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Precision Medicine and Personalizing Therapy in Pulmonary Hypertension: Seeing the Light From the Dawn of a New Era

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ABSTRACT
The initiation and progression of pulmonary hypertension (PH) and pulmonary arterial hypertension (PAH), two severe cardiopulmonary illnesses, are influenced by the interplay of many genes with behaviourial and environmental variables. The long-term survival rate is still inadequate, despite the fact that the introduction of therapeutic drugs that alter anomalies in the three main pathobiological pathways for PAH has completely changed the way we treat the disease. A growing body of research has shown that a variety of variables, including genetic variants that vary from person to person, influence clinical outcomes and therapeutic responses in PAH. Precision medicine, often referred to as stratified medicine or personalized medicine, offers a lot of potential benefits since it seeks to better focus interventions to the individual while optimizing benefit and reducing damage. Together with the potential and prospects for their usage in the near future, this page attempts to compile and explain the many projects that are now taking place in the PH/PAH sectors.

INTRODUCTION

Breathlessness, exhaustion, weakness, angina and syncope are among the nonspecific symptoms of PH that often take years to manifest, typically after the condition has progressed to a more severe state. PH occurs in a wide range of disorders and may be caused by either pre-capillary (arterial) or post-capillary (venous) pathogenic processes[1,2]. A clinical classification was developed using a precision medicine approach since the second world symposium on PH was held in Evian in 1998. This classification aims to individualize and group together various categories of PH that share similar hemodynamic criteria, types of pulmonary vascular lesions and similar management[1,2]. In fact, the current clinical classification for PH includes four different disease categories: PH associated with left heart disease (group 2), PH associated with lung diseases and hypoxia (group 3), PH due to chronic thromboembolism (group 4) and PH due to unclear multi factorial mechanisms (group 5). This splits conditions with a predominantly pulmonary arterial disease component (group 1, also known as pulmonary arterial hypertension (PAH)) from those with a predominantly pulmonary arterial disease component (group 1). In addition to enabling a quicker introduction of tailored therapy, preventing damage and boosting benefit, this clinical PH categorisation method is generally acknowledged and utilized in the day-to-day work of PH specialists. It also facilitates outcome prediction and research plans. This "one size fits all" strategy, however, is not the best for selecting therapy for individual patients., instead, it produces an average treatment result for the average patient. It's likely that certain patient groups in a clinical study may react very well to a medication, while other patient groups will either respond badly or worsen. Although there are still a number of obstacles to overcome, the next stage would be to use biomarkers, proteomics and genomes to further create precision medicine techniques that would result in personalized medication for PH patients. This review's goal is to provide a concise summary of the body of available research while also summarizing some of the most prevalent difficulties. The implementation of customized anti hypertensive treatment requires overcoming obstacles. There is a tendency to approach hypertension treatment algorithms on a population-based basis due to the high incidence of hypertension. In fact, using data from the ACCORD trial, the Eighth Joint National Committee (JNC 8) loosened and simplified therapeutic goals[3,4]. In previous JNC revisions, several of the disease-specific blood pressure (BP) limits were eliminated. The SPRINT study has since forced a reevaluation of blood pressure goals in high-risk people[5]. The American Heart Association/ American College of Cardiology Task Force has proposed stricter blood pressure objectives based on SPRINT data[6]. JNC 8 only suggested four kinds of first-line drugs for agent selection: angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), angiotensin converting enzyme inhibitors (ACEIs) and thiazide-type diuretics. The only real personalisation was the prioritisation of ACEI and ARB use in people with chronic kidney disease and the opposite for people over 75 and people of African-American (AA) heritage. It's possible that race acted as a stand-in for genetic markers of anti hypertensive class response. The Pharmacogenomics Research Network, International Consortium for Anti hypertensive Pharmacogenomics Studies (ICAPS) and other contributors have produced strong evidence showing the interaction of genotype with anti hypertensive agent response, which is in contrast to the dominant population-based algorithms[7]. A person's reaction to a certain blood pressure medicine or class may be predicted using the variations that have been found. Overall, nevertheless, these exchanges have fallen short of CPIC's evidential requirements. Expert agreement on dosage recommendations has not been reached for the majority of agents. The polygenic nature of anti hypertensive drug response, population heterogeneity, population size, poly pharmacy, varying clinical trial designs with relatively small patient populations, the small effect size of individual variants and the relative lack of major anti hypertensive drug toxicities are all contributing factors. Overcoming therapy noncompliance[8], great inter-and intra-patient BP variability[9,10] and differences in BP measurement strategies[11,12] may be of equal or greater importance in improving clinical effectiveness than genotype-guided prescribing. Provider inertia is an additional barrier due to a lack of familiarity with pharmacogenomics[13,14]. Clinicians may believe they have "individualized" anti hypertensive treatment even before genotype-phenotype relationships were discovered because of the wide variety of anti hypertensive medications available. Therefore, until further replication and validation are carried out, the use of Pharmacogenomics data to hypertension treatment has been put on hold.

