

Pharmacogenomics in the Management of Pulmonary Arterial Hypertension: Current Perspectives

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Abstract: Pulmonary arterial hypertension (PAH) is a rare disease with heterogeneous causes that can lead to right ventricular (RV) failure and death if left untreated. There are currently 10 medications representative of five unique pharmacologic classes that are approved for treatment. These have led to significant improvements in overall clinical outcome. However, substantial variability in dosing requirements and treatment response is evident, leading to suboptimal outcome for many patients. Furthermore, dosing is empiric and iterative and can lead to delays in meeting treatment goals and burdensome adverse effects. Pharmacogenomic (PGx) associations have been reported with certain PAH medications, such as treprostinil and bosentan, and can explain some of the variability in response. Relevant genes associated with treprostinil include *CYP2C8*, *CYP2C9*, *CAMK2D*, and *PFAS*. *CYP2C8* and *CYP2C9* are the genes encoding the major metabolizing liver enzymes for treprostinil, and reduced function variants (*2, *3) with *CYP2C9* were associated with lower treatment persistence. Additionally, a higher *CYP2C9* activity score was associated with a significantly less risk of treatment discontinuation. Other genes of interest that have been explored with treprostinil include *CAMK2D*, which is associated with right ventricular dysfunction and significantly higher dose requirements. Similarly, *PFAS* is associated with lower concentrations of cyclic adenosine monophosphate and significantly higher dose requirements. Genes of interest with the endothelin receptor antagonist (ERA) class include *GNG2* and *CYP2C9*. A genetic variant in *GNG2* (rs11157866) was linked to a significantly increased rate of clinical improvement with ERAs. The *2 variant with *CYP2C9* (encoding for the major metabolizing enzyme for bosentan) was significantly associated with a higher risk for elevations in hepatic aminotransferases and liver injury. In summary, this article reviews the relevant pharmacogenes that have been associated to date with dosing and outcome among patients who received PAH medications.

Keywords: pulmonary hypertension, pulmonary arterial hypertension, pharmacogenomics

Introduction

Pulmonary arterial hypertension (PAH) is a rare and progressive disease with a complex pathobiology that results in increased pulmonary vascular resistance. Pulmonary vasoconstriction, vessel remodeling, and thrombosis are hallmarks of the disease resulting in neointimal proliferation and vaso-occlusive lesions.^{1,2} Ultimately, disease progression results in right ventricular failure and death if left untreated.^{1,3} The main heritable risk factor is bone morphogenetic protein receptor type 2 (*BMPR2*) which alters transforming growth factor beta (signaling). However, many other genetic risk factors have also been identified.² PAH can result from a heterogeneous group of disorders, including idiopathic and heritable forms, and associated conditions (ie, connective tissue diseases, infection, congenital heart disease, and drugs/toxins).³ Therapeutic targets address major pathways associated with PAH. An imbalance in vasodilators such as a deficiency of nitric oxide (NO) and prostaglandin I₂ (prostacyclin) and an excess of vasoconstrictors such as endothelin-1 (ET-1) contribute to vascular dysfunction. NO and prostacyclin also inhibit platelet activation and have antiproliferative effects, whereas ET-1 exerts mitogenic effects.^{1,3} Pharmacotherapeutic approaches to PAH are primarily based on clinical factors, such as disease severity, and dosing is empiric. However, an evolving understanding of

pharmacogenomics in this patient population offers the promise of a precision approach to treatment. Pharmacogenes of interest that influence the dosing and response to prostacyclins and endothelin receptor antagonists (ERAs) are key examples that will be highlighted.

Overview of Pharmacotherapy for PAH

Despite PAH being a rare disease, there have been more than 40 randomized clinical trials that have led to the regulatory approval of ten medications in five distinct pharmacologic classes over the past 25 years.⁴ Furthermore, these medications are commercially available by four routes of administration (intravenous, subcutaneous, oral, and inhaled). The nitric oxide (NO)-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) pathway can be enhanced through phosphodiesterase-type 5 inhibitors (PDE5i) (eg, sildenafil, tadalafil) and SGC stimulators (eg, riociguat). The endothelin-1 (ET-1) pathway can be attenuated through non-selective (eg, bosentan, macitentan) and selective (ambri-sentan) endothelin receptor antagonists (ERAs). Finally, the prostacyclin pathway can be augmented through prostaglandin analogues (eg, epoprostenol, treprostinil, iloprost) and selective IP receptor agonists (eg, selexipag).

