

Personalized medicine for patients with asthma

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Key words: Asthma, variability, polymorphisms, corticosteroid, adherence

ASTHMA IS A COMPLEX CONDITION

Asthma is a complex inflammatory disorder characterized by intense allergic inflammation, smooth muscle contraction, bronchial hyperresponsiveness, hypertrophy and hyperplasia of smooth muscle, hypersecretion of bronchial mucus, activation of mast cells, eosinophils, lymphocytes, epithelial cells, macrophages, disruption of the bronchial epithelium, and production of free radicals such as expired nitric oxide (eNO) and 8-isoprostane. The presence of asthma implies multiple potential targets of therapy, risk of future exacerbations, impaired quality of life, and potential for accelerated loss of FEV₁. Patients with persistent asthma have a high likelihood of the comorbidities allergic rhinitis, rhinosinusitis, and gastroesophageal reflux. Furthermore, responses to pharmacotherapy vary for β_2 -adrenergic agonists,^{1,2} inhaled³⁻⁵ and oral corticosteroids,⁶ leukotriene receptor antagonists,^{7,8} and biosynthesis inhibitors,⁹ and to omalizumab.¹⁰ In considering factors that could affect the response to optimal treatment recommendations, patients vary in their adherence to professional advice, individual beliefs about medications, perception of dyspnea, allergen exposures and sensitization, racial and ethnic backgrounds, neighborhood or in-home exposure to violence or stress, body weight, smoking status, and air quality.¹¹ It is not surprising that many patients report having incompletely controlled asthma¹² even with seemingly appropriate and intensive treatment.¹³

PERSONALIZED MEDICINE: PHARMACOGENOMICS

It is envisioned that care for patients should be improved with a tailored or personalized approach. Studies of pharmacogenomics assess the role of how sets of genetic information explain pharmacokinetics (absorption, distribution, metabolism, and elimination of medications) and pharmacodynamics (interactions

of medication and receptor producing the desired response or untoward effect). Pharmacogenetics refers more narrowly to effects of variability of specific genes or single nucleotide polymorphisms (SNPs), insertions, deletions, and splice variations on responses. There is a potential hierarchy of clinically useful pharmacogenetic information such as SNPs that affect activity *in vitro*, SNPs that alter pharmacokinetics, SNPs that improve/reduce drug response, and SNPs that alter a clinical outcome.¹⁴

COMPARATIVE EFFECTIVENESS RESEARCH AND THE SCIENCE OF IMPLEMENTATION

In contrast with personalized medicine, comparative effectiveness research (CER) compares head-to-head active interventions obtained from large data bases or treatment populations that policy makers then can use for decision-making. The Institute of Medicine describes comparative effective research as follows:

CER is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition, or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers and policy makers to make informed decisions that will improve health care at both the individual and population level.¹⁵

It is hoped that comparative effectiveness research will allow for improved reimbursement decisions by payers and management decisions and clinical strategies by physicians and other health care professionals, thereby benefiting society in general and patients in particular. An extension of comparative effectiveness research is the science of implementation or evidence translation¹⁶ of new findings into health care itself. For example, to what extent and in which patients with newly diagnosed asthma is the prompt administration of inhaled corticosteroids or other intervention associated with improved FEV₁ and effective control of asthma? How many hours/days of symptoms or evidence of worsening of asthma are there before the action plan fails to prevent emergency department care or hospitalization? In other words, the science of implementation explores the system-wide steps involved for the translation of information (early institution of inhaled corticosteroids in newly diagnosed asthma) into actual treatment for patients.

IDENTIFYING GOOD RESPONDERS

A practical goal is to identify the patients who are the best responders to specific therapies and initiate the therapy expeditiously. There are important advances in our understanding of phenotypes and genotypes of patients with larger responses to therapy of asthma. As an example, in a placebo-controlled, double-blind crossover study in children age 6 to 17 years with persistent mild or moderate asthma, fluticasone propionate by

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Supported by the Ernest S. Bazley Grant to Northwestern Memorial Hospital and Northwestern University Feinberg School of Medicine.

