Measuring the corticosteroid responsiveness endophenotype in asthmatic patients

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Background: Inhaled corticosteroids are the most commonly used controller therapies for asthma, producing treatment responses in 6 clinical phenotypes: lung function, bronchodilator response, airway responsiveness, symptoms, need for oral steroids and frequency of emergency department visits and hospitalizations. We hypothesize that treatment response in all of these phenotypes is modulated by a single quantitative corticosteroid responsiveness endophenotype.
Objective: We sought to develop a composite phenotype that combines multiple clinical phenotypes to measure corticosteroid responsiveness with high accuracy, stability across populations, and robustness to missing data.
Methods: We used principal component analysis to determine a composite corticosteroid responsiveness phenotype that we tested in 4 replication populations. We evaluated the relative accuracy with which the composite and clinical phenotypes measure the endophenotype using treatment effect area under the receiver operating characteristic curve (AUC).
Results: In the study population the composite phenotype measured the endophenotype with an AUC of 0.74, significantly exceeding the AUCs of the 6 individual clinical phenotypes, which ranged from 0.56 ($P < .001$) to 0.67 ($P = .015$). In 4 replication populations with a total of 22 clinical phenotypes available, the composite phenotype AUC ranged from 0.69 to 0.73, significantly exceeded the AUCs of 14 phenotypes, and was not significantly exceeded by any single phenotype.
Conclusion: The composite phenotype measured the endophenotype with higher accuracy, higher stability across populations, and higher robustness to missing data than any clinical phenotype. This should provide the capability to model corticosteroid pharmacologic response and resistance with increased accuracy and reproducibility. (J Allergy Clin Immunol 2015;136:274-81.)

Key words: *Asthma, corticosteroids, drug therapy, endophenotype, pharmacogenetics, pharmacologic response*

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Inhaled corticosteroids (ICSs) are the most commonly used[1,2] and efficacious controller therapies for asthma. Variation in treatment response to ICSs has been well identified, and within-person variation in ICS treatment response is highly repeatable.[3] ICS treatment response has a genetic basis using the change in lung function as the clinical phenotype.[4,5] Current asthma guidelines characterize treatment response in terms of lung function, symptoms, or exacerbations.[2] ICSs also produce a significant treatment response in bronchodilator response and airway responsiveness.[6]

Nonresponse to corticosteroids is a common clinical problem, with up to 24% of patients with severe asthma who take oral corticosteroids not responding with a greater than 15% improvement in prebronchodilator FEV_1.[7] Identifying steroid nonresponse is clinically difficult, rendering it underrecognized, even though steroid nonresponse poses a significant patient risk because patients are more likely to experience adverse outcomes. When patients prescribed ICSs experience adverse outcomes, clinicians often attribute these problems to environmental triggers or medication nonadherence. In reality, these patients might share a group of common phenotypes that suggest steroid nonresponse.

For 15 years, asthma researchers have considered these phenotypes individually; however, this approach presents significant problems. For example, in pharmacogenetic modeling researchers aim to define an interaction between a genomic feature or variation and response to a particular pharmacologic agent. When studying the pharmacogenetics of corticosteroid response in asthmatic patients, there are many potential pharmacologic responsiveness phenotypes from which to choose. Choosing a specific phenotype is typically based on the characteristics of the cohort available. Nevertheless, this choice carries with it many repercussions for the researcher. Different clinical phenotypes will have differing statistical power, and different phenotypes will have different rates of missing data; most importantly, different phenotypes will be assessed in other

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Abbreviations used

AMSYM: A clinical phenotype measuring the trend in average morning symptoms as recorded in daily diary card
AUC: Area under the receiver operating characteristic curve
BDRABPCT: A clinical phenotype measuring the trend in BDR
BURSTS: A clinical phenotype measuring the trend in cumulative number of courses of oral corticosteroid treatment
CAMP: Childhood Asthma Management Program
EDHOS: A clinical phenotype measuring the trend in cumulative number of emergency department visits and hospitalizations
ICS: Inhaled corticosteroid
IMPACT: Improving Asthma Control Trial
LNPC20: A clinical phenotype measuring the trend in the natural log of PC_{20}
PACT: Pediatric Asthma Controller Trial
PC: Principal component
PCA: Principal component analysis
PREFEV: A clinical phenotype measuring the trend in FEV_1
ROC: Receiver operating characteristic
SHARP: Single Nucleotide Polymorphism Health Association-Asthma Resource Project
SOCS: Salmeterol or Corticosteroids Study

cohorts with varying frequencies, leading to difficulties in replication of the pharmacogenetic findings. As a result of such factors, the choice of a single clinical phenotype to characterize the ICS treatment response is problematic.