Current PAH Treatment Paradigm

The current treatment paradigm for PAH entails multiparametric risk stratification to guide pharmacotherapy.⁴ Several variables are assessed, such as symptom progression, right heart failure, functional class, exercise testing, 6-minute walk distance performance, hemodynamics, cardiac imaging and biomarkers. Upon risk assessment, guidelines direct clinicians to several evidence-based medication options (monotherapy or combination) yet with similar levels of evidence.^{3,5} With the relative lack of head-to-head clinical comparisons within a given class or between classes, clinicians often select risk-appropriate medications based on factors such as dosing convenience, cost, and other patient preferences. Certain treatment tenets apply, such as the use of upfront oral combination therapy with a PDE5i plus an ERA as a first-line approach for most low-to-intermediate risk patients who are treatment naïve.^{3,6} Additionally, infusion prostacyclins are recommended for patients with more advanced symptoms of PAH based on their potency.^{4,7}

Variability in PAH Medication Response: A Basis for Pharmacogenomic Exploration

With significant advances in treatments for PAH, survival in the current era has dramatically improved in contrast to the early 1980s.^{8,9} However, clinical outcomes remain unsatisfactory and significant variability in response to these medications is apparent.¹⁰ The notion of “super responders” to PAH pharmacotherapy has been evident to clinicians for many years.⁵ While there is no consensus definition on this phenomenon, evidence for heterogeneity in response is apparent with several medication classes.⁵ Perhaps, the most notable example is the identification of patients (<10%) who have a positive response to long-term calcium channel blocker therapy (after meeting criteria based on vasoreactivity testing).^{11,12} These patients have a substantially better long-term prognosis than non-responders.¹² Prostacyclins are another important example of treatment response being highly patient dependent. Furthermore, factors that predict response are insufficiently understood.⁵ Epoprostenol is the most potent and efficacious treatment and typically used for those with the most advanced symptoms.⁴ However, some patients are able to survive long term, while others advance to right heart failure, transplant, or death despite treatment.¹³ Still, other patients are able to successfully wean off of epoprostenol and transition to other less potent, oral therapies.¹⁴ Regardless of response, the ability to predict whether (and to what extent) an individual patient will respond to a PAH medication, such as epoprostenol, carries important prognostic and treatment implications.¹⁵

The current treatment approach to PAH is iterative and empiric and largely determined by clinical risk stratification.⁴ Pharmacogenomics (PGx) provides a basis for understanding how genetics influences medication response.¹⁶ Currently, pharmacogenomic studies of PAH are relatively limited. However, genomic studies that provide insight into the disease process itself are more commonplace.^{17–19} A precision approach to PAH pharmacotherapy offers the promise of identifying those individuals most likely to have a favorable response with minimal adverse effects.^{20,21} Table 1 summarizes the pharmacogenes that have been associated to date with dosing and outcome among patients who received PAH medications.

Table I Pulmonary Hypertension Medications and Pharmacogenes of Interest

Medication	Gene	Variants	Functional Consequences
Treprostinil	<i>CYP2C8</i> <i>CYP2C9</i>	*3, *4 *2, *3	Reduced function Reduced function, ↓ treatment persistence, ↑ activity score associated with ↓ risk of treatment discontinuation
	<i>CAMK2D</i>	rs10023113	↑ <i>CAMKII</i> δ, RV dysfunction, ↑treprostinil dose needed
	<i>PFAS</i>	rs11078738	↓cAMP, ↑treprostinil dose needed
Bosentan, Ambrisentan	<i>GNG2</i>	rs11157866	↑ likelihood and rate of clinical improvement
Bosentan	<i>CYP2C9</i>	*2	↑ALT, AST, and liver injury

Note: Data from these studies.^{22–25,26}

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; *CAMK2D*, calcium/calmodulin dependent protein kinase II delta; cAMP, cyclic adenosine monophosphate; *CAMKII*δ, calcium/calmodulin-dependent serine/threonine kinase-δ; *CYP2C8*, cytochrome P450 2C8 isoenzyme; *CYP2C9*, cytochrome P450 2C9 isoenzyme; *GNG2*, G protein subunit gamma 2; *PFAS*, phosphoribosylformylglycinamide synthase; RV, right ventricular.