Disclosure of potential conflict of interest: P. A. Greenberger was Chair of an ad hoc DSMC at Novartis; has provided expert testimony on the subjects of allergic bronchopulmonary aspergillosis, drug allergy, immunotherapy, and anaphylaxis; and is President of the American Academy of Allergy, Asthma & Immunology.

Received for publication November 6, 2009; accepted for publication November 12, 2009.

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J Allergy Clin Immunol 2010;125:305-6.

0091-6749/\$36.00

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doi:10.1016/j.jaci.2009.11.038

inhalation was compared with montelukast.⁴ The primary outcome variable was percentage change of FEV₁ for each treatment period. For fluticasone propionate, 29% of children had a 5% to 9% improvement of FEV₁, and 30% of children experienced a 10% or greater change. With montelukast, 17% of children had a 5% to 9% response, and 16% of children increased the FEV₁% by 10% or more.⁴ These data also tell us that many children did not have such an increase in FEV₁ with either medication. There was some degree of concordance between the features that occurred in responders to fluticasone propionate or montelukast. The responders to fluticasone propionate had lower prebronchodilator FEV₁, lower FEV₁/forced vital capacity, lower methacholine PC₂₀, elevated eosinophilic cationic protein concentration, and greater serum IgE concentration. The responders to montelukast had lower prebronchodilator FEV₁, had lower FEV₁/forced vital capacity, and were female. In this issue, Szefer and Martin¹⁷ describe “lessons learned” from clinical trials of asthma therapy with insights into identifying the best or good responders to inhaled corticosteroids and leukotriene receptor antagonists on the basis of patient characteristics, physiologic findings, and biomarkers. It is clear that there is a significant distribution of responses of FEV₁ to inhaled corticosteroid or montelukast in patients entered in clinical trials with seemingly consistent inclusion criteria. When patients were enrolled in the Predicting Response to Inhaled Corticosteroid Efficacy (PRICE) study³ on the basis of a history of asthma but not an inclusion criterion of a specified response to albuterol, factors associated with a good response to inhaled corticosteroid included bronchodilator response with albuterol, decreased FEV₁/forced vital capacity, and lower FEV₁%. These findings contribute to an expanding base of evidence regarding more precise use of medications for asthma.

FitzGerald and Shahidi¹⁸ explore the options for achieving optimal control of patients with persistent mild and moderate asthma. They argue that the benefits of long-acting β_2 -agonists, when added to inhaled corticosteroids, outweigh the perceived risks. They address the often ineffective response to doubling the inhaled corticosteroid doses in patients not controlled with recommended doses, and they review evidence for effects of selected educational interventions and other interventions.

Studies of pharmacogenomics have expanded our knowledge of specific SNPs or other genetic variants that characterize the very good or nonresponders to most classes of medications for asthma. Kazani, Wechsler, and Israel¹⁹ examine the unfavorable effects of albuterol in patients homozygous for arginine at the β_2 -adrenergic receptor and how these findings were not replicated with salmeterol. They consider the pharmacogenetic findings for the differential responses to leukotriene receptor antagonists, biosynthesis inhibitors, and corticosteroids and suggest how pharmacogenomic information might be used prospectively.

Although the prevalence of asthma continues to increase and the number of hospitalizations on a per capita basis has not decreased since 1980,²⁰ we know much about this very complex disorder and have more options for achieving control of asthma. The scientific basis for use of avoidance measures, pharmacotherapy, immunotherapy, and an immunodulator is established.^{11,21,22} Future studies should help clarify how to achieve effective control, decrease hospitalizations and legitimate emergency department

care, and reduce fatalities while identifying the good or essentially nonresponders to medications. We are at the dawn of more precise use of treatments for patients with asthma.

