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Phenotypic Predictors of Long-term Response to Inhaled Corticosteroid and Leukotriene Modifier Therapies in Pediatric Asthma

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Abstract

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

Objective—Identify phenotypic characteristics retaining predictive value for the difference in treatment responses between twice daily fluticasone and once-daily montelukast.

Methods—Data from the Pediatric Asthma Controller Trial (PACT) 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 one-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 tests. The mean %-predicted pre-bronchodilator FEV₁ was 97.8 +/-12.9, median PC₂₀ was 0.93 mg/ml and median exhaled nitric oxide (eNO) was 25.2 ppb. A history of parental asthma best predicted the expected treatment benefit with fluticasone compared to montelukast in terms of gain in ACDs (adjusted p=0.02) and time to first exacerbation

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Clinical Implications In children with mild to moderate persistent asthma, a parental history of asthma, airway hyperresponsiveness or elevated measures of inflammation may predict superior response to an inhaled corticosteroid over a leukotriene receptor antagonist.

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(adjusted $p=0.05$). Elevated baseline eNO predicted the differential treatment response for fluticasone regarding the gain in ACDs (adjusted $p=0.01$). Prior inhaled corticosteroid (ICS) use (adjusted $p=0.01$) and low PC₂₀ (adjusted $p=0.03$) 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 parental history of asthma, elevated eNO, low PC₂₀, or history of ICS use can expect the best long-term outcomes with ICS therapy, as compared to treatment with leukotriene receptor antagonists.

Keywords

asthma; biomarkers; exhaled nitric oxide; fluticasone propionate; inhaled corticosteroids; montelukast; pulmonary response

Introduction

In children with mild-moderate asthma, current National Asthma Education and Prevention Program (NAEPP) guidelines call for a daily controller medication to prevent symptoms(1). The Childhood Asthma Management Program (CAMP) trial(14) examined the long-term effects of twice-daily budesonide, nedocromil or placebo in children ages 5-12, treated for four to six years. Although none of the three treatment arms resulted in long-term improvement in lung function, this landmark trial established the superiority of ICS therapy compared to nedocromil for the treatment of asthma. Improvement in airway 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(15-19).

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 or not 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 ICS (2-8) and LTRAs(8-13), thus providing a mechanism whereby asthma therapy could be individualized. However, most of the data has been applied to short-term outcomes.

Given the concerns regarding both the perceived and actual systemic side effects from ICS, the question arose as to whether adding a long-acting beta agonist (LABA) to a reduced dose of ICS would achieve comparable asthma control, while lowering the potential for growth effects. PACT was a parallel, double-blind, randomized trial which sought to compare asthma control over a full year between three different treatment regimens in children with mild-to-moderate persistent asthma.(20) Fluticasone monotherapy, fluticasone/salmeterol combination therapy and montelukast monotherapy comprised the three study arms, with asthma control days as the primary outcome. The subjects randomized to fluticasone gained an average of 42 more asthma control days per year compared to 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 if the differential response to fluticasone or montelukast is associated with certain historical, physiologic, or atopic characteristics.

Methods

The PACT primary outcome report(20) outlines complete inclusion and exclusion criteria. Briefly, participants between the ages of 6 and 14 with mild-moderate asthma (by diary-reported symptoms, beta-agonist use, or peak flow criteria) with an $FEV_1 \geq 80\%$ of predicted at screening and a positive methacholine challenge (indicative of airway hyperresponsiveness) were followed for one year, while adhering to one of three treatment arms outlined below. Enrolled children were not on controller medications for at least two weeks prior to randomization. They were nonsmokers, free of other chronic lung diseases and had not experienced recent or >3 asthma exacerbations requiring recurrent courses of oral corticosteroids in the prior year. Pregnant or lactating females were not included in this trial.