Treprostinil Metabolism and the Role of *CYP2C8/CYP2C9*

PGx variants that affect prostacyclin metabolism and transport have not been extensively studied. Treprostinil is a prostacyclin analogue approved for PAH and can be given subcutaneously, intravenously, inhaled, and orally.⁴ The hepatic cytochrome P-450 (CYP) isoenzyme system is the enzyme pathway responsible for treprostinil metabolism. Both the *CYP2C8* and *CYP2C9* isoenzymes are involved, although the medication is metabolized less extensively by *CYP2C9*. The CYP pathway is known to be polymorphic with variants in *CYP2C9* (*2 and *3 alleles) having population frequencies of approximately 35% in Caucasians.^{27,28} These alleles are associated with reduced or no function (intermediate or poor metabolizer phenotypes). Transporters also have the potential to affect medication response. ATP-binding cassette (ABC) transporters are transmembrane proteins that use ATP for the active transport of various medications, leading to their elimination. Multidrug resistance protein 4 (MRP4 encoded by *ABCC4*) is highly polymorphic transporter of treprostinil.²⁹

A single-center study explored the potential impact of PGx as a source of variability in treatment persistence and dosing with oral treprostinil.²² Treprostinil diolamine (Orenitram®) was the first oral prostacyclin approved for PAH. It can be appropriate for low-to-intermediate risk patients and in carefully selected and stable patients who seek to transition from infusion therapy.^{4,30} Although, like other prostacyclins, it is also associated with substantial interpatient variability in dose requirements and therapeutic response.^{30–33} Clinical outcomes are most optimal in those patients who can attain higher doses and remain on therapy long term; however, many develop intractable adverse effects (eg, gastrointestinal) or require a switch to other formulations.^{33–36} This study evaluated 15 patients who were newly started on oral treprostinil and those who switched from other treprostinil formulations (intravenous, subcutaneous, or inhaled). Variants in *CYP2C8*, *CYP2C9*, and *ABCC4* were associated with treatment persistence (defined as maintenance on medication without discontinuation). For *CYP2C8*, variants tested included *3 (rs10509681, rs11572080) and *4 (rs1058930) alleles that have an expected frequency of 10–20% in the Caucasian population. *CYP2C9* variants tested were the *2 (rs1799853, decreased function) and *3 (rs1057910, no function) alleles. Tested variants in *ABCC4* included rs1751034 and rs3742106 and have expected minor allele frequencies of 20% and 40%, respectively.³⁷ *CYP2C9* predicted phenotypes were based on diplotype to activity score mappings by the Clinical Pharmacogenetics Implementation Consortium (CPIC), in which *1 = 1, *2 = 0.5, and *3 = 0.²⁸ *CYP2C8* predicted phenotypes were determined to be intermediate or poor metabolizer status when one or two decreased or loss-of-function alleles were detected, respectively.

The study population included mostly Caucasian females and the majority were on a PDE5i and/or an ERA. Nine of 15 patients were on both a PDE5i and an ERA. The study group included both *de novo* patients and patients who were switched from other treprostinil formulations. Oral treprostinil dosing was highly variable with a more than four-fold difference in total daily dose requirements. Forty percent of patients stopped treatment, primarily owing to intractable adverse events. About 27% of patients had a variant in *CYP2C8* (*1/*3 or *1/*4), while 47% had a variant in *CYP2C9* (*1/*2, *1/*3, or *2/*2). Minor allele frequencies for *ABCC4* (rs1751034 and rs3742106) were 0.17 and 0.43,

