

Phenotypic predictors of long-term response to inhaled corticosteroid and leukotriene modifier therapies in pediatric asthma

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Background: In children with mild-to-moderate persistent asthma, identification of phenotypic predictors to guide selection of a controller regimen is essential.

Objective: We sought to identify phenotypic characteristics having predictive value for the difference in treatment responses between twice-daily fluticasone and once-daily montelukast.

Methods: Data from the Pediatric Asthma Controller Trial were assessed with multivariate analysis. Outcomes included the change in asthma control days (ACDs), FEV₁, peak expiratory flow, and time to first asthma exacerbation measured over a 1-year treatment period.

Results: The mean age was 9.6 ± 2.1 years, 60% were male, 50% had a parental history of asthma, and 78% had positive aeroallergen skin prick test responses. The mean percent predicted prebronchodilator FEV₁ was $97.8\% \pm 12.9\%$, the median PC₂₀ value was 0.93 mg/mL, and the median exhaled nitric oxide (eNO) level was 25.2 ppb. A history of parental asthma best predicted the expected treatment benefit with fluticasone compared with montelukast in terms of gain in ACDs (adjusted $P = .02$) and time to first exacerbation (adjusted $P = .05$). Increased baseline eNO levels predicted the differential treatment response for fluticasone regarding the gain in ACDs (adjusted $P = .01$). Prior inhaled corticosteroid (ICS) use (adjusted $P = .01$) and low PC₂₀ values (adjusted $P = .03$) each

predicted the expected treatment benefit with fluticasone over montelukast regarding time to first exacerbation. No phenotypic characteristics predicted treatment benefits for montelukast over fluticasone for either outcome.

Conclusions: Physicians treating children with a parental history of asthma, increased eNO levels, low PC₂₀ values, or a history of ICS use can expect the best long-term outcomes with ICS therapy compared with treatment with leukotriene receptor antagonists. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Asthma, biomarkers, exhaled nitric oxide, fluticasone propionate, inhaled corticosteroids, montelukast, pulmonary response

In children with mild-to-moderate asthma, current National Asthma Education and Prevention Program guidelines call for a daily controller medication to prevent symptoms.¹ The Childhood Asthma Management Program trial² examined the long-term effects of twice-daily budesonide, nedocromil, or placebo in children ages 5 to 12 years treated for 4 to 6 years. Although none of the 3 treatment arms resulted in long-term improvement in lung function, this landmark trial established the superiority of inhaled corticosteroid (ICS) therapy compared with nedocromil for the treatment of asthma. Improvements in airway

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Abbreviations used

ACD:	Asthma control day
ACQ:	Asthma Control Questionnaire
API:	Asthma Predictive Index
CLIC:	Characterizing the Response to a Leukotriene Receptor Antagonist and an Inhaled Corticosteroid
ECP:	Eosinophil cationic protein
eNO:	Exhaled nitric oxide
ICS:	Inhaled corticosteroid
LABA:	Long-acting β -agonist
LTRA:	Leukotriene receptor antagonist
PACT:	Pediatric Asthma Controller Trial
ULT:	Urinary leukotriene E ₄

hyperresponsiveness and overall asthma control were both clearly evident for the group randomized to scheduled budesonide. Since that time, leukotriene receptor antagonists (LTRAs) have documented efficacy as asthma controller therapy in both pediatric and adult populations.³⁻⁷

The clinician is presented with the task of choosing an appropriate asthma controller regimen that, while achieving efficacy, also considers potential side effects. Frequently, this initial choice of a daily-use asthma medication is guided by such factors as ease of administration and not by evidence derived from clinical trials. Identifying patient characteristics that can predict whether a given patient will respond to a certain type of therapy would be extremely useful for the practicing clinician and would have the potential for improving asthma treatment outcomes. The literature does offer some insight as to which phenotypic characteristics or biomarkers, if any, could potentially serve as response predictors to ICSs⁸⁻¹⁴ and LTRAs,¹⁴⁻¹⁹ thus providing a mechanism whereby asthma therapy could be individualized. However, most of the data have been applied to short-term outcomes.

