SCIEPublish

Commentary

Commentary on "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"

Shao-Fei Liu [1,*,†], Meng-Yu He [2,†] and Wolfgang M. Kuebler [3,*]

[1] Department of Cardiology, Changhai Hospital, Naval Medical University, Shanghai 200433, China
[2] Department of Pulmonary and Critical Care Medicine, The First Affiliated Hospital with Nanjing Medical University, Nanjing 210029, China; myhe@njmu.edu.cn (M.-Y.H.)
[3] Institute of Physiology, Charité-Universitätsmedizin Berlin, 10117 Berlin, Germany

* Corresponding author. E-mail: liushaofei_med@163.com (S.-F.L.); wolfgang.kuebler@charite.de (W.M.K.)

† These authors contributed equally to this work.

Received: 15 March 2025; Accepted: 31 March 2025; Available online: 1 April 2025

We have read with great interest the case report by David Langleben and colleagues, which describes the ineffectiveness of sotatercept in a patient with heritable pulmonary arterial hypertension (HPAH) who carried a missense mutation in the *GDF2* gene (*BMP9*, c.1276 T>C, p. [Cys 426 Arg]) [1]. Although caution is required when drawing general conclusions from findings in a single patient, the reported case study may add novel insights to our understanding of the complex interplay between genetic mutations and targeted therapies in PAH. Currently, more than 50 cases of *GDF2* mutations have been reported in PAH patients [1–12], with studies suggesting that *GDF2* mutations account for approximately 1% of all adult PAH cases [13]. BMP9, encoded by *GDF2* and acting via the heteromeric receptor ALK1/BMPR2 is a key agonist of the BMP signaling pathway and crucial for maintaining vascular integrity [14]. In the reported case, the mutation was classified as a variant of uncertain significance (VUS), and its exact pathological consequences remain unclear. Previous studies indicate, however, that *GDF2* mutations can lead to either loss of function or the production of aberrant proteins, thereby disrupting normal vascular homeostasis [5].

In the specific case reported by Langleben and colleagues, several potential causes for the ineffectiveness of sotatercept may be considered:

1. Advanced Pulmonary Vascular Remodeling

In the respective patient, PAH was initially diagnosed in 1998 at the age of 41. As a result, the patient had experienced disease progression for more than two decades in spite of aggressive treatment with intravenous epoprostenol (since 1998), PDE-5 inhibitors (since 2009), and selexipag (since 2018). By the time sotatercept treatment was initiated in 2022, the patient's pulmonary vascular resistance (PVR) had already exceeded 4 Wood units (WU), indicating extensive and likely irreversible pulmonary vascular remodeling. It seems fair to consider that any additional therapeutic intervention, including sotatercept, may no longer be effective in reversing the disease course at this advanced stage. The findings of the initial phase 3 trial of sotatercept in PAH patients, however, showed an improvement in exercise capacity in patients with an even higher mean PVR of >9 WU and a long PAH history of 9.2 ± 7.3 years (mean ± SD), and thus, argue against such an explanation [15]. PAH patients have significantly elevated plasma levels of activin A (583.7 ± 46.5 pg/mL) and activin B (121.9 ± 6.7 pg/mL) compared to healthy controls, and the demonstrated effectiveness of sotatercept in the initial multicenter trials suggests that sotatercept is able to target such levels [16].

https://doi.org/10.70322/jrbtm.2025.10003

Furthermore, the initial phase 3 trial also indicated that sotatercept, when added to stable background therapy—whether dual or triple therapy—can further enhance treatment efficacy and improve patient outcomes. This suggests that sotatercept may provide additional therapeutic benefits even in patients receiving optimized PAH therapy.

2. Distinct Signaling Pathways

Sotatercept aims to balance homeostatic BMP9/BMPR2 signaling against disease-promoting activin/TGFR-β signaling. This strategy may be effective in conditions where activin ligand levels are elevated, as sotatercept can counteract their pathological effects. However, in cases where BMPR2 signaling is insufficient or absent, the drug may be ineffective, as its mechanism of action relies on the presence of an—at least partially—functional BMP9/BMPR2 axis. While this provides a logical explanation, it remains unclear why sotatercept is not similarly ineffective in patients with BMPR2 mutations.

3. Potential Complex Effects of *GDF2* Mutations

GDF2 mutations not only reduce BMP9 protein levels and impair BMP signaling but may also lead to the production of aberrant BMP9 proteins with unknown effects. At present, our understanding of how BMP9 mutations drive PAH is still rudimentary. The dual nature of BMP9 signaling—which is essential for vascular development at low concentrations but may have adverse effects at high concentrations—adds further complexity. As such, in addition to the well-taken argument by Langleben and colleagues that sotatercept binding of activins may be insufficient to overcome the reduced BMPR2 signaling in case of a BMP9 mutation [1], BMP9 mutations may drive lung vascular remodelings by mechanisms largely independent of activin receptor signaling that are hence not sensitive to sotatercept treatment.

Additional complexity arises from the heterogeneous manifestations of *GDF2* mutations. *GDF2* variants have been implicated in both PAH and hereditary hemorrhagic telangiectasia (HHT). Recent studies have indicated that approximately 90% of *GDF2* variant carriers develop PAH, while only 10% display HHT-related manifestations [17]. This phenotypic divergence may be attributed to variant-specific functional impacts, with certain variants selectively disrupting BMP9-mediated pulmonary vascular homeostasis, whereas others primarily perturb HHT-associated pathways. Analogously, different GDF2 variants may also variably affect the response to sotatercept, highlighting an important direction for future research for precision medicine. Alternatively, PAH may precede HHT or vice versa. Given the paucity of data on non-BMPR2 variants, multicenter collaborative efforts are imperative to delineate the frequency, clinical trajectories, and genotype-phenotype correlations of *GDF2* variants, ultimately refining risk stratification and individual therapeutic strategies for this molecularly distinct PAH subset.