respectively.²² Increased *CYP2C9* activity score was associated with decreased risk for treatment discontinuation (HR: 0.13; 95% CI: 0.02, 0.91; $p = 0.04$). In summary, patients with an estimated *CYP2C9* activity score of 2 were only 13% as likely to discontinue therapy compared to those with an activity score of 1. Eighty-three percent of patients with one or more decreased or no function alleles in *CYP2C9* stopped treatment due to adverse effects. In contrast, no association was seen between predicted *CYP2C8* activity and outcome. However, it should be noted that *CYP2C8* and *CYP2C9* are in linkage disequilibrium and both enzymes metabolize treprostinil which makes it challenging to determine which gene was responsible for the effect.³⁸ Although tested genetic variants were not associated with dose or frequency, the single lowest total daily dose was observed in the patient with *CYP2C9* *2/*2 (predicted intermediate metabolizer and in the lowest *CYP2C9* activity score (1) group).²⁸ A similar trend was found between alleles that predicted decreased *CYP2C8* metabolizer status (*3, *4) and dose.

In summary, this study concluded that PGx may be an important contributor to treatment persistence with oral treprostinil.²² Variants in the genes that account for treprostinil metabolism were highly prevalent. A significant association was seen between carriers of *CYP2C9* decreased function alleles and lower treatment persistence. Additionally, increased *CYP2C9* activity score was associated with lower risk for discontinuing treatment. Variants in the tested genes were not associated with dosing; however, this observation may have been subject to small sample size. Future studies should evaluate the impact of PGx on medication response and dosing with other PAH medications.

Other Genes Associated with Treprostinil Dose Requirements

A genome-wide association study (GWAS) was conducted by Thomeas-McEwing et al to explore predictors of a stable treprostinil dose.²³ Ninety-eight adult patients of European ancestry were treated with intravenous treprostinil and confirmed to be on their ultimate stable dose, defined as the dose at which the provider determined further titration would not result in clinical improvement, and the dose remained unchanged for at least 3 months. Broad genotyping was performed on the Illumina Omni Express array (Illumina, Inc., San Diego, CA, USA). Approximately 80% of the cohort was female, and about 50% had idiopathic PAH. The median dose (IQR) was approximately 70 (38) ng/kg/min. GWAS included 715,000 single nucleotide polymorphisms (SNPs). No SNP was associated with treprostinil dose at the conventional significance threshold ($p < 5 \times 10^{-8}$). However, five SNPs showed suggestive associations. Two SNPs of potential significance were chosen for further evaluation.

The first SNP (rs10023113) was in the myocardial contractility-regulating gene calcium/calmodulin-dependent serine/threonine kinase- δ (*CAMKII δ*) on chromosome 1. For each copy of the variant allele, the patient was found to require a dose of 26.3 ng/kg/min higher than the median dose for the cohort. *CAMK2D* is the gene encoding the *CAMKII δ* . When upregulated, this kinase reduces cardiac myofibril contractility. The functional consequence of this variant (frequency of 14%) was hypothesized to be increased *CAMKII δ* expression. This variant was explored in a separate registry by the study authors and found to be associated with greater right ventricular dysfunction as seen by higher right ventricular end-diastolic pressures and mean right atrial pressures. The authors hypothesized that this gene variant may be a marker for greater risk for right ventricular dysfunction, and that these patients might be more responsive to the pharmacologic effects of prostacyclins.

Another SNP of interest (rs11078738) was in the phosphoribosylformylglycinamide synthase (*PFAS*) locus on chromosome 17. This non-synonymous variant was associated with an increased dose of 20.7 ng/kg/min above the median for each allele. *PFAS* encodes for an enzyme necessary for purine biosynthesis, and prostacyclins regulate vasodilation by augmenting the production of the purine cyclic adenosine monophosphate (cAMP). The functional consequence of this variant (frequency of 24%) was hypothesized to be lower cAMP production. In response to stimuli from exogenous prostacyclins, those who carry this variant produce lower concentrations of cAMP. Therefore, the authors proposed that individuals who carry this gene variant may require higher doses of prostacyclins (or more rapid titration to higher doses) to achieve the target therapeutic effect.