Body: Numerous genetic variations and loci have been shown to predict the response to beta-blockers (Table 2), hydrochlorothiazide (HCTZ) (Table 1) and CCBs or rennin-angiotensin system inhibitors (Table 3). Numerous Pharmacogenomics cohorts and trials, such as the Pharmacogenomics Evaluation of Anti hypertensive Responses (PEAR), the Genetic Epidemiology of Responses to Anti hyper tensives (GERA) study, the Genetics of Drug Responsiveness in Essential Hypertension (GENRES) study, the SOPHIA study, the Milan Hypertension Pharmacogenomics of Hydrochlorothiazide (MIHYPHCTZ), the

Pharmacogenomics of Hydrochlorothiazide Sardinian Study (PHSS), the Nordic Diltiazem (NORDIL) Study, the International Verapamil SR Trandolapril (INVEST) Study, the Campania Salute Network (CSN), the Nordic Diltiazem (NORDIL) Study, the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) and GenHAT[15]. The use of genetic testing for anti hypertensive drugs in clinical practice is made much more difficult by the polygenic character of their effectiveness. As of yet, no comprehensive multigene model has been created to guide drug selection or dosage for these medications.

Genetic Epidemiology of Responses to Anti Hypertensive: These multi-ethnic prospective cohort studies, known as the Genetic Epidemiology of Responses to Anti hypertensive (GERA1 and GERA2) investigations, were the first pharmacogenetics research in anti hypertensive drugs and look at the inter individual variability of response to these drugs[16,17]. GERA1 assessed 505 patients' (280 Caucasian and 225 AA) responsiveness to 4 weeks of HCTZ monotherapy after a 4-week washout. GERA2 evaluated the response to candesartan monotherapy in 439 White and AA persons. Both discovery and replication studies have made use of the GERA cohorts. Pooling these studies has been crucial for boosting the sample size to facilitate identification and increase the generalizability of any found variations, since many original cohort studies featured several medicines or participants from diverse ethnic backgrounds.

Genetics of Drug Responsiveness in Essential Hypertension and Losartan Intervention For Endpoint Reduction in Hypertension: The GENRES trial was a single-center crossover that was controlled with a placebo. 228 Finnish males were among the subjects, and they were given amlodipine, bisoprolol, HCTZ, or losartan as monotherapy in a sequential but randomised sequence[18]. In contrast to PEAR and GERA, the research used 24-hour ambulatory blood pressure monitoring rather than measuring blood pressure at home or at work. The missense variable rs3814995 in nephrin (NPHS1), which is enriched in the Finnish population and linked to losartan responsiveness, was crucially discovered by the GENRES project[19]. The GERA2 and SOPHIA cohorts were the first to duplicate this variation. Later, the Losartan Intervention for Endpoint reduction in hypertension (LIFE) trial, another Finnish cohort study that included both men and women, looked at 927 patients' responses to atenolol and losartan[20]. Unlike GENRES, LIFE was retroactively collected and did not incorporate an a priori Pharmacogenomics result.