Author Contributions

Author contributions: S.-F.L.: Methodology, Formal analysis, Writing—original draft; M.-Y.H.: Methodology, Writing—original draft; W.M.K.: Conceptualization, Methodology, Supervision, Writing—review & editing.

Ethics Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Funding

This research received no external funding.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Langleben D, Lesenko L, Fox BD, Eintracht S, Foulkes WD, Rosenblatt DS. 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. *Chest* **2025**, *167*, e37–e39.
2. Wang G, Fan R, Ji R, Zou W, Penny DJ, Varghese NP, et al. Novel homozygous BMP9 nonsense mutation causes pulmonary arterial hypertension: a case report. *BMC Pulm. Med.* **2016**, *16*, 17.
3. Gräf S, Haimel M, Bleda M, Hadinnapola C, Southgate L, Li W, et al. Identification of rare sequence variation underlying heritable pulmonary arterial hypertension. *Nat. Commun.* **2018**, *9*, 1416.
4. Eyries M, Montani D, Nadaud S, Girerd B, Levy M, Bourdin A, et al. Widening the landscape of heritable pulmonary hypertension mutations in paediatric and adult cases. *Eur. Respir. J.* **2019**, *14*, 53.
5. Wang XJ, Lian TY, Jiang X, Liu SF, Li SQ, Jiang R, et al. Germline BMP9 mutation causes idiopathic pulmonary arterial hypertension. *Eur. Respir. J.* **2019**, *3*, 53.
6. Hodgson J, Swietlik EM, Salmon RM, Hadinnapola C, Nikolic I, Wharton J, et al. Characterization of GDF2 Mutations and Levels of BMP9 and BMP10 in Pulmonary Arterial Hypertension. *Am. J. Respir. Crit. Care Med.* **2020**, *201*, 575–585.
7. van den Heuvel LM, Jansen SM, Alsters SI, Post MC, van der Smagt JJ, Handoko-De Man FS, et al. Genetic Evaluation in a Cohort of 126 Dutch Pulmonary Arterial Hypertension Patients. *Genes* **2020**, *11*, 1191.
8. Hernandez-Gonzalez I, Tenorio-Castano J, Ochoa-Parra N, Gallego N, Pérez-Olivares C, Lago-Docampo M, et al. Novel Genetic and Molecular Pathways in Pulmonary Arterial Hypertension Associated with Connective Tissue Disease. *Cells.* **2021**, *10*, 1488.
9. Hodgson J, Ruiz-Llorente L, McDonald J, Quarrell O, Ugonna K, Bentham J, et al. Homozygous GDF2 nonsense mutations result in a loss of circulating BMP9 and BMP10 and are associated with either PAH or an "HHT-like" syndrome in children. *Mol. Genet. Genomic Med.* **2021**, *9*, e1685.
10. Zhu N, Swietlik EM, Welch CL, Pauciulo MW, Hagen JJ, Zhou X, et al. Correction to: Rare variant analysis of 4241 pulmonary arterial hypertension cases from an international consortium implicates FBLN2, PDGFD, and rare de novo variants in PAH. *Genome Med.* **2021**, *13*, 106.
11. Eichstaedt CA, Saßmannshausen Z, Shaukat M, Cao D, Xanthouli P, Gall H, et al. Gene panel diagnostics reveals new pathogenic variants in pulmonary arterial hypertension. *Respir. Res.* **2022**, *23*, 74.
12. Chomette L, Hupkens E, Romitti M, Dewachter L, Vachiery JL, Bailly S, et al. Pediatric pulmonary arterial hypertension due to a novel homozygous GDF2 missense variant affecting BMP9 processing and activity. *Am. J. Med. Genet. A* **2023**, *191*, 2064–2073.
13. Upton P, Richards S, Bates A, Niederhoffer KY, Morrell NW, Christian S. A rare homozygous missense GDF2 (BMP9) mutation causing PAH in siblings: Does BMP10 status contribute? *Am. J. Med. Genet. A* **2023**, *191*, 228–233.
14. Long L, Ormiston ML, Yang X, Southwood M, Gräf S, Machado RD, et al. Selective enhancement of endothelial BMPR-II with BMP9 reverses pulmonary arterial hypertension. *Nat. Med.* **2015**, *21*, 777–785.
15. Hoeper MM, Badesch DB, Ghofrani HA, Gibbs JS, Gomberg-Maitland M, McLaughlin VV, et al. Phase 3 Trial of Sotatercept for Treatment of Pulmonary Arterial Hypertension. *N. Engl. J. Med.* **2023**, *388*, 1478–1490.
16. Guignabert C, Savale L, Boucly A, Thuillet R, Tu L, Ottaviani M, et al. Serum and Pulmonary Expression Profiles of the Activin Signaling System in Pulmonary Arterial Hypertension. *Circulation* **2023**, *147*, 1809–1822.
17. Grynblat J, Bogaard HJ, Eyries M, Meyrignac O, Savale L, Jaïs X, et al. Pulmonary vascular phenotype identified in patients with GDF2 (BMP9) or BMP10 variants: an international multicentre study. *Eur. Respir. J.* **2024**, *4*, 63.