

Original Article

Markers of Differential Response to Inhaled Corticosteroid Treatment Among Children With Mild Persistent Asthma

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What is already known about this topic? Specific markers of allergic inflammation and/or greater disease burden tend to identify groups of children with mild asthma who exhibit greater benefit from inhaled corticosteroid treatment than do children without such markers.

What does this article add to our knowledge? This article reaffirms that markers of allergic inflammation (serum IgE and skin test result status) and disease burden (previous oral corticosteroid use and asthma control) appear to identify children who obtain the greatest benefit from inhaled corticosteroid treatment.

How does this study impact current management guidelines? When children with mild persistent asthma exhibit markers of allergic inflammation and/or greater disease burden, clinicians can expect inhaled corticosteroid treatment to meaningfully reduce exacerbation risk and increase symptom control.

BACKGROUND: Inhaled corticosteroids are recommended as first-line therapy for children with mild persistent asthma; however, specific patient characteristics may modify the treatment response.

OBJECTIVE: Identify demographic, clinical, and atopic characteristics that may modify the inhaled corticosteroid treatment response among children enrolled in the Treating Children to Prevent Exacerbations of Asthma trial.

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METHODS: Children aged 6 to 18 years with mild persistent asthma were randomized to 44 weeks of combined, daily, rescue, or placebo treatment. Daily treatment consisted of 40 µg of beclomethasone twice daily. Rescue treatment consisted of 40 µg of beclomethasone accompanying each symptom-driven albuterol actuation. Combined treatment consisted of both. Outcomes included time to first exacerbation and proportion of asthma control days. Fourteen baseline characteristics were selected for interaction testing on the basis of their clinical relevance.

RESULTS: Two hundred eighty-eight children were randomized. Seventy-five percent were white, and 55% were male. As measured by time to first exacerbation, 4 characteristics identified children who received greater benefit from treatment: non-Hispanic ethnicity, positive aeroallergen skin test result, serum immunoglobulin E level of 350 K/µL or more, and history of oral corticosteroid use in the year before enrollment. As measured by asthma control days, 4 characteristics identified children who received greater benefit from treatment: male sex, positive aeroallergen skin test result, serum immunoglobulin E

level of 350 K/µL or more, and incomplete run-in asthma control.

CONCLUSIONS: Children with mild persistent asthma who have markers of atopic asthma or who have greater asthma burden may obtain greater benefit from beclomethasone therapy. Additional study is needed to confirm whether these markers can guide individualized therapy. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;■:■-■)

Key words: Asthma; Pediatric; Inhaled corticosteroid; Stratified analysis

Asthma is no longer thought to define a single disease, but rather to encompass a number of phenotypes characterized by clustering of specific clinical and physiologic features that predict the natural course of disease and its response to treatment.¹ This latter feature is most relevant to clinicians because not all children may respond equally to the current mainstay of treatment, inhaled corticosteroids.² In the future, advances in

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Abbreviations used

ACD- Asthma control day

HR- Hazard ratio

TFE- Time to first exacerbation

TREXA- Treating Children to Prevent Exacerbations of Asthma

pharmacogenomics may lead to individually tailored treatment based on the presence of unique biologic markers.³ Until this new paradigm is realized, clinicians need better information on how to best use existing treatments for persistent asthma.

Inhaled corticosteroids are the most efficacious treatment for children with mild-to-moderate asthma.⁴ However, clinical trials comparing inhaled corticosteroid treatment with placebo or montelukast have suggested that some subgroups of children may experience greater benefits from inhaled corticosteroids than do others.⁵⁻⁷ These trials suggest that children with markers of allergic asthma or markers of more severe asthma may experience greater benefits from inhaled corticosteroid treatment than children without such markers.² Responders appear to have asthma that is preferentially mediated by abnormalities in the T_H2 immune pathway.¹ This allergic asthma phenotype is associated with atopy, type 1 hypersensitivity reactions, and eosinophilic inflammation; it is also more prevalent among children than among adults. Cluster analyses of children with more severe asthma have demonstrated that only a portion of children express this phenotype, which is considered to be steroid responsive.⁸

The Treating Children to Prevent Exacerbations of Asthma (TREXA) trial, a randomized, double-blind, placebo-controlled trial of 3 inhaled corticosteroid dosing strategies among children with mild persistent asthma, provided an opportunity to investigate whether specific demographic, asthma burden, and atopic characteristics modified the clinical response to treatment with inhaled corticosteroids as compared with placebo.