The PACT protocol(20) consisted of seven visits, with screening visit 1 occurring between weeks -4 and -2. A 2-4 week run-in period ensued, during which the children used only an open-label, as-needed albuterol metered-dose inhaler (MDI) for asthma symptoms while taking both a twice-daily placebo Diskus (GlaxoSmithKline, Research Triangle Park, NC) and a pre-bedtime, placebo capsule. At visit 2, (day 0) double-blind, double-dummy randomization occurred and the subject was started on one of the original three study treatment arms for 48 weeks: fluticasone propionate 100 mcg morning and 100 mcg evening (Flovent Diskus®, GSK); fluticasone propionate 100 mcg/salmeterol 50 mcg (Advair Diskus®, GSK) in the morning and salmeterol 50 mcg (Serevent Diskus®, GSK) in the evening (PACT combination); or montelukast 5 mg (Singulair®, Merck) in the evening.(20) The following studies were performed at randomization: Complete blood count, serum eosinophilic cationic protein, serum IgE, urinary leukotriene E4, aeroallergen skin prick testing, spirometry, methacholine challenge and eNO. 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 since the combination ICS/LABA therapy used in PACT was not the full dose of ICS usually recommended in combination of ICS/LABA therapy and it 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 25ppb (median), Asthma Control Questionnaire score (ACQ) 1.10 (mean), blood eosinophils 5% (median), serum IgE 150kU/L (median), and the provocative concentration of methacholine required to decrease the forced expiratory volume in the first second of expiration by 20% ($FEV_1 PC_{20}$ or “ PC_{20} ”) 2 mg/ml (stratification variable in randomization scheme). Other variables were dichotomous in nature: presence or absence of any positive aeroallergen skin test, prior ICS use, eczema, parental asthma, furred pets at home, and smoke exposure.

The primary outcome in PACT was the percent improvement in asthma control days. This percent improvement was defined by comparing the 48-week treatment period to 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 non-study asthma medications; daytime symptoms; nighttime awakenings; unscheduled health care visits, ER visits, or hospitalizations for asthma; and school absenteeism for asthma. A secondary outcome of 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, 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: asthma control days, percent predicted morning peak expiratory flow, percent predicted FEV₁ and time until first asthma exacerbation. The asthma control days, peak flow and FEV₁ outcomes were analyzed as change from baseline using ANOVA. Time until first exacerbation was analyzed using proportional hazards regression. The predictive value of each candidate sub-grouping factor under consideration was determined by examining the subgroup by treatment interaction term in a model which also included main effects for treatment and subgroup. The treatment effect within each sub-group was assessed by examining linear contrasts from this model. These analyses were performed for each candidate predictor separately. Subgroup factors 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 mean and standard deviation for continuous outcomes were calculated. All analyses were carried out using 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 1). The mean age was 9.6 +/- 2.1 years, 60% were male, 50% had a parental history of asthma and 78% had one or more positive skin prick tests to aeroallergens. Also, the mean number of positive aeroallergen skin tests per subject for this cohort was 2.5 (± 2.0) out of 8 possible (cat, dog, cockroach, dust mite, tree, grass, weed, mold). The mean %-predicted pre-bronchodilator FEV₁ was 97.8 +/- 12.9, median PC₂₀ was 0.93 mg/ml and median eNO was 25.2 ppb. As specified by protocol, participants had persistent asthma defined by only 29% ACDs during the run-in/characterization period.

Change in asthma control days (Table 2)

By univariate analysis, baseline levels of eNO ≥ 25 ppb (p=0.0017), blood eosinophils >5% (p=0.005), serum IgE > 150 kU/L (p=0.03), and PC₂₀<2 mg/ml (p=0.007) compared to 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 the ACQ score (p=0.0810), positive parental history of asthma (p=0.07), and having one or more positive skin prick tests (p=0.13). 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=0.02) and eNO ≥ 25 ppb (p=0.01).

Time to first exacerbation (Table 2)

By both univariate and multivariate analysis, a history of ICS therapy use in the prior year (p=0.01), a parental history of asthma (p=0.05), or a PC₂₀<2mg/ml (p=0.03) were all associated with a longer time to a first asthma exacerbation with fluticasone compared to montelukast treatment.

Lung Function Outcomes (Table 2)

No cut-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 to montelukast during the year trial.

Discussion

Generally, clinical intervention trials attempt to identify treatment superiority using predefined outcomes, 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 identify the specific long-term responders to the therapies.

