Tailoring Drug Therapy Based on Genotype

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Introduction

There is substantial variability among individuals in response to medications. For example, when treating a group of patients with similar drug therapy for a given disease, the majority will most likely have a favorable response and acceptable drug tolerability. However, a subset of patients may have little to no response to the medication, and another subset may experience serious adverse effects. Currently, it is difficult if not impossible to predict into which response group a patient will fall. A number of factors, including age, body size, and concomitant diseases, are often considered when making drug therapy decisions. However, these are often insufficient in themselves to predict drug response. It is now recognized that genotype contributes to how a patient will respond to medication. In the future for many drugs (and presently for some drugs) clinicians may consider genotype in addition to other factors, such as age and concomitant diseases, in choosing drug therapy.

What is pharmacogenetics?

Pharmacogenetics is the study of how gene variations lead to inter-individual differences in drug response.[1] The goal of pharmacogenetics is to choose the drug with the greatest potential for benefit with the least potential for harm for a patient based on that patient's genotype. The terms pharmacogenetics and pharmacogenomics are often used interchangeably. Pharmacogenetics is often used to refer to a single gene affecting drug response whereas pharmacogenomics refers to the combination of genes affecting response to a drug. For example, pharmacogenetics would refer to examination of the cytochrome P450 2C9 (*CYP2C9*) gene alone for its effects on warfarin response, whereas pharmacogenomics would refer to study

of both the *CYP2C9* and vitamin K epoxide reductase (*VKOR*) genes on warfarin response. In this review, the term pharmacogenetics will be used throughout.

Background on single nucleotide polymorphisms (SNPs)

As a review, the human genome is composed of 4 nucleotides: adenine (A), cytosine (C), thymidine (T), and guanine (G). Three consecutive nucleotides at a given chromosomal locus form a codon. Each codon specifies an amino acid or amino acid chain termination. For example, CGT (cytosine-guanine-thymidine) codes for the amino acid arginine. The most common type of variant in the human genome is a single nucleotide polymorphism (SNP). A SNP occurs when one nucleotide is replaced by another. An example of a SNP is the substitution of T for C in the codon, CGT. This results in the codon, TGT, which codes for the amino acid cysteine. This is an example of a missense or nonsynonymous SNP since the nucleotide substitution results in an amino acid substitution. Nonsynonymous SNPs occurring in coding regions of the gene may alter the function of the encoded protein. If the protein is involved in drug metabolism, drug transport, or eliciting drug effects, the SNP may have significant consequences for drug response. If the T in the codon CGT is replaced by an A, the amino acid would remain the same because both the CGT and CGA code for arginine. This is an example of a synonymous SNP. Synonymous SNPs occurring in regulatory regions of the gene, such as promoter regions which regulate gene transcription, can also have significant effects on drug response.

SNPs affecting drug disposition

A SNP in the thiopurine S-methyltransferase (*TPMT*) gene is a well documented SNP affecting response to the drug, 6-mercaptopurine.[2] 6-mercaptopurine is commonly prescribed to treat childhood lymphoblastic leukemia. Once 6-mercaptopurine enters the bone marrow cell, it is either inactivated by TPMT or converted to thioguanine, which has potent hematopoietic effects. About 10% of the population has a variant that renders a dysfunctional TPMT protein. In these patients, more of the 6-mercaptopurine is converted to thioguanine, thus increasing the risk for serious anemia when usual doses of the drug are administered.

There are numerous SNPs in genes for cytochrome P450 enzymes that can influence drug disposition and response [3] These include genetic variants for the CYP2C9 enzyme that metabolizes the more potent S-enantiomer of warfarin. Variants in *CYP2C9* that decrease enzyme activity can lead to supratherapeutic plasma concentrations of S-warfarin, over-anticoagulation, and increased bleeding risk.[4,5]

In the case of clopidogrel, *CYP2C19* gene variants leading to a dysfunction protein can reduce drug efficacy and increase risk for adverse cardiovascular events.[6] In this case, CYP2C19 is required to convert the clopidogrel to its active thiol metabolite. Individuals with a dysfunction CYP2C19 enzyme may be unable to produce adequate quantities of the active metabolite to sufficiently inhibit platelet aggregation and prevent cardiac events.

SNP affecting drug sensitivity

Warfarin exerts its anticoagulant effects by inhibiting the vitamin K epoxide reductase (VKOR) enzyme, thus preventing carboxylation and activation of clotting factors, II, VII, IX, and X. A variant commonly occurs in the gene encoding for VKOR and affects sensitivity to warfarin.[7] African Americans have a high frequency of the VKOR variant leading to reduced

VKOR enzyme sensitivity to warfarin. As a result, African Americans generally require higher doses of warfarin to obtain therapeutic anticoagulation compared to those of other racial groups.[8] In contrast, Asians have a high frequency of the *VKOR* variant leading to increased sensitivity to warfarin and generally require lower doses of warfarin than those of other racial groups.

