**Pharmacogenetics of ADRs**

This lesson highlights a few key, clinically relevant examples of ADRs with pharmacogenetic mechanisms. The goals of this lesson are to: explain the differences in drug response that may occur due to genetic variations of patients. **The program ID # for this lesson is 707-000-16-008-H01-P for pharmacists & 707-000-16-008-H01-T for technicians.**

Participants completing this lesson by July 31, 2019 may receive full credit. Release date: August 1, 2016.

To obtain continuing education credit for this lesson, you must answer the questions on the quiz (70% correct required), and return the quiz. Should you score less than 70%, you will be asked to repeat the quiz. Computerized records are maintained for each participant.

If you have any comments, suggestions or questions, contact us at the above address, or call 1-847-945-8050. **Please write your name, NABP eProfile (CPE Monitor®) ID Number & birthdate (MM/DD) in the indicated space on the quiz page.**

The objectives of this lesson are such that upon completion participants will be able to:

**Pharmacists:**
1. Define basic pharmacogenetics concepts.
2. Describe the contribution of genetic variation in drug metabolizing enzymes & drug transporters to ADRs.
3. Comment upon the role of genetic variation in the HLA system on ADRs.

**Technicians:**
1. Define basic pharmacogenetics concepts.
2. Describe the contribution of genetic variation in drug metabolizing enzymes & drug transporters to ADRs.
3. Comment upon the role of genetic variation in the HLA system on ADRs.

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INTRODUCTION

It has been estimated that between 770,000 and 2 million ADRs (adverse drug reactions) occur in the U.S. every year. These result in significant morbidity and mortality and increased healthcare costs. One report estimates that ADRs result in up to $5.6 million per hospital. A common source of ADRs is inter-individual variability in drug response. There are several sources for variability in drug response that are well understood by pharmacists: patient specific factors, environment, diseases, drug interactions, and genetics. However, pharmacists have less understanding of the role of pharmacogenetics in ADRs. The volume of research in this field is rapidly increasing and some ADR related pharmacogenetics information has been included in the FDA prescribing information for medications. This lesson highlights a few key, clinically relevant examples of ADRs with pharmacogenetic mechanisms.

The first reports of the potential for pharmacogenetics to cause ADRs were theoretical. One study assessed 27 drugs which most commonly cause ADRs and found that 59% are metabolized by at least one enzyme with a pharmacogenetic variant associated with decreased metabolism. However, only 7-22% of randomly selected drugs were found to be metabolized by enzymes with this type of variability. The authors concluded that drug therapy based on an individual’s genetic makeup may decrease ADRs. Since that paper was published, many studies have been done to assess the effect of pharmacogenetics on drug metabolism through these enzymes.

Pharmacogenetic variability does not only occur in drug metabolizing enzymes. There are genetic sources of variability in both the pharmacokinetics and pharmacodynamics of many
medications. Pharmacogenetic differences may manifest in variability in enzymes, transporters, cell membrane receptors, intracellular receptors or components of ion channels.

GENERAL PHARMACOGENETICS

While inter-individual variability in drug response had been well known for many years, pharmacogenetic research did not grow until the completion of the human genome project in 2003.4 The human genome contains 30,000-35,000 genes; however, less than 2% percent of the human genome codes for proteins. The rest of the genome is considered “non-coding,” and its function is not well understood. The simplest cause of inter-individual genetic variation in drug response is a point mutation of a nucleotide. These point mutations are called single nucleotide polymorphisms (SNPs). This may impact the protein-coding capacity of a gene, the way it is spliced or the way it is expressed or regulated. A SNP that affects the amino acids of a protein is called a non-synonymous polymorphism. A SNP that does not change the amino acids in the protein is called a synonymous polymorphism. The genetic code contains a significant amount of redundancy; therefore, many SNPs are synonymous and do not result in any change in the protein. There are other more complicated forms of genetic variability including frame shift mutations, insertions, and deletions. This has been reviewed elsewhere. Patients are homozygous if they possess two of the same alleles and heterozygous if they possess two different alleles.

MECHANISMS BEHIND PHARMACOGENETICS AND ADRs

Genetic polymorphisms can lead to variability in drug response through many different mechanisms. Specifically, genetic variation can affect the pharmacokinetics of a medication. In addition, there has been a recent focus on the role of pharmacogenetics in hypersensitivity reactions to medications. Polymorphisms in genes encoding enzymes responsible for drug metabolism may make the enzymes more or less effective. Impaired enzymes do not metabolize drugs efficiently and lead to increased concentrations of the medication. When a drug concentration extends beyond its therapeutic window, patients can experience toxicity and ADRs. Many of the ADRs with pharmacogenetic mechanisms reviewed in this lesson are due to pharmacokinetic changes. The role of genetic variability in hypersensitivity reactions is a growing field as well. It has long been believed this phenomenon has an inherited component; however, only recently have specific polymorphisms been found to support this.5

ADVERSE DRUG REACTIONS WITH PHARMACOGENETIC MECHANISMS

This lesson will review a sample of clinically relevant ADRs with pharmacogenetic mechanisms. This is a rapidly growing field. Concepts reviewed here have been assessed in multiple populations and validated by multiple investigators.

