Pharmacogenomics and adverse drug reactions: Primetime and not ready for primetime tests

David A. Khan, MD *Dallas, Tex*

INFORMATION FOR CATEGORY 1 CME CREDIT

Credit can now be obtained, free for a limited time, by reading the review articles in this issue. Please note the following instructions.

Method of Physician Participation in Learning Process: The core material for these activities can be read in this issue of the Journal or online at the JACI Web site: www.jacionline.org. The accompanying tests may only be submitted online at www.jacionline.org. Fax or other copies will not be accepted.

Date of Original Release: October 2016. Credit may be obtained for these courses until September 30, 2017.

Copyright Statement: Copyright © 2016-2017. All rights reserved.

Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates this journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

List of Design Committee Members: David A. Khan, MD

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: D. A. Khan has received a grant from the Vanberg Family Foundation, has received speaker honoraria from Genentech, and is a member of the data safety materials board for Aimmune.

Activity Objectives:

1. To become familiar with pharmacogenetic associations of drug hypersensitivity.
2. To be able to recognize pharmacogenetic associations with immediate and delayed hypersensitivity drug reactions.
3. To identify US Food and Drug Administration (FDA)–issued alerts for pharmacogenetic screenings.

Recognition of Commercial Support: This CME activity has not received external commercial support.

List of CME Exam Authors: Saritha Kartan, MD, Rebecca Koransky, MD, and Rachel Miller, MD.

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: The exam authors disclosed no relevant financial relationships.

Adverse drug reactions (ADRs) are a relatively common cause of morbidity and mortality. Many factors can contribute to ADRs, including genetics. The degree to which genetics contributes to ADRs is not entirely clear and varies by drug, as well as the type of ADR. Pharmacogenetics and, more recently, pharmacogenomics have been applied to the field of ADRs for both predictable ADRs and hypersensitivity drug reactions. Evaluations for glucose-6-phosphate dehydrogenase and thiopurine S-methyltransferase are commonplace clinical tests to reduce hematologic problems associated with drugs, such as dapsone and azathioprine, respectively. Numerous pharmacogenetic associations have been discovered for immediate hypersensitivity reactions to β-lactams, aspirin, and nonsteroidal anti-inflammatory drugs; however, the clinical utility of testing for these genetic associations has not been established. In contrast, pharmacogenetic testing for *HLA-B*1502* before carbamazepine in patients of certain Asian ethnicities and testing for *HLA-B*5701* before abacavir treatment are recommended. This review will focus on pharmacogenetics and pharmacogenomics and their role in reducing ADRs, especially those caused by drug hypersensitivity reactions. (J Allergy Clin Immunol 2016;138:943-55.)

Key words: *Pharmacogenetics, pharmacogenomics, drug allergy, adverse drug reactions, drug hypersensitivity, β-lactam, nonsteroidal anti-inflammatory drug, abacavir, carbamazepine*

Medications are a cornerstone of the therapeutic armamentarium for most clinicians. The goal of pharmacotherapy is to cure or control a specific condition or disease without causing adverse effects. Unfortunately, adverse drug effects are common and not always predictable. Adverse drug reactions (ADRs) have been defined as reactions that are noxious and unintended and occur at doses normally used in human subjects.[1] ADRs can be related to a number of factors, including known pharmacologic activity of a drug, drug interactions, drug toxicity,

From the Department of Internal Medicine, Division of Allergy & Immunology, University of Texas Southwestern Medical Center.

Supported by the Vanberg Family Foundation.

Received for publication July 22, 2016; revised August 24, 2016; accepted for publication August 24, 2016.

Corresponding author: David A. Khan, MD, University of Texas Southwestern Medical Center, Division of Allergy & Immunology, 5323 Harry Hines Blvd, Dallas, TX 75390-8859. E-mail: dave.khan@utsouthwestern.edu.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

0091-6749/$36.00

© 2016 American Academy of Allergy, Asthma & Immunology

http://dx.doi.org/10.1016/j.jaci.2016.08.002

Abbreviations used
ADR: Adverse drug reaction
AERD: Aspirin-exacerbated respiratory disease
ALL: Acute lymphoblastic leukemia
CYSLTR: Cysteinyl leukotriene receptor
DRESS: Drug reaction with eosinophilia and systemic symptoms
G6PD: Glucose-6-phosphate dehydrogenase
GWAS: Genome-wide association study
LTC4S: Leukotriene C_4 synthase
NSAID: Nonsteroidal anti-inflammatory drug
OR: Odds ratio
SCAR: Severe cutaneous adverse reaction
SJS: Stevens-Johnson syndrome
SNP: Single nucleotide polymorphism
TEN: Toxic epidermal necrolysis
TPMT: Thiopurine S-methyltransferase

and drug hypersensitivity. ADRs are a relatively common cause of morbidity and mortality.

