Pharmacogenomic considerations in a pretransplant statin tolerant, post-transplant intolerant liver transplant patient: A case report

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Abstract
As pharmacogenomics testing is becoming more common, it can be used in more medical settings to assist in clinical decision making. This is a case study examining the implications of a patient having potentially different cytochrome P-450 enzyme phenotypes in the donor liver once transplanted. This patient tolerated statin therapy prior to liver transplantation but was intolerant to the same statin after liver transplant.

Keywords: liver transplant, pharmacogenomics, PGx, statin therapy, myalgias

Introduction

Pharmacogenomics (PGx) is revolutionizing medication therapy management. We can now predict with increasing accuracy the potential for drug-gene interactions (DGIs) in patients to help guide medication therapy in preventing medication related problems (MRPs).[1-2] Using PGx helps eliminate trial and error prescribing to decrease office visits and communications regarding drug selection and dosing, drug-drug-gene interactions (DRGIs) and help eliminate other MRPs to improve patient outcomes.[1-2]

Using PGx clinically remains underutilized even though the science and testing have been available for some years.[3] PGx can guide therapies away from DGIs and DDGIs in advance of prescribing if test results are available. It can also explain why a MRP was experienced by a patient in the past, why a current medication is not working adequately or causing an adverse drug reaction (ADR).[1-2]

Cytochrome P-450 (CYP) genes are particularly important because they encode for CYP enzymes produced in the liver and intestinal tract and metabolize many medications on the market today.[4]

Important pharmacogenes in statin metabolism are CYP3A, SLCO1B1, ABCG2 and CYP2C9 in the case of rosuvastatin.[5-6]

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Liver transplant is a lifesaving process by which a portion of a living donor liver or a deceased donor's entire liver may be transplanted into another person with end stage liver disease.[7] After liver transplant, hepatic metabolic and transport capacity is determined by the donor liver. PGx testing conducted in the recipient pretransplant represents the recipient hepatic function which may be discordant with donor testing and function.[8-9] In theory, if one could obtain DNA from the liver donor, one could likely obtain a more representative phenotype of hepatic phenotype of the transplanted organ.[9]

To illustrate potential statin ADR risk, a case is reported here of a patient who had originally taken and tolerated low dose atorvastatin and then developed end stage liver disease, needing a transplant. The atorvastatin was stopped when the patient had liver failure and not started again until after transplantation. The patient encountered serious myopathies when the atorvastatin was restarted post-transplant and the patient was referred to the pharmacotherapy PGx service for consultation.

Case Report

Patient is a 49-year-old male recently transplanted with a liver from a deceased donor taking standard medications post-liver transplant including atorvastatin 10 mg but with daily fluconazole for a chronic fungal infection post-transplant. (Table 1) His tacrolimus dose had been titrated down to account for the CYP3A4/5 inhibiting fluconazole prior to restart of the atorvastatin 10 mg. The atorvastatin was soon discontinued post-transplant as a result of debilitating myopathies. The patient's provider was concerned about his blood lipids and still desired him to be on a statin.

Table 1

Medication	Dose	Time/freq.	Indication
Acetaminophen	500 mg	Take 500 mg by mouth every 6 (six) hours as needed for pain. Maximum 2 grams per day.	Pain
Amlodipine	5 mg	Take 5 mg by mouth daily.	Blood Pressure
Carvedilol	6.25 mg	Take 6.25 mg by mouth 2 (two) times a day with meals.	Blood Pressure
Esomeprazole	40 mg	Take 40 mg by mouth daily 30 minutes before morning meal.	GERD
Fluconazole	200 mg	Take 2 tablets (400 mg total) by mouth daily.	Antifungal
Tacrolimus	0.5 mg	Take 0.5 mg by mouth 2 (two) times a day.	Immunosuppression
Tacrolimus	1 mg	Take 1 mg by mouth 2 (two) times a day.	Immunosuppression
Ursodiol	500 mg	Take 1 tablet (500 mg total) by mouth 3 (three) times a day.	Bile ducts
Cholecalciferol (vitamin D3)	2,000 units	Take 2000 units by mouth daily.	Deficiency
Magnesium oxide	400 mg	Take 400 mg by mouth 2 (two) times a day.	Deficiency
Multivitamin	-	Take 1 tablet by mouth daily. At noon.	Supplement
Vitamin A	10,000 units	Take 1 each by mouth twice daily	Deficiency