PHARMACOGENETICS OF DRUG METABOLISM AND ADRs

Irinotecan and UGT1A1

Irinotecan (CAMPTOSTAR®) is a topoisomerase I inhibitor used in the treatment of metastatic colorectal and lung cancers. Irinotecan is readily converted to an active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38) by carboxylesterases.6 SN-38 is then metabolized by UDP-glucuronosyltransferase 1 – A1 (UGT1A1) to SN-38glucuronide (SN-38G) which is then cleared from the body. Impaired clearance of SN-38 by dysfunctional UGT1A1, leads to increased SN-38 concentrations and toxicity (neutropenia and diarrhea). The most well studied UGT1A1
variants are UGT1A1*28, an insertion of 7-TA repeats in the promoter region, and UGT1A1*6, 226G>A.6 Possession of 2 UGT1A1*28 alleles occurs infrequently in Asians (approximately 2%), moderately in Europeans (approximately 11%) and most frequently in African Americans (approximately 19%).7 In contrast, UGT1A1*6 is found almost exclusively in Asians. A prospective study of 250 colorectal cancer patients receiving irinotecan therapy found that possession of the UGT1A1*28 allele was associated with a significant increase in hematological toxicity (OR 8.63).8 Other studies have demonstrated similar results with UGT1A1*6 and the combination of *6 and *28.6,9

Given the preponderance of data with irinotecan and UGT1A1, the FDA updated the label for this medication.10 The dosing section of the irinotecan package insert states “...a reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele.” Genotyping for these alleles is widely available throughout the United States; however, genotyping has not been widely adopted into clinical practice.11 This is likely because specific dosing recommendations are not currently available from U.S. based guidelines. However, two European organizations (French and Dutch) have made specific dosing recommendations based on UGT1A1 genotype.6,12 In addition, while UGT1A1*28 predicts increased risk for ADRs, not all patients who are homozygous for the UGT1A1*28 allele will experience toxicity. In addition, patients without UGT1A1 variants can experience adverse events, thus all patients need to be monitored while receiving therapy. Therefore, it is difficult to recommend genotyping for all patients receiving irinotecan therapy. However, those patients receiving high dose therapy or those who have experienced irinotecan ADRs in the past may be good candidates for genotyping.

**Warfarin and CYP2C9**

Warfarin has a narrow therapeutic range, multiple drug-drug and drug-food interactions, and the frequency of major bleeding is reported to be as high as 10%-16%.13 Yet over 25 million prescriptions are written in the United States for warfarin annually.13 The risk of major and minor hemorrhage with warfarin therapy has been reported to be approximately 7% and 20% respectively.14 Several factors have been associated with warfarin bleeding risk, including: increasing international normalized ratio (INR), the first 90 days of anticoagulation, decreasing time in therapeutic INR range or quality of anticoagulation control, increasing age, female gender, non-adherence, limited warfarin knowledge, inconsistent dietary intake of vitamin K containing foods, heart failure, renal dysfunction, diabetes, increasing blood pressure, malignancy, interacting medications, and recent hospitalization.15 However, even when one considers the known clinical variables that alter warfarin dosing and bleeding risk, it is still difficult to predict dose requirements and those at risk for bleeding. The genes encoding two enzymes, CYP2C9 and vitamin K epoxide reductase complex subunit 1 (VKORC1), contribute significantly to warfarin pharmacokinetics and pharmacodynamics.

Warfarin is highly metabolized and hence its effects can be altered by genetic variation that modify drug metabolism.14 Warfarin is a racemic mixture (R and S isomers) with the S-isomer being significantly more potent. The S-isomer undergoes extensive metabolism via the CYP2C9 isoenzyme. CYP2C9*1 encodes for the wild-type enzyme that is consistent with normal extensive metabolism of warfarin. There are two common single nucleotide polymorphisms (SNPs), CYP2C9*2 and CYP2C9*3. The CYP2C9*2 variant is a non-synonymous SNP, which occurs in about 10-20% of Caucasians and rarely in African Americans and Asians. CYP2C9*3
is also a non-synonymous SNP, which occurs in about 7-9% of Europeans. Overall, CYP2C9*2 variants have about 30% reduction in enzymatic activity corresponding to a 17% reduction in dose if one variant is present. CYP2C9*3 has an 80% reduction in activity equivalent to a 37% reduction in dose if at least one variant is present. Other alleles, CYP2C9*5, *6, and *11, are also reported, with CYP2C9*6 having little effect on metabolic activity but reduced activity has been reported with CYP2C9*5 and *11. However, these polymorphisms have not been consistently or independently associated with variability in response to warfarin. When considering warfarin dose requirements, there is a gene-dose relationship, where *1/*1, *1/*2, and *1/*3 subjects require average dosages of 5.63, 4.88, and 3.32 mg of warfarin daily, respectively. Multiple variants were associated with even lower daily dosages.

This change in pharmacokinetic properties may be what causes patients possessing a CYP2C9*2 or *3 allele to be at increased risk of both time above goal INR range and serious or life-threatening bleeding. Studies have found that possession of a CYP2C9*2 and *3 allele is associated with decreased time to the first INR greater than 4, increased time outside of the therapeutic INR range, and increased time above INR range during therapy. However, only a few studies have found an association between CYP2C9 genotype and major hemorrhage, as this event is relatively uncommon. The gene encoding the active site for warfarin (VKORC1) has also been identified. VKORC1 SNPs have been associated with warfarin dose requirements, but not ADRs associated with warfarin.