METHODS

TREXA's study design, statistical approach, and results have been detailed elsewhere.⁹ Briefly, children aged 6 to 18 years from 5 clinical centers in the United States were randomized to 1 of 4 treatment groups: combined, daily, rescue, or placebo. Daily treatment consisted of 40 µg of beclomethasone dipropionate (hereafter called beclomethasone) twice daily. Rescue treatment consisted of one 40-µg beclomethasone actuation to accompany each symptom-driven albuterol actuation. Combined treatment consisted of concurrent daily and rescue use. Children were provided with placebo inhalers for daily and rescue use to ensure blinding.

Eligible children had mild persistent asthma and demonstrated good asthma control and high protocol adherence during the study's 4-week run-in period. Children also had to demonstrate airway reversibility and methacholine responsiveness; however, these requirements were later relaxed to aid recruitment. Children were excluded if they demonstrated any of the following markers of severe asthma: baseline FEV₁ less than 60% of predicted, asthma-related hospitalization within the past year, an asthma exacerbation in the past 3 months or more than 2 in the previous year, or a previous life-threatening exacerbation. The institutional review boards of each participating institution approved the clinical trial protocol; children gave assent, and parents gave consent.

Outcomes included time to first exacerbation (TFE) requiring oral corticosteroids and asthma control days (ACDs) reported on

daily diary cards during the 44-week intervention. ACDs were defined as days without symptom-driven albuterol use, daytime or nighttime symptoms, unscheduled asthma-related health care visits, or asthma-related school absences.

Fourteen baseline characteristics based on clinical relevance and availability were investigated for their potential to modify the treatment response to inhaled corticosteroids: sex (male or female), age group (6-11 or 12-18 years), race (white or nonwhite), ethnicity (Hispanic or non-Hispanic), age of diagnosis (≤ 3 years or > 3 years), history of parental asthma (yes or no), history of eczema (yes or no), positive aeroallergen skin test result (yes or no), serum IgE concentration (< 350 or ≥ 350 K/ μ L), FEV₁ reversibility ($< 12\%$ or $\geq 12\%$), dose of methacholine at which a 20% decline in FEV₁ was observed (PC₂₀ ≤ 12.5 mg/mL or > 12.5 mg/mL), fractional exhaled nitric oxide concentration (< 25 ppb or ≥ 25 ppb), complete asthma control during run-in (yes or no), and use of oral corticosteroids in the 12 months before baseline (yes or no). The fractional exhaled nitric oxide and IgE cutoff points were based on suggestions outlined in the National Institutes of Health and Agency for Healthcare Research and Quality's Asthma Outcomes Workshop report on biomarkers.¹⁰

Analyses and reporting follow established recommendations for stratified analyses.¹¹⁻¹³ All analyses were conducted *post hoc*. Descriptive analyses of categorical variables are presented as proportions or percentages. Descriptive analyses of continuous variables are presented as means and SDs or medians with 95% CIs.

To identify characteristics that predicted a differential response to inhaled corticosteroid treatment, each characteristic was individually evaluated using a test of formal interaction. This approach provides the strongest evidence to support a treatment response modification. Two types of interactions are possible: interactions in which the direction of effect is different (qualitative) and interactions in which the direction is similar but the magnitude is different (quantitative).¹² Interaction testing is preferred to simple pairwise comparisons within strata because it minimizes type I error; however, interaction testing typically requires a larger sample and/or effect size to identify significant relationships.¹⁴

An interaction was deemed present if the interaction term was significant at the $P < .10$ level (3 treatment groups $\times$ 14 characteristics $\times$ 2 outcomes = 84 total comparisons). If the interaction term was significant, pairwise comparisons (stratified analyses) were conducted, with comparisons being made between each treatment group and placebo. All stratified analyses controlled for clinical center and the original eligibility criteria (met vs not met). Additional covariates were included only if a significant univariate relationship existed between the covariate and the specified outcome. For example, analyses using TFE also controlled for ethnicity and analyses using ACDs controlled for age group, ethnicity, skin test result status, IgE level, history of eczema, and run-in asthma control. Stratified analyses were considered significant at $P < .05$.

Analyses of TFE were conducted using Cox proportional hazards models, and analyses of ACDs were conducted using multivariate linear regression. Analyses of TFE were reported as hazard ratios (HRs), and analyses of ACDs were reported as mean change in days per year. All analyses were conducted using STATA 12 (College Station, Tex).