In 1998, Lazarou et al[2] performed a meta-analysis of 39 prospective studies in the United States evaluating ADRs in hospitalized patients. They reported an overall incidence of serious ADRs of 6.7% and fatal ADRs of 0.32%. Based on data from 1994, they estimated that 106,000 fatalities occurred in the United States from ADRs, making these reactions between the 4th and 6th leading cause of death. A more recent review of 51 studies on ADRs in hospitalized patients from different countries found severe ADRs ranging from 10.9% to 74.5% of all ADRs.[3]

Although predictable type A reactions (eg, bleeding from warfarin) are the most common cause of ADRs, hypersensitivity reactions can represent up to one third of ADRs.[4] In the aforementioned study by Lazarou et al,[2] the frequency of hypersensitivity reactions among all ADRs was reported for 8 studies, with a mean of 23.8%, but no studies reported the types of reactions among severe or fatal reactions. In a follow-up study of the Boston Collaborative Drug Surveillance Program, 2.2% of hospitalized patients were determined to have benign exanthems to drugs, with antibiotics being the most frequent culprit.[5] Other studies from different countries and settings have shown very similar results.[6]

Although in the past ADRs were often viewed as unpredictable and unavoidable problems associated with pharmacotherapy, several strategies have now been used to reduce ADRs. Errors in dosing and nonadherence account for a substantial portion of medicine-related problems and can be minimized through a number of approaches. Genetics are another significant contributing factor in ADRs. Genetic factors can play a role in pharmacokinetics, pharmacodynamics, and susceptibility to hypersensitivity responses. The degree to which genetics contributes to ADRs is not entirely clear and varies by drug, as well as the type of ADR. One author has estimated that genotyping just for P450 would lead to a reduction in ADRs by 10% to 15%[7]; however, this remains unproved. This review will focus on pharmacogenetics and pharmacogenomics and their role in reducing ADRs, especially those caused by drug hypersensitivity.

BACKGROUND ON PHARMACOGENETICS

At its most basic, the term pharmacogenetics describes any influence that genetics can have on drug therapy. The newer term pharmacogenomics is often used interchangeably with pharmacogenetics, but there are some subtle differences. Pharmacogenetics mainly deals with single drug-gene interactions. In contrast, pharmacogenomics incorporates genomics and epigenetics to look at the effect of multiple genes on drug responses. Pharmacogenomics is considered the future of drug therapy and is a rapidly growing field in the area of precision (personalized) medicine. Fig 1 illustrates how pharmacogenomic approaches have been used in drug hypersensitivity.

Many factors can determine whether differences in genetic polymorphisms will be clinically relevant.[8] The therapeutic index of a drug is one important factor. A polymorphism affecting the concentration of a drug that is safe over a wide range of concentrations is unlikely to have a clinically relevant effect. However, if a drug has a narrow therapeutic window (eg, warfarin), minor variations in concentrations from polymorphisms could be important. If the metabolite of a drug has a similar effect as the parent drug, polymorphisms in the enzyme creating the metabolite are unlikely to be important. If multiple metabolic or elimination pathways are present for a drug, the effect of a polymorphism affecting one pathway might also be negligible. Regarding drug hypersensitivity, polymorphisms must not only be associated with a significant risk but also have a degree of specificity that would not eliminate a large proportion of patients who would unlikely be harmed by taking the drug.

HISTORY OF PHARMACOGENETICS

One of the earliest examples of pharmacogenetic observations is from Pythagoras, who noted in 510 BC that some subjects would have an acute illness and even die after ingestion of fava beans.[9] It was not until 1956 that we discovered that a deficiency in the enzyme glucose-6-phosphate dehydrogenase (G6PD) was the cause of hemolytic anemia from ingestion of fava beans or drugs such as primaquine.[10] Shortly after this, pseudocholinesterase deficiency was discovered as a genetic cause for prolonged apnea from anesthesia with succinylcholine.[11] Fig 2 shows a timeline of some important discoveries of pharmacogenetics regarding ADRs.

One of the most well-known early examples of the genetics of drug metabolism is the acetylation polymorphism. Studies from the early 1950s observed that isoniazid, which was at the time a recently introduced treatment for tuberculosis, had marked differences in excretion among patients. These differences were discovered to be related to differences in a subject's ability to convert isoniazid to acetylisoniazid, and "slow acetylators" were more likely to have peripheral neuropathy.[12] These studies triggered many further epidemiologic, pharmacologic, and clinical studies in numerous countries, providing a model of how pharmacogenetic traits could be analyzed.[13] This acetylation polymorphism also influenced the metabolism of other drugs, including sulfonamides, dapsone, hydralazine, procainamide, and many others. Many decades later, the molecular causes of these traits were discovered. Cloning of cDNA encoding the enzyme N-acetyltransferase led to identification of 2 common alleles, *NAT2*5* and *NAT*6*, which account for more than 90% of slow-acetylator alleles.[13]

In 1957, Motulsky[14] highlighted the genetic basis of adverse reactions to primaquine and succinylcholine in an article entitled

Download English Version:

https://daneshyari.com/en/article/5646649

Download Persian Version:

https://daneshyari.com/article/5646649

Daneshyari.com