Given the volume of data supporting the use of pharmacogenetics for warfarin dosing, two prospective warfarin genotyping studies were completed. The Clarification of Optimal Oral Anticoagulation through Genetics (COAG) trial was completed in the United States and included 1,015 patients who were randomized to receive warfarin dosing according to an algorithm that contained genotype and clinical variables, including early INR data, or one with only clinical variables. The investigators found no significant difference in time in therapeutic range between the two algorithms, bleeding was not a primary endpoint. The European study from the European Pharmacogenetics of AntiCoagulant Therapy (EU-PACT) included 455 patients. These patients were also randomized to genotype guided or standard therapy. In contrast to the COAG study where a clinical algorithm was used, patients in the standard therapy arm in this study were given either 10 mg or 5 mg of warfarin for three days based on age, and then the warfarin dose was adjusted based on INR. The genotype-guided group had significantly greater percentage of time in therapeutic range compared to standard of care. Patients in the genotype-guided group were also statistically significantly less likely to have an INR≥4 and had a significantly shorter time to reach therapeutic INR. Although other safety outcomes were assessed, no major bleeding events occurred during the study. These studies highlight the difficulty in assessing adverse drug events that do not occur very frequently. The conflicting data are difficult to interpret but are likely due to differences in warfarin dosing methods and racial makeup of the groups.

Based on the previously described results and prior to publication of the EU-PACT and COAG studies, warfarin became the first cardiovascular drug to have a change in its package insert adding pharmacogenetic information, specifically stating that “...the patient’s CYP2C9 and VKORC1 genotype information, when available, can assist in selection of the starting dose.” The potential benefit of pharmacogenetic guided dosing is to achieve the correct INR sooner, maintain the INR within range better, and to prevent complications. The Clinical Pharmacogenetics Implementation Consortium (CPIC) has provided guidelines on how to interpret and apply genetic test results to warfarin dosing when such results are available.
The CPIC guideline does not, however, address when or who to genotype, leaving this to the discretion of the clinician. The CPIC guidelines were written in recognition that the available data strongly support a genetic influence on dose requirements and that the dose should be adjusted when genotype is known. Warfarin pharmacogenetics is being used in clinical practice today; however, adoption has not been widespread and is likely to be slowed by the conflicting results from prospective clinical trials.

**Clopidogrel and CYP2C19**

Despite the well documented benefits of clopidogrel, there is significant variability in platelet inhibition between patients. This variability leads to some patients having decreased inhibition of platelet aggregation with clopidogrel, or non-responsiveness, and this has been associated with increased risk of cardiovascular events. The primary source of the variability in clopidogrel responsiveness lies in the pharmacokinetics of clopidogrel. Clopidogrel is a prodrug that requires activation by the CYP450 system to the active thiol metabolite. This metabolite then irreversibly inhibits the P2Y₁₂ receptor. Drug interactions with and genetic variation in cytochrome P450 (CYP450) 3A4, 3A5, and 2C19 enzymes have been implicated in decreased active metabolite production. This has resulted in a change in the clopidogrel prescribing information, which now includes information on CYP2C19 genotyping and concomitant use of CYP2C19 inhibitors.

CYP2C19 polymorphisms appear to be the primary source of variability in clopidogrel response. The CYP2C19*2 allele, along with the *3, *4, and *5 alleles, have been associated with decreased metabolic activity and have thus been termed “loss of function” alleles. In contrast, the CYP2C19*17 allele is associated with increased CYP2C19 activity and is associated with “ultra-rapid” metabolism. Approximately 30%-40% of Europeans and African Americans possess at least one CYP2C19*17 allele; however, the frequency is less than 5% in Asians.

Several studies have demonstrated that CYP2C19 genotype affects the pharmacokinetics and pharmacodynamics of clopidogrel. Specifically, possession of CYP2C19 loss of function alleles leads to decreased production of clopidogrel active metabolite and a diminished effect on platelets. Studies have also recently documented that possession of two losses of function CYP2C19 alleles is associated with an increased risk of cardiovascular events with clopidogrel therapy. In contrast, possession of a CYP2C19*17 allele causes ultra-rapid metabolism and increased production of the clopidogrel active metabolite with subsequent significant inhibition of platelet aggregation. In 2011, CPIC guidelines regarding the pharmacogenetics of clopidogrel were published and then updated in 2013. The guidelines work under the assumption that genotype information is already available. They recommend considering an alternative antiplatelet agent (e.g., prasugrel or ticagrelor) in patients who possess at least one CYP2C19*2 or *3 allele. However, these guidelines do not make any specific recommendations related to CYP2C19*17.

Genotyping for CYP2C19*17 may aid in predicting those patients at increased risk of bleeding with clopidogrel therapy. Those patients possessing two CYP2C19*17 alleles are at increased risk of bleeding (OR 3.3 95% CI 1.33-8.10) due to excessive inhibition of platelet aggregation. In 2011, CPIC guidelines regarding the pharmacogenetics of clopidogrel were published and then updated in 2013. The guidelines work under the assumption that genotype information is already available. They recommend considering an alternative antiplatelet agent (e.g., prasugrel or ticagrelor) in patients who possess at least one CYP2C19*2 or *3 allele. However, these guidelines do not make any specific recommendations related to CYP2C19*17.