In summary, this study identified genetic variants associated with decreased responsiveness to prostacyclins and more severe right ventricular dysfunction. The polymorphisms associated with treprostinil dose phenotype have a direct relation to the pharmacodynamic effects of prostacyclins. Therefore, the authors surmise that this observation could be

extended to other prostacyclins (epoprostenol, iloprost, beraprost) or prostacyclin receptor agonists (eg, selexipag) based on their individualized patient titration schema (with distributions of low-, medium-, and high-doses).²³

Endothelin Receptor Antagonists

ERAs are a commonly used medication class to treat PAH patients who are at low-to-intermediate risk of 1-year mortality.⁴ ERAs also provide a compelling use case for PGx. Endothelin-1 (ET-1) expression is increased in PAH and serves as a major contributor to the pathobiologic effects of vasoconstriction and smooth muscle cell proliferation that leads to disease progression.³⁹ ERAs improve exercise capacity, functional class, time to clinical worsening, and in some cases, a composite of PAH morbidity and mortality.^{3,40} However, interindividual variability in response to ERAs suggests possible genetic underpinnings.^{41–43} For example, the effect of ERAs is diminished in men compared to women and in Black versus White individuals.⁴⁴ Multiple genetic polymorphisms in genes regulating the ET-1 pathway, corresponding receptors (ET-1 A and B), and associated G-proteins involved in subcellular signaling processes have been suggested.²⁴

Benza et al conducted a large study (n = 715) to explore the interaction of ET-1 pathway polymorphisms and outcomes in European descent PAH patients who were treated with ERAs.²⁴ The genes studied were ET-1 (*EDNI*), the A and B receptors (*EDNRA* and *EDNRB*), and guanine nucleotide binding proteins (alpha, beta, and gamma subunits). These candidate genes in the ET-1 pathway were identified from an existing GWAS (global sites participating in the STRIDE trial of sitaxsentan).⁴⁵ Approximately 51% of patients received sitaxsentan (no longer available due to liver toxicity), 43% received bosentan, and 6% received ambrisentan.

A variant in the gene *GNG2* (rs11157866) associated with the G-protein complex had a significantly higher rate of reaching the first clinical improvement outcome measure (composite of improvement in 6-minute walk distance and functional class) at 12, 18, and marginally at 24 months. The minor allele frequency for this variant was 12.7%. Those who were homozygous for the minor allele T/T attained the improvement faster than individuals with other genotypes. The function of *GNG2* is related to proliferation, transcription, cell migration, inflammation, cellular apoptosis, and medication response. However, the specific effects in the context of ERA therapy remain uncertain. The authors concluded that ET-pathway-associated polymorphisms may help to predict the effect of ERA treatment for PAH.²⁴

Bosentan is an oral non-selective ERA that was the first in-class ERA approved for PAH.⁴⁶ However, its use is limited by a risk for liver toxicity manifested by increased aminotransferases in 10–12% of patients.^{46,47} Potential mechanisms of bosentan-induced hepatotoxicity are postulated to be due to a reduction in metabolism through cytochrome P450 isoenzymes (CYP) enzymes, a decrease in hepatic uptake by organic anion-transporting polypeptide (OATP) 1B1/1B3 (encoded by the *SLCO1B1/IB3* genes), and intra-hepatic bile acid accumulation (a result of bosentan inhibition of hepatic efflux transporters, such as the bile salt export pump [BSEP; encoded by *ABCB11*]) and multidrug resistance-associated protein 2 [MRP2; encoded by *ABCC2*]).^{48–53} Therefore, Markova et al explored associations between bosentan-induced liver injury and reduced-function single-nucleotide polymorphisms (SNPs) in genes that encode for proteins involved in the drug's disposition (*CYP2C9*, *CYP3A4*, *SLCO1B1* and *SLCO1B3*, *ABCB11*, and *ABCC2*).²⁵ A total of 92 ethnically diverse patients with PAH were studied; however, only the Caucasian group (n = 56) was of sufficient size for PGx analysis. In a multivariate model, *CYP2C9**2 was significantly associated with increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and medication-induced liver injury. This allele encodes for a variant with approximately 50% decreased function and is a common polymorphism associated with a poor metabolizer phenotype.²⁷ The minor allele frequency for this variant is 10–15% in Caucasian and Hispanic populations, in contrast to 4% in African-Americans and 0% in Asians.⁵⁴ The *CYP2C9**3 variant (characterized by almost complete loss of function) was not found to have an association with liver injury in this study; however, this may have been due to sample size limitations as this variant is less common than the *2 allele.^{25,54} The authors concluded that *CYP2C9**2 is a potential genetic marker for prediction of bosentan-induced liver injury.²⁵