Given the concerns regarding both the perceived and actual systemic side effects from ICSs, the question arose as to whether adding a long-acting β -agonist (LABA) to a reduced dose of ICS would achieve comparable asthma control while decreasing the potential for growth effects. The Pediatric Asthma Controller Trial (PACT) was a parallel, double-blind, randomized trial that sought to compare asthma control over a full year among 3 different treatment regimens in children with mild-to-moderate persistent asthma.²⁰ Fluticasone monotherapy, fluticasone/salmeterol combination therapy, and montelukast monotherapy comprised the 3 study arms, with asthma control days (ACDs) as the primary outcome. The subjects randomized to fluticasone gained an average of 42 more ACDs per year compared with those randomized to receive montelukast. In addition, fluticasone was superior to montelukast in terms of extending the time until the first course of prednisone taken for an asthma exacerbation. The purpose in performing these planned *post-hoc* analyses was to determine whether the differential response to fluticasone or montelukast is associated with certain historical, physiologic, or atopic characteristics.

METHODS

The PACT primary outcome report²⁰ outlines complete inclusion and exclusion criteria. Briefly, participants between the ages of 6 and 14 years with mild-to-moderate asthma (based on diary-reported symptoms, β -agonist

use, or peak flow criteria) with an FEV₁ of 80% of predicted value or greater at screening and a positive methacholine challenge result (indicative of airway hyperresponsiveness) were followed for 1 year while adhering to one of 3 treatment arms outlined below. Enrolled children were not taking controller medications for at least 2 weeks before randomization. They were non-smokers, were free of other chronic lung diseases, and had not experienced recent or more than 3 asthma exacerbations requiring recurrent courses of oral corticosteroids in the prior year. Pregnant or lactating female subjects were not included in this trial.

The PACT protocol²⁰ consisted of 7 visits, with screening visit 1 occurring between weeks -4 and -2. A 2- to 4-week run-in period ensued, during which the children used only an open-label, as-needed albuterol metered-dose inhaler for asthma symptoms while taking both a twice-daily placebo Diskus (GlaxoSmithKline, Research Triangle Park, NC) and a prebedtime placebo capsule. At visit 2 (day 0), double-blind, double-dummy randomization occurred, and the subject was started on one of the 3 study treatment arms for 48 weeks: 100 μ g of fluticasone propionate in the morning and 100 μ g in the evening (Flovent Diskus, GlaxoSmithKline); 100 μ g of fluticasone propionate/50 μ g of salmeterol (Advair Diskus, GlaxoSmithKline) in the morning and 50 μ g of salmeterol (Serevent Diskus, GlaxoSmithKline) in the evening (PACT combination); or 5 mg of montelukast (Singulair; Merck, Whitehouse Station, NJ) in the evening.²⁰ The following studies were performed at randomization: complete blood count, serum eosinophil cationic protein (ECP) measurement, serum IgE measurement, urinary leukotriene E₄ (ULT) measurement, aeroallergen skin prick testing, spirometry, methacholine challenge, and exhaled nitric oxide (eNO) measurement. Using these baseline parameters, we sought to identify phenotypic characteristics associated with differences in treatment response between the controller therapies. The present analysis does not include the PACT combination arm because the combination ICS/LABA therapy used in the PACT was not the full dose of ICS usually recommended in combination ICS/LABA therapy and was less effective than full-dose ICS in the PACT analysis.²⁰

Cutoffs for continuous predictors were determined by using the median or mean values of the study population and are as follows: eNO, 25 ppb (median); Asthma Control Questionnaire (ACQ) score, 1.10 (mean); blood eosinophils, 5% (median); serum IgE level, 150 kU/L (median); and PC₂₀ value, 2 mg/mL (stratification variable in randomization scheme). Other variables were dichotomous in nature: presence or absence of any positive aeroallergen skin test result, prior ICS use, eczema, parental asthma, furred pets at home, and smoke exposure.