**Codeine and CYP2D6**

Codeine is a widely prescribed opiate for the treatment of mild to moderate pain and as an antitussive in children and adults. Codeine itself is a prodrug with no analgesic effect
that requires metabolism via CYP2D6 to morphine, the active metabolite. Morphine has approximately 600 fold greater affinity for the opioid receptor than codeine and exerts the analgesic and antitussive effects seen in patients. Codeine has recently come under scrutiny from the FDA and the codeine product labeling was subsequently updated. The FDA stated that nursing mothers and their infants could experience morphine overdose, which is potentially fatal, with codeine therapy. In addition, a warning by the FDA was issued in 2012 warning about codeine use in children, particularly following tonsillectomy with or without adenoidectomy for obstructive sleep apnea. The announcement was released after reports of codeine related deaths and serious adverse drug reactions after tonsillectomy in young children. The reports suggested that children who were CYP2D6 ultra-rapid metabolizers were at increased risk for breathing problems and death. In February 2013, the FDA announced its strongest black box warning against codeine use in children for postoperative pain following tonsillectomy with or without adenoidectomy. This black box warning came after FDA review of the codeine related deaths and serious adverse drug reactions. The FDA warning is applicable to all children undergoing tonsillectomy with or without adenoidectomy irrespective of their obstructive sleep apnea status or CYP2D6 genotype/phenotype.

These updates to the codeine prescribing information highlight the importance of CYP2D6 genotype in codeine metabolism. CYP2D6 is highly polymorphic with over 100 genetic variants. Patients with three or more functional copies of CYP2D6 are classified as ultra-rapid metabolizers. In contrast, poor metabolizers have genetic variants that disrupt CYP2D6 function or cause CYP2D6 deletions. Patients who are ultra-rapid metabolizers rapidly convert codeine to morphine and are at increased risk for adverse events, while patients who are poor metabolizers make little morphine and receive little benefit from codeine therapy.

In 2011, CPIC guidelines regarding the pharmacogenetics of codeine were published and then updated in 2014. The guidelines work under the assumption that genotype information is already available. These guidelines recommend against use of codeine in patients who are ultra-rapid metabolizers due to increased risk of adverse events. They recommend utilization of alternative medications that are not affected by CYP2D6 such as morphine and non-opioid analgesics. Unfortunately, tramadol and hydrocodone/oxycodone (to a lesser extent) are not good alternatives as their metabolism is affected by CYP2D6. Similarly, codeine should not be used in poor metabolizers due to lack of efficacy.

Due to the recent updates to the prescribing information, pregnant women, neonates, and children undergoing tonsillectomy with or without adenoidectomy should not receive codeine regardless of CYP2D6 genotype. However, for all other patients, CYP2D6 genotype can be very informative for predicting risk of adverse events.

**Tacrolimus and CYP3A5**

Tacrolimus is a potent immunosuppressant used for the prevention of organ rejection following solid organ transplantation. Tacrolimus is in a class of drugs called the calcineurin inhibitors. It works by inhibiting calcineurin in T-lymphocytes. This inhibition prevents transcription of several cytokines, with the most notable being interleukin-2. It is vital for a successful transplantation to maintain the appropriate balance between under and over-immunosuppression to maximize efficacy and minimize the risk of toxicity. Adverse effects related to tacrolimus include nephrotoxicity, neurotoxicity, hypertension, and gastrointestinal disturbances. Therapeutic drug monitoring (TDM) of tacrolimus is routinely performed with the dosages adjusted.
Tacrolimus displays a wide variation between individuals in blood concentrations achieved with a given dose. Various factors have been reported to influence the pharmacokinetics of tacrolimus which include transplant type, hepatic and renal function, co-administered medications, patient age and race, diurnal rhythm, food administration, diarrhea, levels of cytochrome P450 (CYP) 3A and P-glycoprotein expression. Tacrolimus is a substrate for the CYP3A enzymes (CYP 3A4 and CYP 3A5) and is transported out of cells by P-glycoprotein efflux pumps. Different expression of these enzymes and transporters leads to inter-patient variability in the absorption, metabolism and tissue distribution of calcineurin inhibitors.

CYP3A enzymes and P-glycoprotein form a barrier against absorption of tacrolimus in the small intestines. Tacrolimus is pumped out of the intestinal enterocytes by P-glycoprotein. In addition, tacrolimus is metabolized by CYP3A4 and CYP3A5 enzymes in the small intestine, liver and kidney. P-glycoproteins limit access to various compartments in the body (i.e. blood brain barrier, testes, placenta, heart, liver and kidneys.)