After evaluation of the patient and pretransplant PGx report, the pharmacist determined the previous PGx report to be invalid because of the patient's liver transplant and now potentially different SLCO1B1 and CYP3A phenotypes. The lab used for this patient does not test ABCG2. The recipient phenotypes pretransplant for CYP3A4 (*1/*1), CYP3A5 (*3/*3), and SLCO1B1(*1/*1) were all normal. CYP3A5 (*3/*3) defines normal dosing guidelines even though this diplotype is phenotypically poor.[1] Post-transplant the patient now had different liver DNA that could potentially encode for CYP enzymes and SLCO1B1 differently than the original liver. PGx test results were not available from the donor. There was some concern with CYP3A4 inhibiting tacrolimus and fluconazole, so alternatives to CYP3A4/5 substrates were only considered as adjunct cholesterol medication treatment. Taking a liver biopsy to determine the DNA makeup and SLCO1B1 status of the transplanted liver was not desired by the transplant team so an empiric approach was used for an alternative lipid lowering agent.

Outcome

Since tacrolimus therapy was required and fluconazole change was not in the best interest of the patient because of being immunocompromised, rosuvastatin was recommended to avoid CYP3A4/5 interaction with the tacrolimus and fluconazole even though the new liver SLCO1B1 genotype status was unknown. A backup plan was in place to consider a protein convertase subtilisin/kexin type 9 (PCSK9) inhibitor such as evolocumab in case the rosuvastatin was not tolerated or ineffective. The change to rosuvastatin was successful and the patient currently has improved blood lipids with no myopathies.

Discussion

Rosuvastatin is not a CYP3A4/5 substrate but is still impacted by SLCO1B1 and only 10% metabolized by CYP2C9 with some CYP2C19 metabolism.[6] Much of rosuvastatin is also eliminated renally (10-28%) and through the fecal route(to 90%).[10] The patient's previous SLCO1B1 had normal functionality and the new liver status of SLCO1B1 was unknown but suspected to have potential decreased function because of the myalgias in the beginning. There was a choice between atorvastatin and the rosuvastatin with regards to CYP and non-CYP metabolism, but possibly no choice if the unknown SLCO1B1 status of the transplanted liver is decreased or a poor phenotype. CYP3A4 variants are rare and though CYP3A5 variants are more common, fluconazole was expected to overall have more inhibitory influence on the predominantly CYP3A4/5 metabolism in the atorvastatin rather than the lower percentage CYP2C9 metabolism in the rosuvastatin, so the rosuvastatin was recommended. It was also hoped that with a low percentage of patients overall having decreased or poor SLCO1B1 function, the chances of the transplanted liver having normal SLCO1B1 status were high compared to decreased to poor function.

After the above analysis and thought process, the pharmacist concluded there was CYP3A inhibition from the fluconazole of the atorvastatin and the myalgias were not from the new liver having decreased SLCO1B1 activity resulting in no myopathies.

Conclusion

Clinicians should consider validity of PGx testing after a liver transplant, knowing that a new liver from a genetic dissimilar liver donor may result in discordant DNA PGx results from a buccal DNA sample of the transplant recipient. CYP and other hepatic tissue genes such as SLCO1B1 can give paradoxical phenotypic results. In addition, normal due diligence of other, non-PGx factors should be considered when investigating a potential iatrogenic MRP.Acknowledgments: Eyob Adane, PhD (statistician)

Funding/Support: None

Disclaimer: The statements, opinions, and data contained in all publications are those of the authors.

Conflict of Interest: None

Treatment of Human Subjects: Per Mayo Clinic Florida policy, this research was considered not considered human subjects research.

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