The primary outcome in the PACT was the improvement in percentage ACDs. This improvement was defined by comparing the 48-week treatment period with the run-in placebo period. An ACD was defined as a day without albuterol rescue use (pre-exercise treatment permitted); use of oral corticosteroids for asthma; use of nonstudy asthma medications; daytime symptoms; nighttime awakenings; unscheduled health care visits, emergency department visits, or hospitalizations for asthma; and school absenteeism for asthma. A secondary outcome of the PACT was the time until the first asthma exacerbation. An asthma exacerbation was defined as the development of acute asthma symptoms (cough, dyspnea, chest tightness, and wheeze) requiring systemic corticosteroids or emergency care (urgent care, emergency department visit, or hospitalization). Management of exacerbations and treatment failures is outlined in the main PACT manuscript.²⁰

A full description of the primary statistical analysis plan and sample size justification was previously reported.²⁰ This report extends those analyses to examine potential predictors of differential long-term response to treatment with either fluticasone or montelukast. The following analysis approach was used for each of the outcome measures: ACDs, percent predicted morning peak expiratory flow, percent predicted FEV₁, and time until first asthma exacerbation. The ACDs, peak flow, and FEV₁ outcomes were analyzed as change from baseline by using ANOVA. Time until first exacerbation was analyzed by using proportional hazards regression. The predictive value of each candidate subgrouping factor under consideration was determined by examining the subgroup-by-treatment interaction term in a model that also included main effects for treatment and subgroup. The treatment effect within each subgroup was assessed by examining linear contrasts from this model. These analyses were performed for each candidate predictor separately. Subgroup factors

TABLE I. Baseline characteristics of the participants by treatment group*

Characteristic	Fluticasone†	Montelukast‡
Participants, n	96	95
Age (y)	9.8 ± 2.2	9.6 ± 2.2
Male sex, no. (%)	57 (59.4)	57 (60.0)
Minority, no. (%)	45 (46.9)	41 (43.2)
Height (cm)	138.6 ± 13.5	138.2 ± 13.8
Weight (kg)	40.6 ± 17.6	38.3 ± 14.7
Age at physician's asthma diagnosis (y)	4.2 ± 3.1	3.8 ± 3.0
Age at onset of asthma symptoms (y)	3.5 ± 2.9	2.9 ± 2.6
Atopic, no. (%)	75 (78.1)	73 (76.8%)
Serum IgE (kU/L)	321 ± 419	311 ± 406
Blood eosinophils (%)	6.0 ± 3.8	6.0 ± 4.0
Serum ECP (μg/L)	25 ± 26	26 ± 38
Urinary leukotriene E ₄ (pg/mg creatinine)	106 ± 51	112 ± 65
Medication use in previous year		
Inhaled/nebulized ICS, no. (%)	58 (60.4%)	55 (57.9%)
Leukotriene modifier, no. (%)	28 (29.2%)	38 (40.0%)
LABA, no. (%)	10 (10.4%)	14 (14.7%)
Theophylline, no. (%)	0	0
Cromolyn/nedocromil, no. (%)	0	1 (1.1%)
>1 Prednisone course, no. (%)	25 (26.0%)	22 (23.2%)
Prebronchodilator FEV ₁ (% predicted)	97.8 ± 12.2	97.7 ± 13.6
Prebronchodilator FEV ₁ /FVC (%)	80.2 ± 7.4	80.1 ± 8.3
Maximum bronchodilator response (%)	10.9 ± 7.1	10.9 ± 7.4
Average morning peak flow during run-in period (L/min)	249.3 ± 68.4	241.2 ± 66.8
Average evening peak flow during run-in period (L/min)	256.6 ± 69.8	246.2 ± 65.4
Peak flow variability during run-in period (%)	9.9 ± 5.7	9.9 ± 5.2
ACDs during run-in period (%)	30 ± 24	27 ± 23
Asthma control questionnaire§	1.1 ± 0.6	1.2 ± 0.6
eNO (ppb), median (Q1, Q3)	24.5 (11.9, 52.1)	27.1 (12.4, 55.2)
Methacholine PC ₂₀ during run-in period (mg/mL), median (Q1, Q3)	0.93 (0.30, 2.72)	0.93 (0.28, 2.51)

FVC, Forced vital capacity.