How Could Precision Medicine Add to Current PAH/PH Management?: Efficient clinical decision-making to deliver the appropriate treatment plan for a patient based on his or her unique features is the aim of personalized medicine. Each patient is categorised into a sub population based on their response to therapy and likelihood of developing a certain illness or phenotype. The more ambitious field of precision medicine includes both illness prevention and therapy based on individual genetic, environmental and lifestyle variations. The availability of molecular profiling tests for a specific clinical disease is a prerequisite for this novel technique. Precision medicine is achievable, as shown by the development of immunotherapy and targeted treatments for the treatment of cancer. Regardless of location or histological examination, this new method has made it possible to introduce cancer medications and therapies more quickly based on the molecular profile of the disease. Despite advancements in medical therapy, the 5-and 7-year survival rates for people with idiopathic /heritable PAH are 57% and 49%, respectively, from the time of diagnostic right-sided cardiac catheterisation[21]. Although there are parallels between PAH and cancer, such as the changed interaction between cells from various tissue types, the inexplicable proliferation and survival of endothelial and pulmonary smooth muscle cells, the metabolic (glycolytic) alterations and the immune system link, PAH is not a cancer[22]. In the absence of significant pulmonary parenchyma alterations or embolic events, PAH is marked by vasoconstrictor, cell accumulation in the vascular wall and intimal thickening of the small- to medium-sized pulmonary arteries ≥500μm)[22-26]. The primary effect of current PAH-specific treatments is to relax the pulmonary arteries. Calcium channel blockers may relax the pulmonary vascular smooth muscle in a limited subset of PAH patients who react to acute vasodilator. The majority of patients, however, are treated with certain drugs that have been authorised by the US Food and Drug Administration (US FDA) to modify anomalies in the three main pathobiological routes for PAH: the endothelin, prostacyclin and nitric oxide pathways. If treatment fails or the condition worsens, lung transplantation is the final resort.

Is Precision Medicine Ready for Use in PAH/PH?: In PH/PAH, precision medicine is not a very novel practice. For many years, the treatment of individuals with PAH has been guided by pulmonary vasodilator testing for inhaled nitric oxide. It is well recognized that patients who fulfil vasoreactive criteria during right heart catheterisation will respond well to oral calcium channel blockers over the long run and will live longer[26,27]. Although precision medicine has the potential to significantly enhance the care of PH/PAH, many obstacles need to be overcome before precision medicine techniques can be widely used. First, a deeper understanding of the potential role that

modified immune responses may play in the beginning, continuation and exacerbation of PAHs is required. It is now well known that PH/PAH is significantly influenced by altered immunological and inflammatory pathways, which attract inflammatory cells, modify the pulmonary vasculature and stimulate autoimmune reactions. In fact, there is intricate interaction between PAH and chronic infections (such HIV, bilharzia and human herpes virus type 8) or autoimmune diseases (including systemic lupus erythematosus, Sjögren's syndrome, scleroderma and thyroiditis). A different outcome from idiopathic PAH may result from the specialized care of certain of these clinical manifestations. For instance, some individuals with lupus or mixed connective tissue disease-associated PAH may be able to reverse their pulmonary vascular disease with immunosuppressive drugs, while systemic sclerosis-associated PAH does not show this kind of reaction to immunosuppressive drugs[28]. Certain types of PAH that are linked to immunological diseases and an inflammatory component that most likely plays a significant role have also been shown to have a unique response to certain PAH medications (such as endothelin receptor antagonists). Therefore, it has been shown that individuals with cirrhosis or HIV have had normalization or quasi-normalization of resting haemodynamics[29,30]. Simonneau G, Adatia I, Gatzoulis MA, *et al.* updated pulmonary hypertension clinical categorisation. D34-D41 in J Am Coll Cardiol. 2013., 62: 25 Suppl.

Expert Commentary: This study demonstrates that some SNPs in genes have been shown to have biological plausibility for a function in hypertension, blood pressure response, or, alternatively, cardiovascular and mortality risk. Since all of the pharmacogenetics research presented in this study needed a minor allele frequency of >0.05, it is not unexpected that the platforms employed would not catch these variations, since only uncommon variants would have a high impact size. The usefulness of many SNPs working together to provide meaningful measurements of the interindividual variability of blood pressure response to several types of anti hypertensive medications is strongly supported by this research. Furthermore, even if there is already evidence of adverse events associated with anti hypertensive treatment, it is quite possible that many additional problems pertaining to the genetic prediction of anti hypertensive drug safety will surface in the future. The two largest obstacles to finding genetic predictors of BP response are power and replication. As stated in this research, combined cohorts are restricted mainly by study design variability that affects patient characteristics, pre-study medication withdrawal techniques and study drug duration and dosage.

CONCLUSION

Over the last several years, interest in the potential of precision medicine has increased dramatically. Even if the conversion of these technologies into clinical tools is taking a while, the PH/PAH area now has a number of new clinically actionable tools that are helpful for precision medicine and their applications are likely to grow in the near future.

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