Our observations suggest that a parental history of asthma or a baseline eNO level > 25 ppb identified those children who responded with a greater improvement in ACDs with fluticasone compared to montelukast. Moreover, a parental history of asthma, marked airway hyperresponsiveness ($PC_{20} < 2$ mg/ml) or prior-year use of ICS for asthma, predicted a delayed time to a first asthma exacerbation with fluticasone therapy compared to montelukast. We were unable to identify any parameter that predicted a better response to montelukast compared to fluticasone as was previously noted by Meyer et al(12) in children ages 2-14. Since the PACT cohort included only children with mild-moderate asthma, we cannot determine whether other non-examined factors or these same predictors would behave differently in more severe asthma than evaluated in 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(8) (CLIC) trial. CLIC demonstrated that elevated markers of allergic inflammation predicted improvements in lung function and ACDs with fluticasone compared to montelukast. In CLIC, the differential treatment response for pulmonary function for fluticasone over montelukast was predicted by an elevated baseline eNO level as well as several other baseline factors including low PC_{20} , low pulmonary function, increased bronchodilator response, and increased eosinophilic cationic protein (ECP) levels(8). Both eNO and ECP levels are markers of ongoing allergic inflammation. eNO measurement is available for clinical use, while ECP measurement is limited to research protocols. In light of these findings, the use of ICS as first-line therapy for pediatric asthma patients exhibiting certain clinical, pulmonary and inflammatory markers was recommended(13).

The Expert Panel Report 3(1) identifies two dimensions of asthma control: impairment and risk. The impairment dimension generally refers to the degree to which symptom burden limits the asthma patient on a day-to-day basis (mild symptoms, activity limitation) and is approximated with a subjective measure such as the ACD. The risk domain, in part, refers to periodic, severe episodes such as exacerbations, hospitalizations or even death. 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 NAEPP guidelines(1) 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 to a LTRA.

The Tucson Children's Respiratory Study, a large birth cohort examining epidemiologic factors relating to asthma, formulated an asthma predictive index(22-24) (API). 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 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 al

(25) note that this predictive nature of parental asthma for allergic sensitization is independent of parental asthma influencing the development of childhood asthma. Others(26) 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 CLIC(8), elevated 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, then, 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 inhaled corticosteroid.

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 play 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, blood eosinophilia, and eNO) were highly predictive of the treatment difference between fluticasone and montelukast in terms of the impairment dimension outcome, ACDs. The likelihood exists that these atopic markers, though, are each measuring the same or 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 al(6) found that a positive family history of asthma as well as frequent occurrences of asthma symptoms in children less than 4 years of age were associated with a favorable response to fluticasone as measured by 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 to the transient wheezer and non-atopic 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. The prevalence of allergic sensitization to common aeroallergens in the early and late groups was identical at age 6. The early group, however, had higher levels of IgE and lower levels of lung function at the ages of 6 and 11. The question that arises is whether IgE level or lung function in this subphenotype could perhaps lead to a difference in response to an inhaled corticosteroid 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 towards individualizing therapy in children. Our analyses suggest that presence of a parental history of asthma, an elevated baseline eNO, marked airway hyperresponsiveness or prior use of ICS should guide the clinician to select fluticasone over montelukast in order to achieve the best long-term therapeutic outcomes.

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Abbreviations

ACD	asthma control day
ACQ	Asthma Control Questionnaire
API	Asthma Predictive Index
CAMP	Childhood Asthma Management Program
CARE	Childhood Asthma Research and Education Network
CLIC	Characterizing the Response to a Leukotriene Receptor Antagonist and an Inhaled Corticosteroid trial
ECP	eosinophilic cationic protein
eNO	exhaled nitric oxide

ICS	inhaled corticosteroid
LABA	long-acting beta-agonist
LTRA	leukotriene receptor antagonist
MDI	metered dose inhaler
PACT	Pediatric Asthma Controller Trial
PC₂₀	provocative concentration of methacholine required to decrease the forced expiratory volume in the first second of expiration by 20%
NHLBI	National Heart Lung and Blood Institute
NAEPP	National Asthma Education and Prevention Program

Table 1**Baseline characteristics of the study participants, by treatment group***

No differences exist in the baseline characteristics between the fluticasone and montelukast groups.