RESULTS

Two hundred eighty-eight children with mild persistent asthma were randomized. Children were similar across all measured characteristics (Table I). Seventy-five percent of the children were white, and 55% were male. Children tended to be

TABLE I. Baseline demographic and clinical characteristics by treatment assignment

Baseline characteristic	Overall	Placebo	Rescue	Daily	Combined
All subjects	288 (100)	74 (100)	71 (100)	72 (100)	71 (100)
Sex: male	159 (55.2)	41 (55.4)	37 (52.1)	42 (58.3)	39 (54.9)
Age 6-11 y	188 (65.3)	50 (67.6)	47 (66.2)	47 (65.3)	44 (62.0)
White	217 (75.3)	59 (79.7)	57 (80.3)	51 (70.8)	50 (70.4)
Hispanic or Latino	103 (35.8)	26 (35.1)	27 (38.0)	26 (36.1)	24 (33.8)
Diagnosis ≤ 3 y	139 (48.9)	37 (50.7)	34 (47.9)	33 (46.5)	35 (50.7)
Parental asthma	131 (48.5)	36 (51.4)	33 (46.5)	30 (46.2)	32 (50.0)
Eczema	143 (49.7)	36 (48.6)	37 (52.1)	34 (47.2)	36 (50.7)
Skin test result positive*	220 (78.0)	54 (73.0)	57 (85.1)	52 (74.3)	57 (80.3)
IgE level* >350 K/ μ L	85 (30.5)	18 (24.7)	25 (36.8)	25 (36.2)	17 (24.6)
FEV ₁ reversibility $\geq 12\%$	59 (20.5)	14 (18.9)	16 (22.5)	15 (20.8)	14 (19.7)
PC ₂₀ ≤ 12.5 mg/dL	191 (66.3)	52 (70.3)	49 (69.0)	44 (61.1)	46 (64.8)
FENO level* <25 ppb	228 (83.2)	57 (80.3)	60 (87.0)	62 (87.3)	49 (77.8)
Complete run-in control	183 (63.5)	51 (68.9)	47 (66.2)	39 (54.2)	46 (64.8)
≥ 1 OCS past year	83 (28.8)	21 (28.4)	24 (33.8)	19 (26.4)	19 (26.8)

FENO, Fractional exhaled nitric oxide; OCS, oral corticosteroid requiring exacerbation.

Values are n (%).

*Indicates missing data: skin test, 6 missing; IgE, 9 missing; FENO, 14 missing.

TABLE II. Stratified analyses of baseline characteristics associated with a significant ($P < .10$) univariate interaction term (Treatment Assignment $\times$ Baseline Characteristic)

Characteristic	HR (95% CI) of TFE as compared with placebo		
	Rescue	Daily	Combined
Ethnicity			
Hispanic			1.16 (0.47-2.86)
Non-Hispanic			0.37 (0.18-0.75)*
Skin test result status			
Positive		0.30 (0.15-0.61)*	
Negative		1.50 (0.47-4.80)	
IgE level (K/ μ L)			
<350			0.56 (0.30-1.07)
≥ 350			0.16 (0.03-0.92)†
OCS past year			
Yes			1.12 (0.48-2.65)
No			0.35 (0.16-0.76)*
	Change (95% CI) in ACDs (per year) as compared with placebo		
	Rescue	Daily	Combined
Sex			
Male		45 (23-68)*	
Female		-1 (-37 to 35)	
Skin test result status			
Positive		37 (14-60)*	
Negative		-15 (-50 to 20)	
IgE level (K/ μ L)			
<350		17 (-5 to 40)	26 (6-47)†
≥ 350		44 (1-88)†	49 (1-98)†
Run-in control			
Complete	-12 (-36 to 11)	15 (-7 to 36)	
Incomplete	18 (-29 to 64)	48 (8-87)†	

OCS, Oral corticosteroid requiring exacerbation.

Empty cells denote the absence of a significant ($P < .10$) univariate interaction between treatment assignment and placebo. Analyses of TFE and ACDs control for clinical center and eligibility criteria. Analyses of TFE also control for ethnicity. Analyses of ACDs also control for age group, ethnicity, skin test result status, IgE level, and run-in control.* $P < .01$.† $P < .05$.

