CHEST

Ineffectiveness of Sotatercept Therapy in a Patient With Heritable Pulmonary Arterial Hypertension Associated With a Previously Unreported Missense Variant in *GDF2*, the Gene for Bone Morphogenic Protein-9

David Langleben, MD; Lyda Lesenko, RN; Benjamin D. Fox, MD, PhD; Shaun Eintracht, MD; William D. Foulkes, MBBS, PhD; and David S. Rosenblatt, MD

Pulmonary arterial hypertension (PAH) frequently is associated with an imbalance in antiproliferative bone morphogenic protein-2 receptor signaling and proproliferative type-II activin receptor signaling, favoring the latter. Sotatercept is an activin ligand trap that reduces the dominant detrimental activin signaling and provides clinical benefit. We report a patient with heritable PAH in whom sotatercept had neither positive nor negative effects; we relate that fact to his PAH being caused by a previously unreported variant of unknown significance (c.1276T>C, p.[Cys426Arg]) in the *GDF2* gene. *GDF2* encodes bone morphogenic protein type-9, the presence of which is required for proper functioning of the pulmonary microvasculature. Low levels of functionally active bone morphogenic protein type-9 contribute to PAH. As we enter an era of precision medicine for patients with PAH with increasingly costly therapies, genetic screening may direct appropriate therapy and limit the use of expensive but likely ineffective therapies.

CHEST 2025; 167(2):e37-e39

KEY WORDS: activin; bone morphogenic protein; pulmonary arterial hypertension; sotatercept; telangiectasia; variant

Pulmonary arterial hypertension (PAH) results from occlusion of precapillary arterioles by cellular proliferation.[1] Reduced antiproliferative bone morphogenic protein (BMP) receptor-2 (BMPR2) signaling and heightened proproliferative type-II activin receptor signaling are important contributors to PAH pathogenesis.[2] Sotatercept, a ligand trap for activins and growth differentiation factors (GDF) that improves the antiproliferative/proproliferative imbalance, is clinically approved.[3] Studies suggest a high clinical response rate to sotatercept, when added to other approved background PAH therapies.[3] We present a patient in whom sotatercept had no clinical or hemodynamic effect.

Case Report

The patient presented in September 1998 at age 41 years with symptomatic idiopathic PAH for 7 months, without telangiectasia or arteriovenous malformations.

ABBREVIATIONS: BMP = bone morphogenic protein; BMPR2 = bone morphogenic protein receptor-2; BMP9 = bone morphogenic protein-9; GDF = growth differentiation factor; PAH = pulmonary arterial hypertension; VUS = variant of unknown significance

AFFILIATIONS: From the Center for Pulmonary Vascular Disease, Division of Cardiology (D. L. and L. L.), the Division of Medical Biochemistry (S. E.), and the Division of Medical Genetics (W. D. F. and D. S. R.), and the Lady Davis Institute for Medical Research (D. L. and W. D. F.), Jewish General Hospital, McGill University, Montreal, QC, Canada; and the Division of Pulmonary Medicine (B. D. F.), Yitzhak Shamir Hospital and Tel Aviv University, Tzrifin, Israel.