REFERENCES

- Hawkins GA, Weiss ST, Bleecker ER. Clinical consequences of ADRbeta2 polymorphisms. *Pharmacogenomics* 2008;9:349-58.
- Sharma S, Litonjua AA, Tantisira KG, Fuhlbrigge AL, Szefer SJ, Strunk RC, et al. Clinical predictors and outcomes of consistent bronchodilator response in the childhood asthma management program. *J Allergy Clin Immunol* 2008;122:921-8.
- Martin RJ, Szefer SJ, King TS, Kraft M, Boushey HA, Chinchilli VM, et al. The predicting response to inhaled corticosteroid efficacy (PRICE) trial. *J Allergy Clin Immunol* 2007;119:73-80.
- Szefer SJ, Phillips BR, Martinez FD, Chinchilli VM, Lemanske RF Jr, Strunk RC, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. *J Allergy Clin Immunol* 2005;115:233-42.
- Knuffman JE, Sorkness CA, Lemanske RF Jr, Mauger DT, Boehmer SJ, Martinez FD, et al. Phenotypic predictors of long-term response to inhaled corticosteroid and leukotriene modifier therapies in pediatric asthma. *J Allergy Clin Immunol* 2009;123:411-6.
- Goleva E, Li LB, Eves PT, Strand MJ, Martin RJ, Leung DY. Increased glucocorticoid receptor β alters steroid response in glucocorticoid-insensitive asthma. *Am J Respir Crit Care Med* 2006;173:607-16.
- Tantisira KG, Drazen JM. Genetics and pharmacogenetics of the leukotriene pathway. *J Allergy Clin Immunol* 2009;124:422-7.
- Lima JJ, Zhang S, Grant A, Shao L, Tantisira KG, Allayee H, et al. Influence of leukotriene pathway polymorphisms on response to montelukast in asthma. *Am J Respir Crit Care Med* 2006;173:379-85.
- Tantisira KG, Lima J, Sylvia J, Klanderman B, Weiss ST. 5-lipoxygenase pharmacogenetics in asthma: overlap with Cys-leukotriene receptor antagonist loci. *Pharmacogenomics* 2009;19:244-7.
- Niebauer K, Dewilde S, Fox-Rushby J, Revicki DA. Impact of omalizumab on quality-of-life outcomes in patients with moderate-to-severe allergic asthma. *Ann Allergy Asthma Immunol* 2006;96:316-26.
- Greenberger PA. Asthma. In: Grammer LC, Greenberger PA, editors. *Patterson's allergic diseases*. 7th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2009. p. 333-88.
- Peters SP, Jones CA, Haselkorn T, Mink DR, Valacer DJ, Weiss ST. Real world evaluation of asthma control and treatment (REACT): findings from a national web-based survey. *J Allergy Clin Immunol* 2007;119:1454-61.
- Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJH, Pauwels RA, et al. Can guideline-defined asthma control be achieved?: the Gaining Optimum Asthma Control study. *Am J Respir Crit Care Med* 2004;170:836-44.
- Flockhart DA, Bertilsson L. Clinical pharmacogenetics. In: Atkinson AJ Jr, Abernethy DR, Daniels CE, Dedrick RL, Markey SP, editors. *Principles of clinical pharmacology*. 2nd ed. Amsterdam: Elsevier; 2007. p. 179-95.
- Sox HC, Greenfield S. Comparative effectiveness research: a report from the Institute of Medicine. *Ann Intern Med* 2009;151:203-5.
- Naik AD, Peterson LA. The neglected purpose of comparative-effectiveness research. *N Engl J Med* 2009;360:1929-31.
- Szefer SJ, Martin RJ. Lessons learned from variation in response to therapy in clinical trials. *J Allergy Clin Immunol* 2010;125:285-92.
- FitzGerald JM, Shahidi N. Achieving asthma control in patients with moderate disease. *J Allergy Clin Immunol* 2010;125:307-11.
- Kazani S, Wechsler ME, Israel E. The role of pharmacogenomics in improving the management of asthma. *J Allergy Clin Immunol* 2010;125:295-302.
- Moorman JE, Rudd RA, Johnson CA, King M, Minor P, Bailey C, et al. National surveillance for asthma—United States, 1980-2004. *MMWR Surveill Summ* 2007; 56(S08):1-54.
- National Heart, Lung and Blood Institute, National Asthma Education and Prevention Program. Expert Panel report 3: guidelines for the diagnosis and management of asthma. Full report 2007. Bethesda (MD): US Department of Health and Human Services; 2007. NIH publication no. 07-4051.
- Global Initiative for Asthma. Global strategy for asthma management and prevention. Bethesda (MD): National Heart, Lung, and Blood Institute, National Institutes of Health; 1995 (updated 2006). NIH publication no. 95-3659. Available at: <http://www.ginasthma.org>. Accessed October 28, 2009.