 1.25)	0.82 (0.56, 1.2)	.3056
≥1 Positive aeroallergen skin test	0.56 (0.41, 0.76)	2.19 (1.85, 2.59)	0.26 (0.18, 0.36)	<.0001
Negative aeroallergen skin test	0.91 (0.67, 1.24)	1.4 (1.12, 1.74)	0.66 (0.45, 0.95)	.0278
Eosinophils ≥4%	0.67 (0.48, 0.95)	1.64 (1.33, 2.02)	0.41 (0.28, 0.61)	<.0001
Eosinophils <4%	0.76 (0.56, 1.03)	1.87 (1.57, 2.22)	0.41 (0.29, 0.58)	<.0001
IgE ≥45 kU/L	0.52 (0.37, 0.74)	1.67 (1.36, 2.06)	0.31 (0.21, 0.47)	<.0001
IgE <45 kU/L	0.98 (0.73, 1.31)	1.83 (1.51, 2.21)	0.54 (0.38, 0.76)	.0004

*The rightmost *P* value corresponds with the test of interaction between the stratifying variable and treatment—that is, is the treatment effect (ICS vs placebo) the same for each level of the stratifying variable? All models are adjusted for the baseline factors.