A study by Seyfarth et al evaluated variants in *CYP2C9*, *ABCB11*, and *NR1H9* (major transcription factor for *ABCB11*) as possible risk factors for bosentan-associated cholestasis.²⁶ The study cohort included patients with (n = 23) and without (n = 25) aminotransferase elevations during bosentan therapy. The threshold for elevations in AST or ALT was >1.5 times the upper limit of normal. The investigators found no association between *ABCB11* and *NR1H9* variants and bosentan-induced liver injury. However, they did report an allele frequency for *CYP2C9**2 and *CYP2C9**3 of 52%

among those with increased transaminases compared to 24% for those without. Consequently, the odds ratio for bosentan-induced liver injury was 3.5 for carriers of these variants versus wild-type. In their initial analysis, they combined the *2 and *3 alleles. Upon evaluating each variant separately, they noted that only the *2 allele was associated with increased transaminases. The authors concluded that cholestatic liver injury from bosentan is a result of drug accumulation in those with the *CYP2C9**2 polymorphism. Bosentan continues to be an option in the ERA class even though newer and safer alternatives have been introduced, including ambrisentan and macitentan.

Discussion

Current evidence shows that PAH mortality remains unacceptably high despite significant advances in pharmacotherapy over the past 20 years.^{9,55,56} Conventional PAH treatment approaches rely on multiparametric clinical risk stratification, with infusion therapies recommended for patients with advanced symptoms.^{3,4} As a whole, the impact of PAH pharmacotherapy on the historical PAH disease surrogate of 6-minute walk distance improvement has been relatively modest.^{18,57} Despite the genetic underpinnings of PAH, no current therapies target these genes and a patient's individual molecular etiology or PGx does not determine treatment.⁵ Therefore, the current empiric approach to medication selection and titration remains the standard of practice.¹⁹ In these instances, prescriber and patient preference as well as convenience have dictated medication and formulation selection. Consequently, for patients with a poor response owing to adverse effects or no benefit, the time lost due to insufficient treatment leads to additional disease progression.^{1,10}

PAH is sufficiently diverse to merit the application of PGx.⁵⁸ Recent advances in the understanding of the PGx of prostacyclins and ERAs provide proof-of-concept towards predicting individual response. Substantial variability in dosing and treatment response with PAH medication classes is clinically evident, and implies an underlying role for genetic differences on the basis of medication response, PAH disease severity, or both. The identification of pharmacogenes of interest in PAH could help to enrich future studies by including those with an enhanced response (ie, "super responders").⁵ The advancement of PGx approaches to PAH care was highlighted by the National Heart, Lung, and Blood Institute and will therefore be a high priority for future research.^{18,20}

Conclusions and Future Directions

The field of PGx will continue to advance with increased applications in rare diseases such as PAH. Many of the summarized studies reported to date have yielded modest signals of association between genetic variants and clinical endpoints of interest.²³ However, these findings have generally not met conventional GWAS *p* value thresholds for statistical significance. Instead, findings that support molecular and clinical functional associations with genetic variants may be more feasible and of equal importance. This may be especially true for rare diseases such as PAH in which enrollment of significant numbers of patients is not possible.⁵⁹ Furthermore, true associations with complex phenotypes among variants with small to moderate effect sizes may be missed through GWAS.^{60,61} Replication, consistency of PGx association, and functional relevance are paramount to explain GWAS results.^{62–64} Additionally, focusing on more precise phenotyping to concentrate on a more limited contribution of genetic variants rather than the overall heritability of PAH as a complex disease itself will be important.^{65,66} Future investigations of PGx associations with treatment response in a wider population of real-world patients with PAH should be conducted. Prostacyclins are of high interest given their widespread use, multiple formulations, and significant cost.

Abbreviations

PAH, pulmonary arterial hypertension; PGx, pharmacogenomics.

Disclosure

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