

Pharmacogenomic Testing in the Asthma Clinic: Will Inhaled Corticosteroids Lead the Way?

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PHARMACOGENOMICS IS DEFINED as “the study of how an individual’s genetic inheritance affects the body’s response to drugs”¹ and has been described as one of the most promising areas of genomic medicine.² The term pharmacogenetics was introduced in 1959,³ and more than 4,000 papers are listed in PubMed (www.ncbi.nlm.nih.gov/pubmed) that include “pharmacogenetic” or “pharmacogenomic” in the title or abstract, and the Food and Drug Administration (FDA) website lists 115 drugs that include pharmacogenomic information in the labeling.⁴ Yet actual pharmacogenomic testing and counseling in the clinical setting is not widespread. The reasons for poor clinical implementation include: waiting for data from randomized controlled trials,^{5–7} lack of “action oriented information” included in FDA labeling,² absence of preemptive testing leading to missed opportunities to alter prescribing, concerns for lack of payer reimbursement, lack of availability of Clinical Laboratory Improvement Amendments (CLIA)-approved laboratory tests, insufficient integration of results into medical record keeping to allow for results to be applied to future medical care, and insufficient awareness by clinicians.^{7–9} While some of these barriers will require cooperation between healthcare stakeholders and time to resolve, it has been suggested that the risks associated with implementing pharmacogenomics is low with the potential for substantial benefits.⁶ With this in mind, the time for implementation of asthma pharmacogenomics in the clinic may have arrived.

Numerous pharmacogenomic studies of the β_2 -receptor gene (*ADRB2*), one of the first drug targets to be cloned and sequenced,¹⁰ have been conducted. Of the 20 nonsynonymous *ADRB2* coding single nucleotide polymorphisms (SNPs),¹¹ only two have been comprehensively studied both *in vitro* and in clinical trials: glycine (Gly) 16 to arginine (Arg) and glutamine (Gln) 27 to glutamate (Glu) because both result in functional changes of the receptor protein observed *in vitro* in patients with agonist-induced changes in β_2 -receptor density, and both occur at high frequency in patients with asthma. However, pharmacogenomic studies of short-acting β_2 -agonists (for bronchodilator response^{12–22} or asthma control^{23–26}) and long-acting β_2 -agonists (for asthma control^{26–34}) have not yielded clinically useful treatment

strategies. Thus clinical application of β_2 -agonist pharmacogenomic testing is not supported by evidenced-based data. However, the most recent evidence for pharmacogenomic variants associating with inhaled corticosteroid response in patients with asthma is stronger (replicated)³⁵ than that observed for inhaled β_2 -agonists and may be sufficient for initiation of pharmacogenomic testing in the clinic when prescribing inhaled corticosteroid therapy.

Response to inhaled corticosteroid therapy is known to be highly variable between patients with asthma but is consistent within patients over time, supporting a genetic basis for response.^{36–39} Tantisira et al.³⁵ published a study in 2011 describing a genome-wide association (GWA) study identifying a functional variant in the glucocorticoid-induced transcript 1 gene (*GLCC1*), which associated with FEV₁ response during treatment with inhaled corticosteroids. In this trial, an initial population (screening population) followed by four independent populations (replicates) were studied consisting of white, non-Hispanic children and adults with asthma. Only non-Hispanic whites were included in order to avoid the potential for spurious associations due to population stratification when multi-ethnic populations are combined in genetic association studies.

The initial screening population was from the Childhood Asthma Management Program (CAMP; $n=188$)⁴⁰ in which DNA (and parental DNA) was genotyped for 547,645 markers to identify SNPs that met two criteria: (1) for being among the top 100 powered SNPs, and (2) the Family-Based Association Testing (FBAT) test statistic was less than 0.05. FBAT uses genotype data from the proband and parents to increase the likelihood of identifying SNPs with the greatest heritability and thus the highest power for replication.³⁵ Thirteen SNPs met the criteria for genotyping and association analysis in the four replicate populations ($n=264$, $n=385$, $n=185$, and $n=101$) with replication defined as a nominal p -value less than 0.05.