There have been at least 11 SNPs identified for CYP3A5, of which the CYP3A5 SNP involving an A to G transition at position 6986 has been the most extensively studied. Surprisingly, the wild-type allele occurs less frequently than the variant allele. The CYP3A5 6986 A is the wild-type and is referred to as CYP3A5*1 and the variant allele (CYP3A5 6986 G) is referred to as CYP3A5*3. The frequency of these variants is dependent on ethnicity; it is present in 5-15% of Caucasians, 45-73% of African Americans, 15-35% of Asians and 25% of Mexicans. Heterozygous or homozygous carriers of the CYP3A5*1 make more CYP3A5 and are considered CYP3A5 expressers. Homozygous carriers of the CYP3A5*3 variant allele produce low or undetectable levels of CYP3A5 (i.e. CYP3A5 non-expressers).

The tacrolimus pharmacokinetics and pharmacodynamics are different between CYP3A5 expressers (CYP3A5*1) and CYP3A5 non-expressers (CYP3A5*3). Multiple studies have indicated that doubling of the tacrolimus dose is required for CYP3A5 expressers compared to non-expressers, indicating a higher metabolic capacity in patients with the wild-type allele (CYP3A5*1). In a population pharmacokinetic study involving 136 renal transplant patients, the overall tacrolimus daily dose was 68% greater in patients carrying at least one CYP3A5*1 allele than in CYP3A5*3 homozygotes. CYP3A5 expressers take a longer time (up to 2 weeks) to reach tacrolimus target blood concentrations post-transplantation. In a study with 136 renal transplant patients, the majority of CYP3A5 expressers failed to achieve the recommended target concentration during the first few weeks post-transplantation. The status of CYP3A5 expression may be useful in determining the correct initial dose of tacrolimus post-transplantation.

While there is a strong association between CYP3A5 polymorphisms and the pharmacokinetics of tacrolimus, there is inconsistent evidence for organ rejection as a result of genotype-related under immunosuppression. There are four studies that fail to demonstrate an association between CYP3A5*1 and *3 genotype and organ rejection (biopsy proven), which include 136 renal transplant recipients, 44 renal transplant recipients, 280 renal transplant recipients and
124 lung recipients. In contrast, two studies demonstrated a reduced incidence of acute rejection in 30 kidney transplant patients, and a longer time to first rejection episode in 178 renal transplant patients in CYP3A5 non-expressers (CYP3A5*3). And more recently, a Korean group of investigators found 29 of the 65 renal transplant patients expressed CYP3A5. These patients had higher incidence of early subclinical rejection at 10 days and CYP3A5 expression was found to be an independent risk factor for T-cell mediated rejection (OR: 2.79, p=0.043). The association between CYP3A5 expression and other adverse effects (i.e. hypertension and renal function) is also inconsistent. There are five studies that found no relationship between transplant patients with CYP3A5 expression and kidney function measured in terms of serum creatinine or clearance. In contrast, there are two studies that indicate conflicting results where a Japanese cohort of liver transplant patients reported an increased incidence of nephrotoxicity in CYP3A5*3 homozygotes (i.e. non-expressers), where the Korean investigators demonstrated a lower glomerular filtration rate at 1 month and 12 months in renal transplant patients with CYP3A5 expression. The CPIC guidelines recommend that patients that are extensive or intermediate CYP3A5 metabolizers should be initiated on tacrolimus at 1.5 to 2 times higher dose but not to exceed 0.3 mg/kg/day. Therapeutic drug monitoring should guide dose adjustment.

The influence of CYP3A5 expression on the pharmacokinetics of tacrolimus has been demonstrated in many studies but the translation into clinical practice and clinical outcomes remains unclear. The utility of genotyping patients prior to transplantation to determine the optimal starting dose of tacrolimus seems reasonable but currently is not routinely performed.

**PHARMACOGENETICS OF DRUG TRANSPORTERS AND ADRs**

**Statins and SLCO1B1**

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, also known as statins, are commonly prescribed medications used to reduce low density lipoprotein (LDL) levels and the risk of cardiovascular disease. Multiple trials involving statin therapy have demonstrated significant reduction in relative risk of major coronary event by 33% in primary prevention and by 26% in secondary prevention trials. In addition, meta-analysis has shown significant reduction in the development of coronary artery disease and cardiovascular disease mortality. Overall, statins are well-tolerated but can produce unexplained myopathies. The symptoms can range from mild myalgias to life-threatening rhabdomyolysis. In clinical trials, the reported incidence of statin-associated myalgias is 3-5%. High-dose statin therapy is associated with an elevated risk of myalgias. Fatal rhabdomyolysis is rare; it is estimated to occur in 1.5 patients per 10 million prescriptions.

The mechanism for statin-associated myopathies is unknown but appears to be related to increased statin concentrations. Statin concentrations are affected by their extensive first-pass uptake into hepatocytes and their rate of metabolism by hepatic CYP450 enzymes. This hepatic uptake appears to be necessary for statin clearance. Genetic variants in hepatic uptake and statin metabolism have been associated with altered statin concentrations and myopathies.