CORRESPONDENCE TO: David Langleben, MD; email: david.langleben@mcgill.ca

DOI: https://doi.org/10.1016/j.chest.2024.09.002

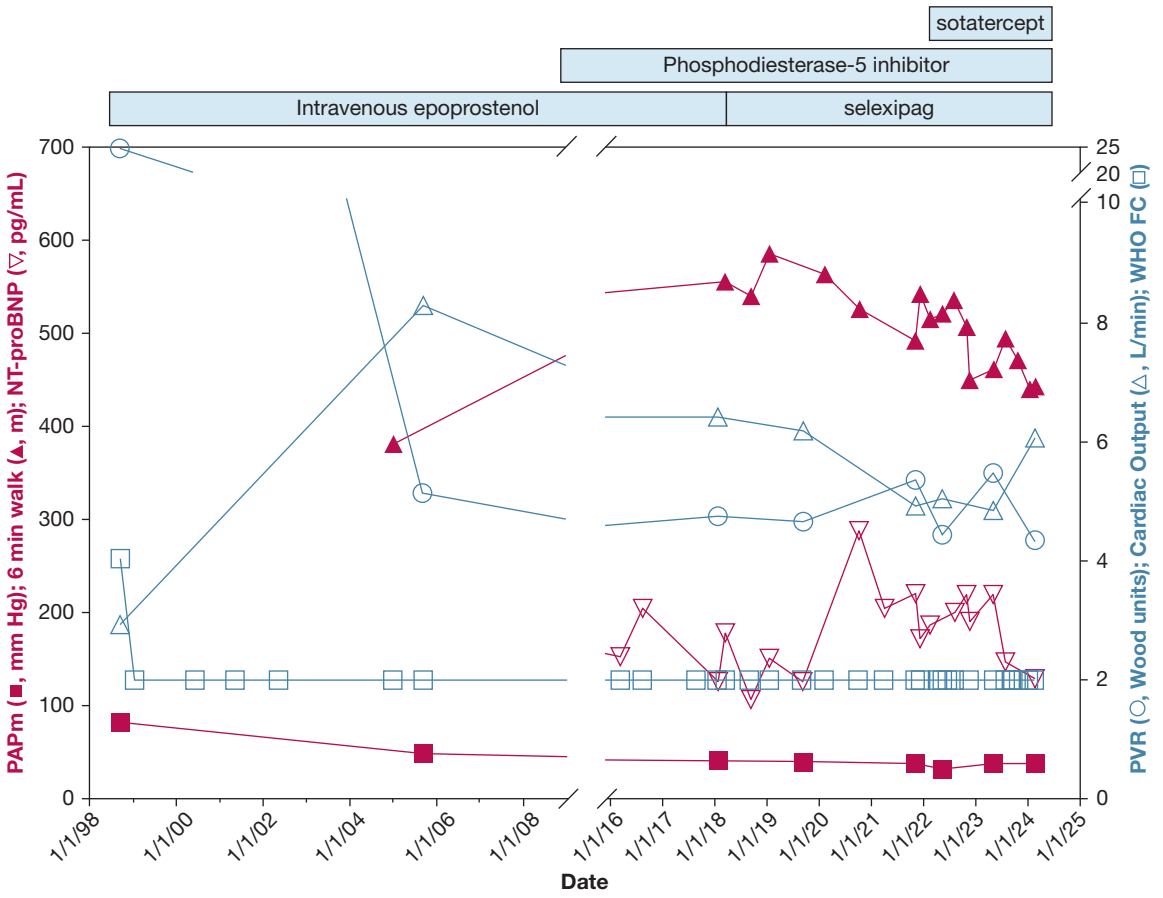

Figure 1 – *Mean pulmonary artery pressure (black square); 6-min walk (black triangle); N-terminal pro Brain Natriuretic Peptide (clear inverted triangle); Pulmonary vascular resistance (clear circle); cardiac output (clear triangle); World Health Organization Functional Class (clear square); as a function of date on the abscissa. Medications are displayed in the boxes at top. NT-proBNP = N-terminal pro brain natriuretic peptide; PAPm = pulmonary artery pressure; PVR = pulmonary vascular resistance; WHO FC = World Health Organization functional class.*

He escaped Vietnam in 1983. A sister in Vietnam experienced PAH in 2004 and died in June 2007 at the age of 59 years. Six other siblings were alive, aged 65 to 80 years. Both parents died (ages 55 and 56 years) without cardiorespiratory illness. No other people in his family had received genetic testing, but the fact that his sister was similarly affected strongly suggested that his PAH was attributable to Mendelian factors. He began IV epoprostenol in 1998 (Fig 1) and phosphodiesterase-5 inhibition in 2009 and transitioned from epoprostenol to selexipag in 2018. In 2020, a heterozygous variant of unknown significance (VUS) was detected, c.1276 T>C, p.(Cys 426 Arg) in the *GDF2* gene, which encodes for bone morphogenic protein-9 (BMP9).

This variant is classified as a VUS because the only American College of Medical Genetics and Genomics codes that can be applied are PM2-supporting and PP3. Notably, this variant very likely disrupts a disulphide bond between the cysteine at amino acid 426 with the cysteine at amino acid 356; the Rare Exome Variant Ensemble Learner score is 0.951, which strongly suggests that the variant is functionally disruptive. The Sorting Intolerant From Tolerant scores the variant as deleterious, and Polymorphism Phenotyping (PolyPhen) indicates it is "probably damaging." It is not present in either gnomAD v.4.1.0 or ClinVar (accessed August 14, 2024). Thus, although the variant remains a VUS, the data point towards a reclassification in the future to likely pathogenic.

Sotatercept was started in November 2022. There were subsequently no improvements in clinical parameters, symptoms, or hemodynamics and no changes in hemoglobin level or platelet level or sotatercept dose adjustments, as have been described in published studies.[3] No new cutaneous or nasopharyngeal telangiectasias were detected during or after the treatment. Sotatercept was stopped in February 2024.

Discussion

Sotatercept therapy provides significant clinical benefit, with a large reduction in risk of deterioration.[3] Patients with known heritable PAH benefit from sotatercept.[3] Most of those patients would likely have had pathogenic variants in the gene *BMPR2*, coding for a type II BMP receptor, BMPR2.[4] Decreased BMPR2 signaling allows for disproportionate activin and GDF signaling via type II activin receptors (A and B), which results in pulmonary microvascular cell proliferation. Sotatercept binds to the activins and GDFs, reducing their signaling.