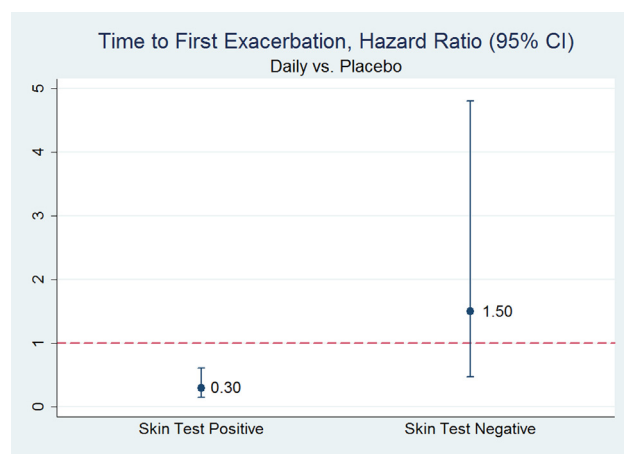


FIGURE 1. HR of TFE among participants treated with a daily inhaled corticosteroid as compared with placebo stratified by skin test result status.

younger (age, 6-11 years) rather than older (age, 12-18 years). Seventy-eight percent of the children had positive skin test results and 50% reported eczema, yet only 31% had IgE levels of 350 K/ μ L or more. Although 21% of the children demonstrated 12% or more reversibility after bronchodilator administration, 66% were responsive to methacholine at a dose of 12.5 mg/dL or less. Few children had markers of poorly controlled asthma: only 17% had a fractional exhaled nitric oxide level of 25 ppb or more, only 36% had less than complete asthma control during the run-in, and only 29% reported oral corticosteroid use in the year before enrollment.

Several baseline characteristics were associated with a more severe natural history of asthma among untreated children (placebo); however, differences were observed only using ACDs and not TFE. Children who had positive skin test results ($P < .05$), had bronchodilator reversible asthma ($P < .05$), or had less than complete run-in asthma control ($P < .001$) reported fewer ACDs than did their respective counterparts. Summary data of TFE and ACDs by baseline characteristic are presented in Tables E1 and E2 in this article's Online Repository at www.jaci-inpractice.org.

Time to first exacerbation

Four characteristics were associated with at least 1 significant interaction term among the combined and daily groups compared with placebo: skin test result status, ethnicity, IgE level, and history of oral corticosteroid use (Table II). No significant interaction terms were identified among children receiving rescue treatment as compared with placebo. Among children receiving daily treatment (as compared with placebo), less frequent exacerbations were observed among children with a positive skin test result (HR, 0.30; 95% CI, 0.15-0.61; $P < .01$) but not among those with a negative skin test result (Figure 1). Among those receiving combined treatment (as compared with placebo), less frequent exacerbations were observed among non-Hispanic children (HR, 0.37; 95% CI, 0.18-0.75; $P < .01$) but not among Hispanic children; less frequent exacerbations were observed among those with IgE levels of 350 K/ μ L or more (HR, 0.16; 95% CI, 0.03-0.92; $P < .05$) but not among those with IgE levels of less than 350 K/ μ L; and less frequent exacerbations were observed among children who did not

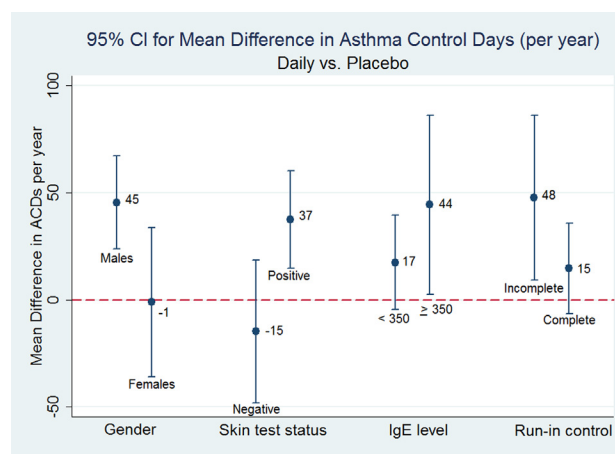


FIGURE 2. Mean change in ACDs among participants treated with a daily inhaled corticosteroid as compared with placebo stratified by sex, skin test result status, IgE level, and run-in asthma control.

report oral corticosteroid use in the year before enrollment (HR, 0.35; 95% CI, 0.16-0.76; $P < .01$) but not among those who did.