The strongest association with genetic factors has been documented with genes affecting statin hepatic uptake. Statins are transported into hepatocytes by the organic anion transporting polypeptide (OATP) - C, which is encoded by the SLCO1B1 gene. OATPs or solute carrier organic anion (SLCO) transporters are vital for drug uptake into tissues and organ systems. These transporters are found in the liver, intestine, and the central nervous system. All statins,
except for fluvastatin, are transported by this mechanism into hepatocytes. There are two main variants, rs2306283 (388A>G) and rs4149056 (521T>C), which affect the transport function of the OATPs.\textsuperscript{43} The 388A>G SNP is associated with increased OATP1B1 activity, therefore, increased statin uptake into hepatocytes and lower statin concentrations. In contrast, the 521T>C SNP is associated with increased statin concentrations due to reduced transporter activity. Patients with SNPs in the SLCO1B1 gene have increased plasma pravastatin concentrations, up to 130% higher, compared to patients without the polymorphism.\textsuperscript{45}

The SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) study demonstrated the association of genetic variability in the SLCO1B1 gene in patients with statin myopathy.\textsuperscript{46} The SEARCH study demonstrated that the SLCO1B1 521T>C SNP is associated with simvastatin-associated myopathy. The SNP was discovered by assessing SNPs in over 300,000 candidate genes in 85 confirmed cases of simvastatin induced myopathy which were compared to 90 controls. The analysis yielded one SNP that was strongly associated with simvastatin. This was a noncoding SNP (rs4363657) located within SLCO1B1 on chromosome 12. The rs4363657 SNP was linked to the well studied rs4149056 (521T>C). The investigators found that patients with the rs4149056 (521T>C) variant had an odds ratio for myopathy of 4.5 for one and 16.9 for two C alleles. These results were replicated in the Heart Protection Study, where there were 23 cases of myopathy among patients who were taking 40mg of simvastatin. The 21 genotyped patients with myopathy were compared to 16,643 genotyped controls (without myopathy) confirmed that rs4149056 was associated with myopathy (P=0.004) but the risk was lower (OR: 2.6, 95% CI, 1.3 to 5.0) per C allele. While the majority of myopathy cases occurred in subjects carrying the rs4149056 (521T>C) C allele, this polymorphism was not associated with all cases of myopathy. The SLCO1B1 haplotypes containing the 521C allele are SLCO1B1*5, *15 and *17.\textsuperscript{45} The magnitude of effect on SLCO1B1 function is the same with all of these haplotypes. Given the strong evidence seen in this study with simvastatin and the understanding of the functional consequence of this SNP, this SLCO1B1 variant and others have been evaluated with other statins and in multiple populations. These SLCO1B1 variants have been extensively studied in racially and geographically diverse groups. Consistent with the study presented above, a study assessing patients receiving atorvastatin, simvastatin, or pravastatin found that the SLCO1B1*5 haplotype was associated with increased adverse effects from statins, defined as statin discontinuation for any side effect, myalgia, or creatinine kinase greater than three times the upper limit of normal.\textsuperscript{47} The association between the SLCO1B1*5 allele and statin-induced myopathy was further validated in several additional studies.\textsuperscript{48–50} However, data from two of these studies, which used strict biochemical definitions for myopathy, suggest the association may be stronger for simvastatin than atorvastatin.\textsuperscript{49,50} In addition, no association was seen between SLCO1B1 SNPs and myalgia in patients receiving rosuvastatin.\textsuperscript{51}

Thus, it is likely that statin myopathy risk differs for each individual medication in the class and other genetic variants and clinical factors play a role in statin-induced myopathy. However, given the strength of data related to simvastatin myopathy and SLCO1B1 genotype, a set of CPIC guidelines were published in 2012 and updated in 2014.\textsuperscript{45,52} These guidelines do not make recommendations for when or who to genotype. Their recommendations are limited to simvastatin, for which the most data exist. Regardless of genotype, the simvastatin 80-mg dose should be avoided. For heterozygotes (CT genotype), the guidelines recommend using a lower simvastatin dose (<40 mg/day) or consideration of an alternative statin. For homozygous variant carriers (CC genotype), either a low simvastatin dose or alternative therapy is recommended.
They specifically recommend pravastatin or rosvastatin as alternative therapy. In the future, genotyping for the SLCO1B1 rs4149056 C allele may allow for the prediction of those patients who require more frequent monitoring for myopathy or lower initial statin doses.

NON-PHARMACOKINETICS RELATED ADRs

G6PD Deficiency

There are 400 million people worldwide who carry a gene for Glucose-6-phosphate dehydrogenase (G6PD) deficiency.\(^\text{53}\) It is considered the most common human enzyme defect and is most commonly found in Africa, southern Europe, the Middle East, Southeast Asia and central and southern Pacific islands. G6PD catalyzes the first reaction in the pentose phosphate pathway, thereby providing reducing power to all cells in the form of NADPH. NADPH enables all cells to counterbalance oxidative stress by oxidant agents, especially red blood cells which do not contain mitochondria. G6PD deficiency is an X-linked deficiency which results in protein variants with different levels of enzyme activity. The deficiency can be confirmed by quantitative spectrophotometric measurement of red blood cell activity.

The clinical manifestations are neonatal jaundice and acute hemolytic anemia when triggered by an exogenous agent. Clinically detectable hemolysis and jaundice can occur within 24-72 hours of drug administration. Dark urine is a characteristic sign of this reaction. After the drug is stopped, the hemoglobin concentrations recover after 8 to 10 days. Patients with known G6PD deficiency should avoid exposure to oxidative drugs. In addition, patients in the above mentioned groups who are likely to receive these medications may benefit from G6PD testing prior to initiating therapy.