FDA responds to pharmacogenetic data

The Food and Drug Administration (FDA) now requires genetic information in the labeling of over 30 drugs. Examples of drugs with pharmacogenetic labeling are listed in Table 1. Only a few drugs, such as the anti-cancer agent, trastuzamab, require genetic testing prior to drug use. Trastuzumab is a recombinant monoclonal antibody that targets the human epidermal growth factor receptor 2 (HER2) and blocks HER2-stimulated growth of cancer cells. Overexpression of HER2 occurs in 20% to 30% of metastatic breast cancers.[9] Trastuzumab treatment of breast cancer in women with HER2-positive tumors significantly slows the progression of cancer, whereas it is ineffective in those without HER2 overexpression.[9] Testing for HER2 overexpression is necessary to determine which patients may benefit from trastuzumab. In the case of carbamazepine, genetic testing can identify individuals at high risk for carbamazepine-induced Stevens Johnson syndrome and toxic epidermal necrolysis.[10] The carbamazepine labeling states that individuals with ancestry from areas (south Asian countries) with a higher frequency of the human leukocyte antigen variant that increases the risk for these serious skin reactions should be screened for the variant. Carbamazepine should be avoided in those testing positive for the variant unless the potential benefit clearly outweighs the risks.

The labeling regarding pharmacogenetics may change from suggested to recommended or required for other drugs pending results of prospective studies. For example, the current

warfarin labeling states that lower doses should be considered in individuals known to have a variant *CYP2C9* or *VKORC1* allele. However, genetic testing is not required or even recommended at this point. A prospective trial is currently comparing warfarin dosing based on genotype plus clinical factors versus clinical factors alone.[11] If genotype-guided therapy is associated with better outcomes, the FDA could change its stance of the importance of genetic testing in candidates for warfarin therapy.

Future of pharmacogenetics

A recently published report gives a glimpse into the future of medicine in the age of pharmacogenetics.[12] The study investigators sequenced the entire genome of healthy 40-year old male with a family history of cardiovascular disease. An analysis of 2.6 million genetic variants showed that the man was at an increased risk for myocardial infarction, diabetes and some cancers. The man also had variants in the *CYP2C19*, 3-hydroxy-3-methyl-glutaryl-CoA (*HMG-CoA*) reductase, solute carrier organic anion transporter family member 1B1 (S*LCO1B1*), and *VKOR* genes suggesting resistance to clopidogrel, good response to statin therapy, and a need for a lower than usual dose of warfarin. If the man does indeed develop cardiovascular disease, this genetic information may be very useful in choosing appropriate drug therapy.

Summary

Pharmacogenetics may allow individualized therapy based on genotype. That is, clinicians may be able to predict the likelihood of response and risk for toxicity with various drugs based on an individual's DNA and choose therapy accordingly. This would help to eliminate the trial-and-error approach to drug prescribing. Rather, clinicians may be able to

choose the drug and dose that will result in the best outcomes for a given patient with the least chance for harm based on genotype. For the majority of patients expected to respond well to traditional therapy based on genotype, such therapy may be instituted. For those at increased risk for adverse effects with traditional therapy (e.g. a candidate for 6-mercaptopurine with a *TPMT* variant or a candidate for carbamazepine with the human leukocyte antigen variant) lower drug doses or alternative therapy may be prescribed. For those expected to have a poor response to traditional therapy (e.g. a candidate for clopidogrel with a reduced function *CYP2C19* genotype), increased drug doses or alternative agents may be used.

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Table 1. Examples of drugs with pharmacogenetic labeling

(http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm)

Drug	Gene	Effect	Testing Status
Abacavir	*HLA-B*	Associated with risk for abacavir hypersensitivity	Recommended prior to abacavir use
Atomoxetine	*CYP2D6*	Increased drug exposure in poor metabolizers	Suggested
Carbamazepine	*HLA-B*	Increased risk for Stevens Johnson syndrome	Recommended for at-risk persons
Warfarin	*CYP2C9; VKORC1*	Altered metabolism and sensitivity	Suggested
Clopidogrel	*CYP2C19*	Determines efficacy	Suggested
Celecoxib	*CYP2C9*	Increased drug exposure in poor metabolizers	Suggested
Irinotecan	*UGT1A1*	Associated with risk for neutropenia.	Suggested
Maraviroc	CCR5	Determines efficacy	Required
Rasburicase	*G6PD*	Severe hemolysis	Recommended for at-risk persons
Trastuzamab	*HER2*	Determines efficacy	Mandated
Cetuximab	*EGFR*	Determines efficacy	Mandated
Voriconazole	*CYP2C19*	Determines drug exposure	Informationonly
Azathioprine (6MP)	*TPMT*	Increased risk for myelotoxicity	Recommended