Asthma control days

Four characteristics were associated with at least 1 significant interaction term among the 3 treatment groups: sex, skin test result status, IgE level, and run-in control (Table II). Among children receiving rescue treatment (as compared with placebo), the interaction term for level of run-in asthma control was significant, but neither complete nor less than complete control was associated with a significant increase in ACDs in stratified analyses. Among children receiving daily treatment (as compared with placebo), a significant improvement in ACDs was observed among males, 45 (95% CI, 23-68; $P < .01$) more days a year, but not among females; a significant improvement was seen among children with positive skin test results, 37 (95% CI, 14-60; $P < .01$) more days a year, but not among those with negative skin test results; a significant improvement was seen among children with an IgE level of 350 K/ μ L or more, 44 (95% CI, 1-88; $P < .05$) more days a year, but not among those with an IgE level of less than 350 K/ μ L; and a significant improvement was seen among children with less than complete run-in asthma control, 48 (95% CI, 8-87; $P < .05$) more days a year, but not among those with complete control (Figure 2). Among children receiving combined treatment (as compared with placebo), a significant improvement was seen among those with IgE levels of 350 K/ μ L or more and among those with IgE levels of less than 350 K/ μ L, 49 (95% CI, 1-98; $P < .05$) and 26 (95% CI, 6-47; $P < .01$) more days a year, respectively.

DISCUSSION

Children who have markers of allergic asthma (eg, positive skin test result) or more burdensome asthma (eg, less than complete run-in control) may obtain greater benefit from beclomethasone treatment than children without such markers. Because differences between the 3 active groups (rescue, daily, and combined) were small, it is not possible to draw any conclusions regarding differential responsiveness between the inhaled

TABLE III. Summary of reported characteristics that may modify the response to daily treatment with an inhaled corticosteroid: TREXA, PEAK, CLIC, and PACT trials

Characteristic	TREXA	PEAK	CLIC	PACT
Population	6-18 y	2-3 y	6-17 y	6-14 y
Sample size	288	285	126	191
Severity	Mild	Positive API	Mild-to-moderate	Mild-to-moderate
Duration	1 y	2 y	16 wk	1 y
ICS	Beclomethasone (40 µg bid)	Fluticasone (88 µg bid)	Fluticasone (100 µg bid)	Fluticasone (100 µg bid)
Comparison	Placebo	Placebo	Montelukast (5-10 mg qd)	Montelukast (5 mg qd)
Risk dimension	TFE	OCSs	% Δ FEV ₁	TFE
	Ethnicity*	Sex	Age	Parental asthma history
	IgE level*	Previous health care use	ACDs	PC ₂₀ <2 mg/mL
	Previous OCS use*	Race	Body mass index	Previous ICS use
	Skin test†	Skin test	Eosinophil cationic protein	
			FEV ₁ /FVC	
		ED and urgent care visits		
		Previous health care use		
		Race		
		Skin test		
Control dimension	ACDs	Episode-free days	ACDs	ACDs
	Sex†	Sex	FENO	FENO >25 ppb
	IgE level*‡	Previous health care use		Parental asthma history
	Run-in control†‡	Race		
	Skin test†			

API, Asthma predictive index; CLIC, Characterizing the Response to a Leukotriene Receptor Antagonist and an Inhaled Corticosteroid; ED, emergency department; FENO, fractional exhaled nitric oxide; FVC, forced vital capacity; ICS, inhaled corticosteroid; PACT, Pediatric Asthma Controller Trial; PEAK, Prevention of Early Asthma in Kids.

*Both symptom-driven and daily ICS treatment (combined).

†Daily ICS treatment (daily).

‡Symptom-driven ICS treatment (rescue).

corticosteroid dosing strategies. These markers could reflect differential physiologic responsiveness to corticosteroid treatment; alternatively, they could distinguish between asthma phenotypes of greater or lesser severity in which one phenotype has more to gain from treatment than the other. Because we did not characterize physiologic and/or immunologic profiles of individual children, we can only speculate as to the link between underlying physiologic differences and differential corticosteroid responsiveness.

