Commentary

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Pharmacogenomics

Pharmacogenomics in liver transplantation: testing the recipient and the *ex-vivo* donor liver

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"While not a standard of care at this time, it certainly would be prudent to test the donor liver, *ex-vivo*, across a typical pharmacogene panel. Doing so before placement of the donor liver is an opportunity that should be strongly considered, if not outright adopted"

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The clinical utility of pharmacogenomics (PGx) has been documented across therapeutic areas and practice settings [1–3]. When considering peroral drug therapy, with PGx as a component of the overall information used in drug/drug-dose selection, the 'path' a drug must travel to eventually reach systemic targets needs to be understood. After ingestion of a given dosage form, the drug must first be in solution when exposed to the relatively large surface area of the small intestine, where enterocytes containing drug transporters and drug metabolizing enzymes (DMEs) can influence how much drug reaches portal blood flow [4]. The portal vein carries per orally administered medication to the liver, where the drug can be further influenced by transporters and DMEs [5]. Drug that escapes the liver and reaches systemic circulation, notwithstanding plasma protein binding, is able to eventually interact with its protein target to potentially elicit the desired clinical effect.

DNA sampling for pharmacogene testing in the liver transplant recipient

Acquiring a DNA sample for PGx testing is most typically accomplished by simple buccal swab collection of cheek cells. In most clinical settings, buccal swab collection of cells provides an adequate sample for analysis of DNA related to genes involved in response to a drug, in other words, pharmacogenes. This is not the case in the setting of liver transplantation (LTx; i.e., cadaveric, living donor, split graft), where the recipient's DNA is different from the DNA in the donor liver [6,7]. It is generally understood that systemic exposure to drugs is variable following LTx and may be unpredictable, with pharmacokinetics (PK) changing over time post-transplant [8–10]. The influence of both the recipient's DNA and the donor liver DNA contributes to the variability that may challenge providers in caring for LTx patients.

A typical PGx panel consists of numerous PK-related pharmacogenes, for example, *SLCO1B1*, *CYP2C9*, *CYP2C19*, *CYP2D6* – among others, as well as pharmacodynamic-related pharmacogenes, for example, *VKORC1*. However, currently fewer pharmacodynamic-related pharmacogenes are included in panels [1]. Additionally, specific panels may be utilized in a given setting, for example, psychiatry, where the drugs utilized may have specific pharmacogene interactions. In the case of LTx, PGx studies have been conducted in relation to immunosuppressant agents, specifically tacrolimus and cyclosporine. Specific genetic testing has noted that the **1* form of the *CYP3A5* pharmacogene of the recipient and the donor liver impacted the PK of tacrolimus in the setting of once daily dosing [11]. In pediatric LTx patients, those with the *CYP3A5*1* form present in the donor liver required higher tacrolimus doses [12]. Overall, nine different pharmacogenes have been associated with tacrolimus or cyclosporine dosing [13]. Certainly the narrow therapeutic ranges of tacrolimus and cyclosporine require specific dosing with consideration of pharmacogenetic variants as described. Furthermore, what about the exposure LTx recipients have

to other drugs? As the liver is the major organ related to drug metabolism, what are the potential consequences of differences in the recipient and donor liver pharmacogenes?

The two sets of pharmacogenes in the liver transplant recipient

Considering that a drug, administered via the peroral route, first is subject to the recipient's PGx (gastrointestinal track; GIT) and then the donor liver PGx; how might this affect the patient's overall exposure to a given medication? In terms of DMEs, using the CYP450 pharmacogene *CYP2C19*, with more than 30 known variants, as an example, five defined metabolizer phenotypes can be considered [14]. Full enzyme activity is expected in the normal metabolizer (NM), decreased enzyme activity is expected in the intermediate metabolizer (IM), while no, or little enzyme activity is expected in the poor metabolizer (PM). Relative to the NM, a rapid metabolizer (RM) is expected to have increased enzyme activity, whereas the ultrarapid metabolizer (UM) is expected to have increased enzyme activity beyond that of the RM [14]. Currently, approximately 40 drugs have evidence-based guidelines related to PGx, with many DME pharmacogene phenotypes defined as above [14].