GDF2 pathogenic variants that cause PAH have been reported, with a prevalence of approximately 1.5%.[5-8] BMP9 normally induces endothelial quiescence and binds with high affinity to the activin like kinase 1/BMPR2 receptor complex. Decreased BMP9 levels, or its dysfunction as a ligand, would result in decreased BMPR2-complex signaling and enhanced activin type-II receptor activation, causing typical PAH. We hypothesize that sotatercept's binding of activins may simply be insufficient to overcome the effects of reduced BMPR2 signaling because of decreased BMP9. However, BMP9 also binds with high affinity to type-II activin receptors[9] and might represent an important ligand for activation of those receptors, particularly during reduced functioning of the BMPR2 system. By contrast, in this patient with a suspicious VUS in the *GDF2* gene, dysfunctional or decreased BMP9 would result in BMP9 being unable to counteract over-active type-II activin receptor signaling in a disease state. In that case, the addition of sotatercept, which acts as a ligand trap for activins that include BMP9, would have imperceptible effects, because the BMP9 was already absent or dysfunctional. *GDF2* variants have also been reported to induce the phenotype of hereditary hemorrhagic telangiectasia. The patient had no findings of hereditary hemorrhagic telangiectasia, prior to or after sotatercept.

This first, to our knowledge, report of sotatercept treatment in a patient with a previously unreported *GDF2* VUS suggests that the effectiveness of sotatercept should be verified in other patients with PAH caused by *GDF2* variants, even if they are not definitely likely pathogenic or pathogenic. As we enter an era of increasingly personalized precision care for PAH, genetic screening of patients with "idiopathic" disease will help to identify those patients who may be unresponsive to a particular medication, thus preventing unneeded use and unnecessary cost and reducing lost time for patients who might receive other effective therapy.

Financial/Nonfinancial Disclosures

The authors have reported to *CHEST* the following: D. L. has served as a consultant, speaker, data safety committee member, or has conducted clinical trials for Acceleron/Merck, Aerovate, Bayer, Gossamer Bio, Janssen, Phasebio. B. D. F. has served as a consultant to MSD. None declared (L. L., S. E., W. D. F., D. S. R.).

Acknowledgments

Author contributions: D. L. had full access to all the data in the study and takes responsibility for the content of the manuscript including data analysis. L. L., B. D. F., S. E., W. D. F., and D. S. R. contributed substantially to the project design, data analysis and interpretation and to the writing of the manuscript

Other contributions: The authors thank Claire Shovlin, MBBS, PhD, and David Szlachtycz, MSc, for their advice on interpretation of the c.1276T.C, (p.Cys426Arg) variant of unknown significance in the *GDF2* gene. *CHEST* worked with the authors to ensure that the Journal policies on patient consent to report information were met.

References

1. Humbert M, Guignabert C, Bonnet S, et al. Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. *Eur Respir J*. 2019;53(1):1801877.
2. Morrell NW, Aldred MA, Chung WK, et al. Genetics and genomics of pulmonary arterial hypertension. *Eur Respir J*. 2019;53(1):1801899.
3. Hoeper MM, Badesch DB, Ghofrani HA, et al. Phase 3 trial of sotatercept for treatment of pulmonary arterial hypertension. *N Engl J Med*. 2023;388(16):1478-1490.
4. Welch CL, Aldred MA, Balachandar S, et al. Defining the clinical validity of genes reported to cause pulmonary arterial hypertension. *Genet Med*. 2023;25(11):100925.
5. Graf S, Haimel M, Bleda M, et al. Identification of rare sequence variation underlying heritable pulmonary arterial hypertension. *Nat Commun*. 2018;9(1):1416.
6. Wang XJ, Lian TY, Jiang X, et al. Germline BMP9 mutation causes idiopathic pulmonary arterial hypertension. *Eur Respir J*. 2019;53(3):1801609.
7. Grynblat J, Bogaard HJ, Eyries M, et al. Pulmonary vascular phenotype identified in patients with GDF2 (BMP9) or BMP10 variants: an international multicentre study. *Eur Respir J*. 2024;63(4):2301634.
8. Hodgson J, Swietlik EM, Salmon RM, et al. Characterization of GDF2 mutations and levels of BMP9 and BMP10 in pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2020;201(5):575-585.
9. Li W, Quigley K. Bone morphogenetic protein signalling in pulmonary arterial hypertension: revisiting the BMPRII connection. *Biochem Soc Trans*. 2024;52(3):1515-1528.