Association analysis in the four replication populations identified one SNP (rs37972) in the *GLCC1* gene that was significantly associated with FEV₁ response to inhaled corticosteroid treatment. Patients with the major allele had an improvement in FEV₁ that was two to four times greater than those with the minor allele. The investigators also conducted elegant work to determine the activity of the functional SNP

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(rs37973, which is in complete linkage disequilibrium with rs37972) and found that *GLCC1* expression is downregulated by the rs37973 minor allele. Thus patients with the minor allele (guanine, G) of the functional SNP, rs37973, would have lower transcription levels in response to inhaled corticosteroid treatment and a lower FEV₁ response.

Other investigators (including Tantisira et al.) have published pharmacogenomic association studies of corticosteroid response with variants in other genes in the glucocorticoid pathway.^{41–44} However, no consistent associations with inhaled corticosteroid response have been observed. These have been candidate gene studies in which genes were selected based upon their expected effects on the pharmacokinetic or pharmacodynamic action of corticosteroids. The candidate gene approach differs from a GWA approach, which is often considered agnostic, by potentially being biased by the investigator's assumptions as to which genes are important to be included. However, both strategies can be used concurrently with GWA identifying novel targets that can then be further interrogated using a deep sequencing candidate gene approach, which may yield important gene–gene interactions. In fact, a recent report suggests that that rs37973 SNP in *GLCC1* when combined with rs1876828 in the corticotropin releasing hormone receptor 1 gene (*CRHR1*) may predicted extreme poor and high responders to inhaled corticosteroids with a predictive performance of 70%.⁴⁵

The data from the study by Tantisira et al. are compelling.³⁵ It meets the standards required for an appropriately designed and analyzed clinically relevant genetic association study set forth in the STrengthening the REporting of Genetic Association Studies (STREGA) guidelines,⁴⁶ including replicate cohorts and functional analysis of the causal SNP. It includes a clinically relevant outcome measure, change in FEV₁, measured over a period of 6 weeks to 16 months. A single measure of FEV₁ is likely clinically relevant to long-term outcomes in the management of asthma. FEV₁ measurements demonstrated high repeatability in the CAMP trial, the screening population in GWA study, after treatments with budesonide, nedocromil, and placebo, which suggests this phenotype is heritable and thus is relevant for a genetic association study.³⁹ In addition, single measures of FEV₁ correlate with asthma exacerbations in long-term follow-up of adults⁴⁷ although this may not be true in children.⁴⁸ Asthma exacerbation rate is a key criterion recommended in the National Asthma Education and Prevention Program Guidelines for assessment of future risk.⁴⁹ Thus change in FEV₁ is relevant both clinically and genetically.

A key strength of this trial is the replication in four independent populations following the screening study. Many genetic association findings are flawed due to sampling in only a single population or failure to replicate across multiple studies.⁵⁰ The independent populations included adults and children with mild and moderate asthma. Also the identification of the causal variant is often absent in genetic association studies but was identified in the Tantisira study.³⁵ The findings represent a class effect of corticosteroids, as the replicate populations included treatment with triamcinolone, flunisolide, or fluticasone in addition to budesonide used in the screening population. A weakness is that the data are not applicable to ethnicities other than non-Hispanic whites. Another weakness is that the genetic association accounted for only 6.6% of the overall variability in the lowest-quartile response to inhaled corticosteroids. It is