HLA & ADRs

HLA-B is a member of the major histocompatibility complex (MHC) gene family located on chromosome 6, consisting of class I, II, and III subgroups. HLA class I molecules are expressed on almost all cells. They are responsible for presenting peptides to immune cells. When cells break down old proteins, they can be attached to MHC molecules and tracked to the cell surface. These breakdown products are recognized as “self.” If a cell becomes infected by a pathogen, the breakdown of foreign proteins is recognized as “non-self.” This will trigger an immune response against the antigen. MHC molecules are critical in transplant immunology, where careful HLA matching between donor and recipient minimizes transplant rejection. In addition, in rare cases, some pharmaceuticals are capable of producing immune-mediated hypersensitivity reactions through interactions with MHC molecules, although the exact mechanism of these interactions remains unclear. Some suggest that these drugs may function as haptens that irreversibly bind to the proteins presented to immune cells, causing them to attack the peptide-hapten conjugate. Alternate theory suggests that these drugs might interact directly with MHC molecules or T-cell receptors, leading to T-cell activation. There are over 1,500 HLA-B alleles identified, but only a few have been attributed to adverse drug reactions.\(^\text{54}\) See Table 1 for summary.

Drug induced liver injury (DILI) is a rare and potentially life threatening adverse event.\(^\text{5}\) This ADR has been seen with many medications including antibiotics and NSAIDs. DILI is a common cause of clinical trial termination for novel medications and early post-marketing withdrawals.\(^\text{42}\) DILI is a complicated phenomenon and the underlying pathophysiology differs for each specific medication. One underlying common theme in DILI may be the importance of human leukocyte antigen (HLA) class I and II genes.\(^\text{5}\) Associations have been seen with genetic variations in these genes and DILI, especially with cholestatic liver injury. The first of
these associations was observed with flucloxacillin. The authors looked at over 1 million genetic variants in 51 cases with flucloxacillin induced DILI and 282 controls. The SNP with the strongest association with DILI was in the major histocompatibility (MHC) region associated the polymorphism HLA-B*5701. These authors replicated this association in two separate case-control cohorts. The odds ratio for development of flucloxacillin induced DILI was 80.6 in this study, representing a very strong association with the HLA-B*5701 polymorphism. While flucloxacillin is not available in the United States, this study provides significant insight into the mechanism behind DILI and provides context for study of other medications with similar outcomes.

Specifically, the genetics of amoxicillin-clavulanate and lapatinib induced DILI have been subsequently studied. Two small studies found an association between amoxicillin-clavulanate induced liver injury and a polymorphism in an HLA class II gene (HLA DRB1*1501 and DQB1*0602). A larger study, including 40 individuals with amoxicillin-clavulanate induced DILI and 191 controls, replicated this association and found evidence that HLA-DRB1*07 alleles may be protective from this ADR. The odds ratio for amoxicillin-clavulanate induced DILI with the HLA DRB1*1501 was 2. This association does not appear to be as strong as that seen with flucloxacillin; however, the data is strong given that it has been replicated in several studies. Finally, lapatinib induced DILI has also been studied. Lapatinib is used to treat advanced breast cancer and has been associated with rare cases of ALT elevation and hepatobiliary ADRs. The authors found an association between the HLA-DQA1*02:01 allele and ALT increases when they assessed 37 cases and 289 controls. They replicated these findings in a set of 24 cases and controls.

The literature review yielded 26 relevant primary studies showing an association between HLA-B*58:01 and allopurinol severe cutaneous adverse reactions (SCAR). Patients with one or two copies of the HLA-B*58:01 allele may have an increased risk of Severe Cutaneous Adverse Reactions, such as Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis, when treated with allopurinol as compared to patients with no HLA-B*58:01:01 alleles or negative for the HLA-B*58:01 test. Other genetic and clinical factors may also influence a patient’s risk of allopurinol-induced adverse reactions.

It is currently recommended by the Panel of Antiretroviral Medications for Adults and Adolescents in the United States to screen for HLA-B*5701 in patients prior to abacavir initiation, and those who screen positive for the allele should not initiate abacavir. Positive status should be documented in the medical record as an abacavir allergy. The HLA-B*5701 testing is only needed once in a patient’s lifetime. If HLA-B*5701 screening is not available or in patients who have a negative test, patient counseling, clinical judgment, and appropriate monitoring are still critically important.