*Differences not significant for any characteristic across treatment groups.

†Fluticasone, 100 μg, dry powder inhaler, twice daily.

‡Montelukast, 5 mg before bedtime.

§Seven-point scale: 0, total control; 6, extremely poor control.

that demonstrated significant interaction with the treatment effect at the 0.10 level were then examined simultaneously in a multivariable model, including main effects and treatment-by-subgroup interaction terms for each factor identified. Descriptive statistics for baseline data, including frequency tables for categorical outcomes and means and SDs for continuous outcomes, were calculated. All analyses were carried out with the SAS statistical software system, version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

At baseline, no significant differences existed between the fluticasone (n = 96) and montelukast (n = 95) treatment arms (Table I). The mean age was 9.6 ± 2.1 years, 60% were male, 50% had a parental history of asthma, and 78% had 1 or more positive skin prick test responses to aeroallergens. Also, the mean number of positive aeroallergen skin test results per subject for this cohort was 2.5 (±2.0) of 8 possible (cat, dog, cockroach, dust mite, tree, grass, weed, and mold). The mean percent predicted prebronchodilator FEV₁ was 97.8% ± 12.9%, the median PC₂₀ value was 0.93 mg/mL, and the median eNO level was 25.2 ppb. As specified by the protocol, participants had persistent asthma with only 29% ACDs during the run-in/characterization period.

Change in ACDs

For more information on change in ACDs, see Table II. By means of univariate analysis, baseline eNO levels of greater than 25 ppb ($P = .0017$), blood eosinophil counts of greater than 5% ($P = .005$), serum IgE levels of greater than 150 kU/L ($P = .03$), and PC₂₀ values of less than 2 mg/mL ($P = .007$) compared with lower levels of these biomarkers were associated with more favorable improvements in ACDs to fluticasone over montelukast. Trends were noted for a greater change (>1.10) in ACQ score ($P = .0810$), positive parental history of asthma ($P = .07$), and presence of 1 or more positive skin prick test responses ($P = .13$). Of note, a higher ACQ score indicates poorer asthma control.

The multivariate predictors of a better ACD response to fluticasone over montelukast were a parental history of asthma ($P = .02$) and an eNO level of greater than 25 ppb ($P = .01$).

Time to first exacerbation

For more information on time to first exacerbation, see Table II. By means of both univariate and multivariate analysis, a history of ICS therapy use in the prior year ($P = .01$), a parental history of asthma ($P = .05$), and a PC₂₀ value of less than 2 mg/mL ($P = .03$)

TABLE II. Univariable and multivariable analyses for predictors of response to fluticasone versus montelukast

Predictor	Subgroup	Percentage ACDs		FEV ₁ percent predicted		Morning PEF percent predicted		Time to first exacerbation	
		Average difference*	P value†	Average difference*	P value†	Average difference*	P value†	Hazard ratio*	P value†
ACQ	≤1.1	2.3 (−9.8 to 14.3)	.08 (.3)						
	>1.1	17.4 (5.5 to 29.2)							
eNO	<25 ppb	−4.0 (−15.9 to 7.9)	.002 (.01)						
	≥25 ppb	23.0 (11.4 to 34.6)							
Eosinophils	<5%	−4.1 (−16.7 to 8.5)	.005 (.9)						
	≥5%	20.5 (9.2 to 31.8)							
IgE	≤150 kU/L	−2.3 (−15.1 to 10.5)	.03 (.6)						
	>150 kU/L	16.6 (5.1 to 28)							
Parental asthma	No	3.9 (−8.9 to 16.8)	.07 (.02)					0.7 (0.4 to 1.4)	.05 (.05)
	Yes	20.1 (8.4 to 31.7)						0.3 (0.1 to 0.5)	
PC ₂₀ (mg/mL)	≥2	−7.2 (−22.1 to 7.7)	.007 (.2)					1.1 (0.5 to 2.5)	.02 (.03)
	<2	17.8 (7.7 to 27.8)						0.4 (0.2 to 0.6)	
ULT	<100			9.1 (4.8 to 13.4)	.08 (.1)				
	≥100			3.5 (−0.9 to 7.9)					
Age at diagnosis	≤3 y			4.1 (−0.1 to 8.3)	.06 (.8)				
	>3 y			9.8 (5.6 to 13.9)					
Age at entry	6–10 y					6.6 (2.9 to 10.4)	.09		
	10–14 y					1.7 (−2.6 to 6.1)			
ICS use (past year)	No							1.0 (0.5 to 2.0)	.008 (.01)
	Yes							0.3 (0.2 to 0.6)	