Our findings suggest that certain demographic and clinical characteristics could be used to identify children who may obtain the greatest benefit from inhaled corticosteroid treatment. However, the converse is not equally true. Our data do not support withholding or delaying treatment among children without such characteristics. First, our results did not identify any characteristics that predict worse outcomes when treated (qualitative interactions). Rather, our analyses identified characteristics that were associated with larger, relative improvements (quantitative interactions). Second, because the TREXA trial was not designed to answer this question, it was underpowered to detect meaningful but small improvements within subgroups. It is quite possible that a number of subgroups experienced benefits that we could not detect; therefore, the absence of observed treatment effect is not sufficient to conclude the absence of effect. More definitive answers will come only from larger trials specifically designed to examine subgroup responses. These trials should also characterize individual immunologic and physiologic factors that might account for differential treatment responsiveness, should include children with more heterogeneous asthma severity, and should account for previous inhaled corticosteroid exposure.

Our estimates likely represent the upper boundary of difference. By design, the TREXA trial preferentially studied children who were most likely to be steroid responders because it excluded children who were unable to maintain asthma control during the 4-week run-in using daily low-dose beclomethasone. Therefore, the predictors we identified may not be as informative in general practice where there is greater heterogeneity of potential treatment response. This concept is illustrated by the Predicting Response to Inhaled Corticosteroid Efficacy trial, which attempted to identify predictors of short- and long-term response to inhaled corticosteroids among adults.¹⁵ Short-term response to treatment, as measured by change in FEV₁, was predicted by markers of pulmonary function such as bronchodilator reversibility. Short-term responders who were maintained on treatment maintained control; short-term responders whose treatment was withdrawn subsequently lost control. Nonresponders did equally well whether their treatment was maintained or withdrawn. TREXA trial's results are most generalizable to children who have already demonstrated a favorable response to an initial trial of daily inhaled corticosteroid treatment.

Our results are consistent with those of other trials investigating differential responses to inhaled corticosteroids (Table III). The Prevention of Early Asthma in Kids trial reported stratified results after treatment with fluticasone or placebo among children aged 2 to 3 years at high risk of asthma.⁵ Daily fluticasone provided greater benefit to children who were male and white, had positive skin test result, had previous asthma-related emergency department visits and/or hospitalizations, or had fewer episode-free days during the study run-in period. Differences in treatment response were observed using multiple outcomes including episode-free

days, oral corticosteroid use, and health care utilization. As in our study, these characteristics seemed to identify children with inherently unequal exacerbation risk and symptom control when untreated. Therefore, it is reasonable to conclude that children who exhibited these markers had more to gain than their counterparts. Once treated, all subgroups appeared to achieve similar levels of exacerbation risk and symptom control.

The Characterizing the Response to a Leukotriene Receptor Antagonist and an Inhaled Corticosteroid trial reported stratified results of children aged 6 to 17 years with mild-to-moderate asthma who were treated with fluticasone and montelukast in a crossover design.^{7,16} The Pediatric Asthma Controller Trial reported stratified results from children aged 6 to 14 years with mild-to-moderate asthma who were treated with either fluticasone or montelukast.⁶ Both trials investigated characteristics that predicted a differential response to fluticasone treatment. Although the absence of a placebo group makes these analyses difficult to reconcile with ours, both found that markers of inflammation tended to predict a greater response to fluticasone than to montelukast. The Pediatric Asthma Controller Trial and the Characterizing the Response to a Leukotriene Receptor Antagonist and an Inhaled Corticosteroid trial data were reanalyzed using the 4 phenotype (cluster) classification derived from the Severe Asthma Research Program: late-onset symptomatic asthma with normal lung function, early-onset atopic asthma with mild airflow limitation, earliest-onset atopic asthma with mild airflow limitation and comorbidity, or early-onset atopic asthma with advanced airflow limitation and greatest medication use.^{8,17} Although treatment response was similar across the 4 clusters, children in the early-onset atopic asthma with comorbidity cluster were least responsive to montelukast or fluticasone treatment; however, this cluster was also the smallest, comprising only 7% of characterized children.

There are a number of limitations that should be considered. Most importantly, the TREXA trial was underpowered to identify differential responses to treatment, especially given 3 active treatment groups. We undertook 84 tests of formal interaction at a significance level of $P < .10$; therefore, 8 significant results would be expected by chance alone. For this reason, our analysis is hypothesis generating and should not be used to guide clinical care. Instead, we have identified the characteristics most likely to yield a differential treatment response and ones that should be of highest priority in future investigations. We had also planned to investigate characteristics associated with a differential response to the 3 inhaled corticosteroid dosing strategies; however, all 3 groups obtained similar benefit, making these comparisons impractical. Furthermore, the TREXA trial investigated children who had mild asthma and who were most likely to be steroid responsive; therefore, generalizability to a broader clinical population is limited. If future studies are conducted, they will require substantially more children to have any reasonable expectation of identifying characteristics associated with a differential treatment response.