Carbamazepine can cause a wide variety of cutaneous adverse reactions including maculopapular eruptions and drug hypersensitivity syndrome including systemic manifestations of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis(TEN). Ten percent of patients develop mild cutaneous symptoms within three months of taking carbamazepine. The HLA-B*15:02 genotype has been associated with carbamazepine SJS/TEN. Highest risk individuals include Han Chinese descent as well as individuals from Vietnam, Cambodia, the Reunions islands, Thailand, India, Malaysia and Hong Kong. The FDA has updated the labeling for carbamazepine to include screening for HLA-B*15:02 allele prior to starting carbamazepine in patients who are the at-risk populations.
Table 1: Summary of therapeutic recommendations based on HLA-B genotype.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotypic implications</th>
<th>Therapeutic recommendations</th>
<th>Level of recommendation by CPIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noncarrier of HLA-B*15:02</td>
<td>Normal or reduced risk of carbamazepine-induced SJS/TEN</td>
<td>Use carbamazepine per standard dosing guidelines</td>
<td>Strong</td>
</tr>
<tr>
<td>Carrier of HLA-B*15:02</td>
<td>Increased risk of carbamazepine-induced SJS/TEN</td>
<td>If patient is carbamazepine-naive, do not use carbamazepine</td>
<td>Strong</td>
</tr>
<tr>
<td>Absence of *57:01 alleles</td>
<td>Low or reduced risk of abacavir hypersensitivity</td>
<td>Use abacavir per standard dosing guidelines</td>
<td>Strong</td>
</tr>
<tr>
<td>Presence of at least one*57:01 allele</td>
<td>Significantly increased risk of abacavir hypersensitivity</td>
<td>Abacavir is not recommended</td>
<td>Strong</td>
</tr>
<tr>
<td>Absence of *58:01 alleles</td>
<td>Low or reduced risk of allopurinol SCAR</td>
<td>Use allopurinol per standard dosing guidelines</td>
<td>Strong</td>
</tr>
<tr>
<td>Presence of at least one*58:01 allele</td>
<td>Significantly increased risk of allopurinol SCAR</td>
<td>Allopurinol is contraindicated</td>
<td>Strong</td>
</tr>
</tbody>
</table>

Adapted from CPIC guidelines.54,57,58

CONCLUSION

The science assessing the pharmacogenetics of ADRs is growing exponentially. This increase is driven by several factors. ADRs are a significant cause of morbidity and mortality in patients and this is associated with a significant increase in healthcare costs.1 In addition, ADRs such as DILI lead to early termination of a drug’s development or potentially withdrawal from the market after approval. Several pharmaceutical companies have joined together to form the Serious Adverse Event Consortium (SAEC). They are working together to discover novel genetic markers, such as HLA, that predict those patients at increased risk for ADRs to hopefully decrease market withdrawal and improve clinical drug development.

Pharmacogenetics is another tool pharmacists can use to predict those patients at highest risk for ADRs and manage these patients accordingly. The examples provided in this lesson are at varying levels of scientific development and clinical utilization. HLA typing prior to abacavir use has become standard of care, and assessment of G6PD is part of routine clinical practice. The other pharmacogenetic factors may not be routinely used in practice but represent the future of medical care.

UPCOMING TOPICS

• New – Approved Drugs
• Validation of Pain Medication Rx
• Pharmacy Considerations Regarding the Opioid Crisis of Abuse
• Vaccines—Truths, Myths, Hesitancy, Controversies
• Update C. diff—do probiotics and/or yogurt help?
REFERENCES


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LESSON EVALUATION
Please fill out this section as a means of evaluating this lesson. The information will aid us in improving future efforts. Either circle the appropriate evaluation answer, or rate the item from 1 to 7 (1 is the lowest rating; 7 is the highest).

1. Does the program meet the learning objectives?
   Define basic pharmacogenetics concepts YES NO
   Describe genetic contribution to ADRs YES NO
   Comment upon role of genetic variation in HLA system YES NO

2. Was the program independent & non-commercial? YES NO

3. Relevance of topic
   Low Relevance 1 2 3 4 5 6 7 Very Relevant

4. What did you like most about this lesson? ______________________________________________________________________________________

5. What did you like least about this lesson? ______________________________________________________________________________________

Please Mark the Correct Answer(s)

1. Which gene associated with ADRs is the most commonly found worldwide?
   A. CYP3A5*1
   B. HLA-B*5701
   C. G6PD deficiency
   D. CYP3A4*1

2. The mechanism for increased statin concentration in patients in the SEARCH study is:
   A. Metabolism by CYP2C9
   B. Reduced OATP transporter activity
   C. Increased OATP transporter activity
   D. HLA-B*5701 increased activity

3. Which of these has product labelling that includes pharmacogenetics testing?
   A. Clopidogrel
   B. Irinotecan
   C. Abacavir
   D. All of these

4. The genotypes associated with increased risk of Irinotecan toxicity include:
   A. UGT1A1*28
   B. CYP2C19*2
   C. SLCO1B1
   D. CYP3A5*1

5. Variants in CYP3A5 result in altered tacrolimus concentrations. CYP3A5 expressers require higher doses than non-expressers. Additionally, there is not a clear association between renal dysfunction and tacrolimus.
   A. True
   B. False

6. The polymorphisms associated with warfarin metabolism results in:
   A. Increased risk of time above goal INR
   B. Serious life threatening bleeding
   C. Reduced doses of warfarin
   D. All of these

7. The presence of HLA-B*5701 is associated with which of the following medications?
   A. Flucloxacillin
   B. Abacavir
   C. Amoxicillin-clavulanate
   D. Tacrolimus
   E. A and B

8. The risk factors for ADRs include:
   A. Drug interactions
   B. Age
   C. Environment
   D. Pharmacogenetics
   E. All of these

9. Which pharmacogenetics variable is associated with clopidogrel responsiveness?
   A. CYP2C19
   B. CYP3A4
   C. CYP3A5
   D. SLCO1B1

10. What percentage of Caucasians are considered CYP3A5 expressers?
    A. <1%
    B. 5-15%
    C. 45-73%
    D. 79%
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