We propose to move away from the focus on single phenotypes to a more holistic approach. We hypothesize that a single quantitative corticosteroid responsiveness endophenotype modulates the asthma disease process (Fig 1). The endophenotype is latent in untreated subjects and active in ICS-treated subjects. Under this hypothesis, clinical treatment response phenotypes are not regulated by separate mechanisms but instead by this endophenotype that influences the asthma disease process to produce the treatment effect observed in all clinical phenotypes. If this hypothesis is true, the endophenotype should characterize steroid response better than individual phenotypes. For the purpose of pharmacologic modeling, our objective is to measure this endophenotype as accurately as possible in each subject. We interpret the various clinical phenotypes as indirect measurements of the endophenotype, which display varying accuracies between different phenotypes and across populations. We propose a composite corticosteroid responsiveness model that combines clinical phenotypes to produce a composite phenotype that measures the endophenotype with higher accuracy, more stability across populations, and more robustness to missing data than any single clinical phenotype. Our objective in the current work is to develop such a composite corticosteroid responsiveness phenotype for patients with mild-to-moderate asthma.

METHODS

Study design

We designed this study (Fig 2) to have the following steps: (1) select clinical phenotypes known to exhibit significant treatment response; (2) select a well-powered and representative study population and suitable replication populations; (3) use principal component analysis (PCA) to determine the composite corticosteroid responsiveness phenotype in the study population; (4) generalize the study population result to a composite corticosteroid responsiveness phenotype model and test in replication populations; and (5) evaluate and compare the relative endophenotype measurement accuracy of all phenotypes.

Clinical phenotypes

We selected 6 clinical phenotypes that display statistically significant ICS treatment response in patients with mild-to-moderate asthma: symptoms, lung function, airway responsiveness, bronchodilator response, emergency department (ED) visits/hospitalizations, and oral corticosteroid bursts. We defined these phenotypes and determined values for each subject phenotype by performing simple linear regression of clinical observations, as described in the Methods section in this article's Online Repository at www.jacionline.org.

Populations

We selected study and replication populations from among the cohorts of the Single-Nucleotide Polymorphism Health Association-Asthma Resource Project (SHARP). SHARP consolidates clinical trial data from 3 National Heart, Lung, and Blood Institute–sponsored asthma clinical research networks: the Childhood Asthma Management Program (CAMP),[6] the Childhood Asthma Research and Education network,[8,9] and the Asthma Clinical Research Network.[10-12]

We selected populations from cohorts that contained a treatment group that received ICSs and a treatment group that did not receive ICSs. In each population we created 2 groups: the ICS group contained subjects who received ICSs or a combination therapy including ICSs. The "non-ICS" group contained subjects who received placebo or a non-ICS drug, such as a leukotriene antagonist. Clinical observations were taken from the SHARP phs000166.v2.p1 dbGaP[13] data set, with the exception of CAMP symptoms, which were taken directly from CAMP trial data sets because the CAMP symptom data were found to be incomplete in the dbGaP data set.

Endophenotype measurement accuracy

We evaluated the relative accuracy with which the composite and clinical phenotypes measure the endophenotype using treatment effect area under the receiver operating characteristic curve (AUC). The rationale for this choice of statistic and the methods used are described in the Methods section in this article's Online Repository.

Composite corticosteroid responsiveness model

We determined a composite corticosteroid responsiveness phenotype from the pattern of treatment response exhibited by the study population. We selected an unsupervised method, PCA, with the expectation that the endophenotype would primarily modulate the first principal component (PC1) of the treatment response, which would comprise a composite phenotype measuring the endophenotype accurately.

We determined clinical phenotypes as described in the Methods section in this article's Online Repository. After discarding subjects for whom phenotypes were missing, we performed PCA on the remaining complete sets of 6 phenotypes with scaling to unit variance using the R version 3.1.0 base stats package prcomp function. We determined the treatment effect AUC of PCs and clinical phenotypes. We set the comparison direction for clinical phenotypes based on clinical experience. Because the sign of components produced by using PCA is arbitrary, we let the pROC package automatically determine the comparison direction for PCs. We analyzed the covariance of PC1 with the covariates typically used in the study of asthma, sex, and age.

We generalized the study population result into a population-independent composite corticosteroid responsiveness model that we tested in each replication population. Clinical phenotypes were determined as described in the Methods section in this article's Online Repository, and treatment effect AUCs were calculated. Missing phenotypes were imputed by being set equal to the center value of the respective phenotype in the study population. The 6 phenotypes were then centered and scaled by using the study population PCA center and scale coefficients, multiplied by the study population PC1 loading coefficients, and summed to produce the composite phenotype value. Finally, composite phenotype treatment effect AUC was determined.