CONCLUSIONS

Our findings, in conjunction with others, indicate that children who exhibit markers of allergic inflammation and/or greater asthma burden obtain a greater benefit from treatment with

inhaled corticosteroids than children without such markers. Because the TREXA trial was not powered to detect small improvements within subgroups, we cannot conclude that subgroups exist in which no benefit accrues. Although the markers examined in this study are clinically relevant, they may be of limited utility in guiding treatment in individual children. Even if the markers were more specific, additional treatment alternatives are needed for potential corticosteroid nonresponders before individualized treatment for children with asthma will be readily viable. Nonetheless, these current markers help identify children who would be expected to obtain the greatest benefit from daily inhaled corticosteroid treatment.

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TABLE E1. Time to first exacerbation in days stratified by baseline characteristic

Baseline Characteristic	PLACEBO N = 74 days (CI _{95%})	RESCUE N = 71 days (CI _{95%})	DAILY N = 72 days (CI _{95%})	COMBINED N = 71 days (CI _{95%})
All Subjects	84 (28,121)	102 (59,137)	109 (49,241)	134 (90,244)
Male	54 (21,124)	108 (55,161)	146 (100,254)	91 (17,189)
Female	92 (26,136)	95 (25,138)	57 (11,291)	184 (93,259)
Age 6-11 years	80 (28,123)	102 (55,127)	137 (49,265)	165 (90,260)
Age 12-18 years	88 (7,125)	110 (29,277)	76 (14,241)	95 (1,247)
White	92 (43,123)	108 (55,137)	136 (49,254)	156 (90,247)
Non-White	28 (14,136)	84 (53,298)	62 (11,123)	93 (1,269)
Hispanic or Latino	88 (21,153)	84 (28,127)	90 (44,245)	134 (90,269)
Non-Hispanic or Latino	80 (32,110)	112 (63,255)	117 (35,254)	139 (18,247)
Diagnosed ≤3 years	80 (24,121)	63 (29,255)	108 (14,241)	187 (92,260)
Diagnosed > 3 years	88 (22,153)	108 (82,127)	169 (35,291)	92 (18,244)
Parental asthma	108 (43,137)	102 (59,137)	100 (14,254)	216 (90,269)
No parental asthma	28 (14,97)	106 (53,255)	116 (44,265)	96 (18,189)
Eczema	45 (24,105)	88 (29,255)	169 (69,291)	99 (42,247)
No Eczema	97 (32,125)	108 (63,137)	80 (14,254)	166 (55,259)
Skin Test Positive	54 (24,110)	95 (59,137)	108 (33,291)	93 (55,184)
Skin Test Negative	136 (18,222)	199 (112,286)	105 (11,265)	244 (146,269)
IgE < 350 K/μL	96 (43,125)	59 (29,161)	110 (49,254)	156 (91,244)
IgE ≥ 350 K/μL	30 (10,110)	123 (63,255)	72 (14,308)	82 (42,122)
FEV ₁ reversibility ≥12%	54 (22,137)	63 (29,161)	59 (11,291)	99 (91,259)
FEV ₁ reversibility <12%	92 (32,123)	108 (82,138)	137 (44,254)	146 (55,244)
Methacholine PC ₂₀ ≤12.5 mg/dL	54 (24,105)	86 (55,123)	69 (33,245)	122 (90,244)
Methacholine PC ₂₀ >12.5 mg/dL	124 (26,137)	138 (25,255)	164 (80,291)	166 (42,269)
eNO <25 ppb	96 (32,125)	95 (55,138)	109 (49,241)	122 (91,244)
eNO ≥25 ppb	20 (7,110)	113 (29,255)	35 (35,35)	104 (18,259)
Complete run-in asthma control	105 (54,136)	95 (63,127)	241 (100,265)	175 (93,260)
Incomplete run-in asthma control	26 (13,95)	112 (29,277)	69 (14,169)	67 (1,259)
≥1 oral ICS past year	92 (26,137)	61 (29,286)	69 (11,245)	107 (55,244)
<1 oral ICS past year	54 (21,123)	114 (82,161)	123 (44,254)	175 (18,260)

IgE, serum immunoglobulin E; *FEV₁*, forced expiratory volume in 1 second; *PC₂₀*, concentration of methacholine that causes a 20% fall in *FEV₁*; *eNO*, exhaled nitric oxide.