Empty cells denote predictors having *P* values of greater than .10 for interaction between treatment and predictor in a univariable model.

*Difference between fluticasone and montelukast: estimate (95% CI).

†*P* values for interaction between treatment and predictor: univariable model (multivariable model).

were all associated with a longer time to a first asthma exacerbation with fluticasone compared with montelukast treatment.

Lung function outcomes

For more information on lung function outcomes, see Table II. No cutoff point in a lung function parameter (change in FEV₁ percent predicted and change in morning peak expiratory flow percent predicted) was identified that was able to distinguish a differential response favoring fluticasone over montelukast, although, as noted previously,²⁰ lung function improvements were significantly better with fluticasone compared with montelukast during the year-long trial.

DISCUSSION

Generally, clinical intervention trials attempt to identify treatment superiority by using predefined outcomes, which is accomplished by examining mean values and comparing the treatment groups involved. The purpose of our planned *post-hoc* analyses was to identify any characteristics of the study participants that would predict differential response to the therapies.

Our observations suggest that a parental history of asthma or a baseline eNO level of greater than 25 ppb identified those children who responded with a greater improvement in ACDs with fluticasone compared with montelukast. Moreover, a parental history of asthma, marked airway hyperresponsiveness (PC₂₀ value, <2 mg/mL) or prior-year use of ICSs for asthma predicted a delayed time to first asthma exacerbation with fluticasone therapy compared with montelukast. We were unable to identify any parameter that predicted a better response to montelukast compared with fluticasone, as was previously noted by Meyer

et al¹⁸ in children ages 2 to 14 years. Because the PACT cohort included only children with mild-to-moderate asthma, we cannot determine whether other nonexamined factors or these same predictors would behave differently in patients with more severe asthma than evaluated in the PACT.

The present findings extend the observations from the short-term, cross-over Characterizing the Response to a Leukotriene Receptor Antagonist and an Inhaled Corticosteroid (CLIC) trial.¹⁴ The CLIC trial demonstrated that increased markers of allergic inflammation predicted improvements in lung function and ACDs with fluticasone compared with montelukast. In the CLIC trial the differential treatment response for pulmonary function for fluticasone over montelukast was predicted by an increased baseline eNO level, as well as several other baseline factors, including low PC₂₀ values, low pulmonary function, increased bronchodilator response, and increased ECP levels.¹⁴ Both eNO and ECP levels are markers of ongoing allergic inflammation. eNO measurement is available for clinical use, whereas ECP measurement is limited to research protocols. In light of these findings, the use of ICSs as first-line therapy for pediatric patients with asthma exhibiting certain clinical, pulmonary, and inflammatory markers was recommended.¹⁹

The Expert Panel Report 3¹ identifies 2 dimensions of asthma control: impairment and risk. The impairment dimension generally refers to the degree to which symptom burden limits the asthmatic patient on a day-to-day basis (mild symptoms and activity limitation) and is approximated with a subjective measure, such as the ACD. The risk domain, in part, refers to periodic and severe episodes, such as exacerbations, hospitalizations, or even death.²¹ A useful approximation of this dimension within the realm of a long-term clinical trial is the time until the first exacerbation

requiring oral corticosteroid use. The National Asthma Education and Prevention Program guidelines¹ emphasize the importance of addressing both the impairment and risk domains in assessing control and asthma therapies. The present analysis reveals several characteristics that should help to identify a patient who would be more likely to improve in either the impairment or risk domain with an ICS compared with an LTRA.