The distribution of metabolizer phenotypes is related to the ancestral origin of the recipient and the donor of the liver. For instance, in the frequency of CYP2C19 metabolizer phenotypes in the North American/European population is approximately 39, 27, 2.5, 27 and 4.5% for the NM, IM, PM, RM and UM categories, respectively [14]. In the east Asian population, the frequency of CYP2C19 phenotypes is approximately 36, 47, 15, 2 and <1% for the NM, IM, PM, RM and UM categories, respectively [14]. Without testing the recipient and the donor liver, the combination of phenotypes would be difficult to predict.

Consider the following examples. While a buccal swab of the recipient may indicate that they are a CYP2C19 NM (i.e., *CYP2C19*1/*1*), with the expected GIT metabolism and presentation of substrate parent drug and metabolite(s) to the portal blood flow, systemic exposure may be quite different than expected as the influence of the donor liver PGx must be realized. If the donor liver metabolic phenotype is that of a PM (e.g., *CYP2C19*2/*2*), there would be the potential for greater systemic exposure to the parent drug. Conversely, if the donor liver metabolic phenotype is that of a UM (i.e., *CYP2C19*17/*17*), there would be the potential for decreased systemic exposure. Of course, these examples are not in the context of other physiologic (e.g., age), pathophysiologic (e.g., recovering liver function) and pharmacologic (e.g., drug interactions) considerations, which can also influence the response a patient has to medications. The point is that there are two sets of genetic influences in the LTx patient! Altered maintenance doses of medications based on inherent genetic variation have been noted and the variability, with multiple phenotype influence in the LTx patient is likely greater [15].

Impacting drug inefficacy & adverse drug events

In 2017, in the USA, there were more than 1.8 million adverse drug reactions reported through the US FDA adverse events reporting system [16]. Of these FDA adverse events reporting system reports, more than 900,000 were serious adverse events, meaning that the event results in death, is life threatening, requires hospitalization, or results in persistent or significant disability [16]. Of the more than 900,000 serious adverse events, more than 164,000 were deaths [16]. Pharmacogenomics has the potential to significantly decrease these numbers. An individual with variability in pharmacogenes is at risk for adverse drug events and this is compounded in the LTx patient, where two sets of pharmacogenes are influencing the response to medications. This information is imperative with regards to many drug–drug, and drug–drug–gene interactions in the LTx population. Most liver transplant recipients are on some type of antifungal regiment immediately post-transplant most commonly being the azole family which are known to have extensive interaction with calcinuerin inhibitors by the inhibition of CYP enzymes. Transplant physicians charged with managing complex drug regimens would be infinitely better equipped to appropriately dose patients in a safe therapeutic range as elevated levels of tacrolimus have a host of effects including but not limited to renal dysfunction and significant neurologic complications such as seizures and posterior reversible encephalopathy [17]. In a related approach, as hepatitis C is a recurring issue in LTx recipients, genotyping for the use of a direct acting antiviral agent is critical in guiding therapy, especially for individuals with genotype 1 HCV [18]. Also, considering that a significant percentage of patients across diagnoses, do not respond to the first drug therapy prescribed speaks to the need to include more patient-specific information to reach efficacy early on in therapy [19]. With multiple metabolic complications, including hypertension, diabetes and hyperlipidemia, among others facing the LTx recipient, it is anticipated that polypharmacy will occur and that these patients will also face inefficacy and/or adverse drug events [17,20].

The testing opportunity in liver transplantation

A unique opportunity exists to gain insight and utilize PGx to a greater degree in the LTx setting. While not a standard of care at this time, it certainly would be prudent to test the donor liver, *ex-vivo*, across a typical pharmacogene panel. Doing so before placement of the donor liver is an opportunity that should be strongly considered, if not outright adopted. The access to sample the donor liver after placement is essentially lost, unless an invasive procedure is undertaken. Currently studies are underway to build phenotype constructs of combinations of drug metabolism phenotypes in LTx patients. Ultimately, evaluations with probe drugs will lead to confirmation of the contribution of the recipient and donor liver pharmacogenes. The end result will be a more comprehensive approach to drug/drug–dose selection to optimize drug therapy for this complex patient population.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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