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TABLE E2. Mean asthma control days stratified by baseline characteristic

Baseline Characteristic	PLACEBO (N = 74) mean (SD)	RESCUE (N = 71) mean (SD)	DAILY (N = 72) mean (SD)	COMBINED (N = 71) mean (SD)
All Subjects	0.83 (0.18)	0.81 (0.19)	0.89 (0.14)	0.91 (0.15)
Male	0.80 (0.18)	0.79 (0.22)	0.90 (0.13)	0.91 (0.12)
Female	0.87 (0.17)	0.83 (0.15)	0.87 (0.16)	0.91 (0.18)
Age 6-11 years	0.80 (0.19)	0.76 (0.20)	0.87 (0.16)	0.89 (0.17)
Age 12-18 years	0.89 (0.14)	0.91 (0.10)	0.93 (0.09)	0.94 (0.10)
White	0.84 (0.18)	0.82 (0.18)	0.88 (0.14)	0.91 (0.12)
Non-White	0.80 (0.18)	0.79 (0.21)	0.92 (0.14)	0.89 (0.20)
Hispanic or Latino	0.88 (0.12)	0.87 (0.17)	0.91 (0.14)	0.94 (0.09)
Non-Hispanic or Latino	0.80 (0.20)	0.78 (0.19)	0.88 (0.14)	0.89 (0.17)
Eczema	0.80 (0.19)	0.77 (0.20)	0.90 (0.12)	0.89 (0.18)
No Eczema	0.86 (0.16)	0.85 (0.17)	0.88 (0.16)	0.93 (0.11)
Diagnosed ≤ 3 years	0.82 (0.18)	0.80 (0.17)	0.89 (0.13)	0.88 (0.18)
Diagnosed > 3 years	0.84 (0.18)	0.82 (0.20)	0.89 (0.15)	0.94 (0.10)
Parental asthma	0.84 (0.17)	0.80 (0.20)	0.88 (0.15)	0.94 (0.07)
No parental asthma	0.81 (0.20)	0.82 (0.18)	0.91 (0.11)	0.90 (0.13)
Skin Test Positive	0.80 (0.20)	0.79 (0.20)	0.90 (0.13)	0.90 (0.16)
Skin Test Negative	0.91 (0.07)	0.89 (0.13)	0.86 (0.17)	0.93 (0.10)
IgE < 350 K/ μ L	0.85 (0.17)	0.84 (0.17)	0.87 (0.15)	0.90 (0.17)
IgE ≥ 350 K/ μ L	0.77 (0.19)	0.77 (0.22)	0.91 (0.13)	0.94 (0.08)
FEV ₁ reversibility $\geq 12\%$	0.74 (0.21)	0.77 (0.18)	0.85 (0.15)	0.90 (0.14)
FEV ₁ reversibility $< 12\%$	0.85 (0.16)	0.82 (0.19)	0.90 (0.14)	0.91 (0.15)
Methacholine PC ₂₀ ≤ 12.5 mg/dL	0.83 (0.18)	0.79 (0.19)	0.88 (0.14)	0.90 (0.17)
Methacholine PC ₂₀ > 12.5 mg/dL	0.84 (0.17)	0.86 (0.17)	0.90 (0.14)	0.93 (0.09)
eNO < 25 ppb	0.83 (0.18)	0.82 (0.18)	0.89 (0.14)	0.91 (0.15)
eNO ≥ 25 ppb	0.84 (0.16)	0.81 (0.17)	0.92 (0.07)	0.89 (0.17)
Complete run-in asthma control	0.88 (0.14)	0.81 (0.19)	0.90 (0.15)	0.94 (0.08)
Incomplete run-in control	0.73 (0.21)	0.81 (0.18)	0.88 (0.13)	0.84 (0.21)
≥ 1 oral ICS past year	0.82 (0.21)	0.76 (0.23)	0.90 (0.07)	0.92 (0.07)
< 1 oral ICS past year	0.83 (0.17)	0.84 (0.15)	0.88 (0.16)	0.90 (0.17)

IgE, serum immunoglobulin E; FEV₁, forced expiratory volume in 1 second; PC₂₀, concentration of methacholine that causes a 20% fall in FEV₁; eNO, exhaled nitric oxide.