The Tucson Children's Respiratory Study, a large birth cohort examining epidemiologic factors relating to asthma, formulated an Asthma Predictive Index (API).²²⁻²⁴ Later modified to reflect the contribution of atopy to asthma development and persistence, the API serves as a useful overall clinical prognostic assessment tool in terms of predicting subsequent development of asthma. One of the major criteria for a positive API result is a physician-diagnosed parental history of asthma. The Tucson birth-cohort study also concluded that parental asthma is a strong predictor for allergic sensitization in children. Of specific interest, Crestani et al²⁵ note that this predictive nature of parental asthma for allergic sensitization is independent of parental asthma influencing the development of childhood asthma. Others²⁶ have observed that children with a paternal history of asthma display a significantly greater degree of airway responsiveness than those without such a family history. Again, as we learned from the CLIC trial,¹⁴ increased allergic markers of inflammation are predictive of the difference in therapeutic response to fluticasone over montelukast. Well-accepted are the concepts that skin test positivity (allergic sensitization) is among these markers of allergic inflammation and that corticosteroids counteract allergic inflammation. If parental asthma is predictive of the development of allergic sensitization in children, one can postulate the mechanism whereby parental asthma is also a predictor for the therapeutic response to an ICS.

A possible explanation for a positive family history of asthma being a stronger multivariate predictor in this PACT analysis is the concept that genetics likely plays a prominent role in driving the overall atopic response or the components of allergic inflammation. In the univariate model we found that several markers of atopy (serum IgE level, blood eosinophilia, and eNO level) were highly predictive of the treatment difference between fluticasone and montelukast in terms of the impairment dimension outcome of ACDs. The likelihood exists that these atopic markers are each measuring the same or a similar underlying process and thereby effectively cancel each other out in the multivariate analysis. These atopic variables would be self-correlating. In terms of our "time to first exacerbation" outcome, it is less clear how the positive family history would retain such a unique predictive index.

Roorda et al¹² found that a positive family history of asthma and frequent occurrences of asthma symptoms in children less than 4 years of age were associated with a favorable response to fluticasone, as measured based on symptom reduction. In the absence of a positive family history, frequent symptoms, or both, no treatment effect was noted. This PACT analysis extends the age range for this observation.

Although an extensive discussion of various asthma phenotypes is beyond the scope of the present analysis, one would be remiss not to consider this notion when examining the variability of response to different therapies. Of particular interest would be further examination of the "atopic wheezer" phenotype described in the Tucson study.²⁴ This wheezing phenotype had the highest wheezing prevalence after 6 years of age when compared with

the transient wheezer and nonatopic wheezer phenotypes. The atopic wheezer phenotype was further divided into "early" and "late" atopic wheezers based on whether they were first reported to have wheezed before or after the age of 3 years. The prevalence of allergic sensitization to common aeroallergens in the early and late groups was identical at age 6 years. The early group, however, had higher levels of IgE and lower levels of lung function at the ages of 6 and 11 years. The question that arises is whether IgE level or lung function in this subphenotype could perhaps lead to a difference in response to an ICS or a leukotriene modifier, among a host of other therapies. Further study in this area is needed.

Just as significant variability in the actual disease course exists, there is also marked variability in treatment response, no doubt driven by currently unknown genetic and environmental factors. A critical future step will be to identify not only the phenotypic predictors of therapeutic response, but also to quantify the expected benefit of one treatment over another, making it possible to intelligently analyze a cost/benefit ratio for the pediatric population. With further work, relevant genotypic or gene expression factors will be elucidated and enable further ability toward individualizing therapy in children. Our analyses suggest that the presence of a parental history of asthma, an increased baseline eNO level, marked airway hyperresponsiveness, or prior use of an ICS should guide the clinician to select fluticasone over montelukast to achieve the best long-term therapeutic outcomes.

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Clinical implications: In children with mild-to-moderate persistent asthma, a parental history of asthma, airway hyperresponsiveness, or increased measures of inflammation might predict a superior response to an ICS over an LTRA.

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