highly likely that other contributing variants that influence response to inhaled corticosteroids are yet to be identified. At the time the GWA was performed, the Illumina chip contained markers for 547,645 SNPs and provided approximately 87% coverage for the 7.5 million common (minor allele frequency $\geq 5\%$) SNPs in the genome.⁵¹ The human genome is estimated to contain approximately 10 million SNPs, and currently available chips contain 5 million SNP markers and can target genetic variation down to a minor allele frequency of 1%.^{52,53} Thus current methods for deep resequencing of the human genome will certainly identify additional variants in steroid pathway genes (or novel genes) that maybe useful for clinical pharmacogenomic testing. But can these data be used to support pharmacogenomic testing in the clinic? The editorial accompanying the study by Tantisira et al.³⁵ suggests that these data be used to support a prospective genotype driven trial to determine if treatment with inhaled corticosteroids using genomic data improves outcomes.⁵ This strategy may be overly conservative slowing the translation to bedside therapeutics and potentially depriving patients of data needed to ensure efficacy and safety of prescribed medicines.^{7,9} In addition, randomized controlled trials are expensive with an estimate of a Phase IIb trial in 2011 costing more than \$47,000 per participant^{54,55} and thus should be conducted when testing critical morbidity and mortality outcomes or when affecting a large public sector.⁶ In the absence of controlled trials, stringent criteria have been proposed for pharmacogenomic testing of drugs at risk of causing serious adverse drug reactions (ADR).⁵⁶ These include identification of medical need (prevalence of ADR, prevalence of risk genotype, severity of ADR events, absence of sufficient means to predict or monitor for ADR), clinical utility (an association between genotype and outcome exists and genotyping is predictive), and ease of use (the assay is available and accurate, and clinicians can interpret the results). While these standards are ideal, for drugs that do not directly increase risk of ADR, an alternative is to view clinical pharmacogenomic testing from a noninferiority perspective rather than as an approach superior to current practice standards.⁶ In this vein, there is little drawback for drugs that are widely used, and testing may provide useful information for choosing or dosing drug treatments.⁶ The costs for testing are marginal for two reasons: genotyping costs continue to decrease at an exponential rate, and pharmacogenomic results are unlikely to spawn follow-up costs (other than a decision to or not to prescribe a drug), unlike testing for disease risk, which likely leads to follow-up medical testing.⁶ In addition, reporting of pharmacogenomic testing outcomes can contribute to developing best-practice cost effective standards.⁹

Clear delineations between responders and nonresponders typically have been limited to drugs with effects attributed to single genes affecting the pharmacokinetic pathway, such as genes for drug metabolizing enzymes. For the majority of drugs such as inhaled corticosteroids, clear separation of responders and nonresponders is not observed for individual genes as response results from the interactions of multiple genes that include pharmacokinetic, drug target, and downstream signaling.^{41–44,57} However, a recent report demonstrated a modeling technique using receiver–operator curve characteristics that successfully identified responders versus nonresponders to inhaled corticosteroids using SNPs in the *GLCC1* and *CRHR1* drug target genes (currently

in abstract form).⁴⁵ Thus as additional pharmacogenetic information becomes available, statistical programs will be used to integrate genetic data that will lead to improved capabilities to direct drug treatments for efficacy and prevention of adverse effects.

With these considerations in mind, how would prescribers use information from genotyping *GLCC1*? Genetic information from the Tantisira study³⁵ can be incorporated into clinical practice at centers with a CLIA-approved laboratory to perform the genotyping, as there is no commercially available assay. From the trial data, a patient who is homozygous GG (27% of the population) at rs37973 has an odds ratio of having a poor response to inhaled corticosteroid treatment, defined as improvement of less than 0%, of 2.36 (95% CI, 1.27 to 4.41) compared to AA (adenine/adenine) homozygotes (23% of the population).³⁵ An odds ratio of 2.36 does not preclude a response to an inhaled corticosteroid and, consistent with the asthma guidelines,⁴⁹ all patients with persistent asthma should be given a trial with inhaled corticosteroid therapy. In those patients who do not respond, genotype information in conjunction with information on adherence, disease impairment and risk, and environmental triggers can help guide treatment decisions for increasing inhaled corticosteroid dose or changing treatment and monitoring strategies. The goal for obtaining genotype information *a priori* is to guide therapy decision making in advance of prescribing expensive therapies or drugs with an increased risk of adverse effects.⁵⁸

In summary, recent published data supports limited pharmacogenomic testing in non-Hispanic whites for the rs37973 variant in the *GLCC1* gene to aid in predicting response to inhaled corticosteroid therapy when used in conjunction with clinical data in patients with asthma. Novel statistical techniques will soon be available that incorporate additional SNPs for predicting inhaled corticosteroid response. Genotyping will be limited to CLIA-approved laboratories until a kit is commercially available. Waiting for results from prospective genotype stratified trials may needlessly delay optimal treatment decisions and follow-up strategies in patients with asthma.

Author Disclosure Statement

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