Characteristic	Fluticasone ¹	Montelukast ²
Participants, n	96	95
Age, years	9.8 ± 2.2	9.6 ± 2.2
Male Gender, n (%)	57 (59.4)	57 (60.0)
Minority, n (%)	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 MD asthma diagnosis, years	4.2 ± 3.1	3.8 ± 3.0
Age at onset asthma symptoms, years	3.5 ± 2.9	2.9 ± 2.6
Atopic, n (%)	75 (78.1)	73 (76.8%)
Serum IgE (k U/L)	321 ± 419	311 ± 406
Blood eosinophils (%)	6.0 ± 3.8	6.0 ± 4.0
Serum Eosinophil Cationic Protein (mcg/L)	25 ± 26	26 ± 38
Urinary Leukotriene E ₄ (pg/mg creatinine)	106 ± 51	112 ± 65
Medication Use in Previous Year		
Inhaled / nebulized ICS, n (%)	58 (60.4%)	55 (57.9%)
Leukotriene modifier, n (%)	28 (29.2%)	38 (40.0%)
Long-acting beta-agonist, n (%)	10 (10.4%)	14 (14.7%)
Theophylline, n (%)	0	0
Cromolyn / nedocromil, n (%)	0	1 (1.1%)
≥ 1 Prednisone Courses, n (%)	25 (26.0%)	22 (23.2%)
Pre-bronchodilator FEV ₁ (% predicted)	97.8 ± 12.2	97.7 ± 13.6
Pre-bronchodilator FEV ₁ /FVC (%)	80.2 ± 7.4	80.1 ± 8.3
Maximum bronchodilator response (%)	10.9 ± 7.1	10.9 ± 7.4
Average am peak flow during run-in period (L/min)	249.3 ± 68.4	241.2 ± 66.8
Average pm 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
Asthma-control days during run-in period (%)	30 ± 24	27 ± 23
Asthma control questionnaire **	1.1 ± 0.6	1.2 ± 0.6
Exhaled nitric oxide (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)

¹ Fluticasone: 100 mcg DPI BID;² montelukast: 5 mg hs

* Differences not significant for any characteristic across treatment groups

** 7 point scale, 0=total control, 6=extremely poor control

Table 2
Univariable and multivariable analyses for predictors of response to fluticasone vs. montelukast

Predictor	Subgroup	Percent Asthma Control Days		FEV ₁ Percent Predicted		AM PEF Percent Predicted		Time to First Exacerbation	
		Average Difference *	P-values †	Average Difference *	P-values †	Average Difference *	P-values †	Hazard Ratio *	P-values †
ACQ	≤ 1.1	2.3 (-9.8, 14.3)	0.08 (0.3)						
	> 1.1	17.4 (5.5, 29.2)							
eNO	< 25 ppb	-4.0 (-15.9, 7.9)	0.002 (0.01)						
	≥ 25 ppb	23.0 (11.4, 34.6)							
Eosinophils	< 5%	-4.1 (-16.7, 8.5)	0.005 (0.9)						
	≥ 5%	20.5 (9.2, 31.8)							
IgE	≤ 150 kU/L	-2.3 (-15.1, 10.5)	0.03 (0.6)						
	> 150 kU/L	16.6 (5.1, 28)							
Parental Asthma	No	3.9 (-8.9, 16.8)	0.07 (0.02)					0.7 (0.4, 1.4)	0.05 (0.05)
	Yes	20.1 (8.4, 31.7)						0.3 (0.1, 0.5)	
PC ₂₀ mg/ml	≥ 2	-7.2 (-22.1, 7.7)	0.007 (0.2)					1.1 (0.5, 2.5)	0.02 (0.03)
	< 2	17.8 (7.7, 27.8)						0.4 (0.2, 0.6)	
Urinary Leukotrienes	< 100			9.1 (4.8, 13.4)	0.08 (0.1)				
	≥ 100			3.5 (-0.9, 7.9)					
Age at Dx	≤ 3 years			4.1 (-0.1, 8.3)	0.06 (0.8)				
	> 3 years			9.8 (5.6, 13.9)					
Age at entry	6-10 years					6.6 (2.9, 10.4)	0.09		
	10-14 years					1.7 (-2.6, 6.1)			
ICS in the past year	No							1.0 (0.5, 2.0)	0.008 (0.01)
	Yes							0.3 (0.2, 0.6)	

Shaded cells denote predictors having p-value greater than 0.10 for interaction between treatment and predictor in univariable model

* Difference between Fluticasone and Montelukast: estimate (95% CI)

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