ATS Journals | American Journal of Respiratory and Critical Care Medicine

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Journal:	*American Journal of Respiratory and Critical Care Medicine*
Manuscript ID	Draft
Manuscript Type:	Research Letter
Date Submitted by the Author:	n/a
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Subject Category:	9.34 Pulmonary Hypertension: Clinical-Treatment < VASCULAR BIOLOGY/PULMONARY CIRCULATION
Keywords:	pulmonary arterial hypertension, activin signaling inhibitor, BMPR2, treatment responsiveness, genetics

Specific *BMPR2* variants may predict response to sotatercept in patients with heritable pulmonary arterial hypertension

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Funding disclosure: This study has not been funded by any external organization.

Word count (body of text): 945 (max. 1,000)

To the editor:

Pulmonary arterial hypertension (PAH) is characterized by obliterative pulmonary vascular remodeling driven by enhanced activin and suppressed bone morphogenetic protein receptor type II (BMPR2) signaling. Sotatercept, a first-in-class activin signaling inhibitor, is a fusion protein of the extracellular domain of human activin type IIA receptor (ACTRIIA) and the Fc domain of human IgG1, aiming at reversing pulmonary vascular remodeling through rebalancing both signaling pathways. Sotatercept has shown high efficacy in reducing morbidity and mortality in patients with PAH (1-4). A recent post-hoc analysis from the phase 2 PULSAR study with sotatercept suggested that *BMPR2* mutation carriers show a similar response to sotatercept treatment than patients with idiopathic PAH (5). However, while some patients improve substantially following sotatercept initiation, others may exhibit limited improvement or response at all. To date, this observation remains unexplained.

BMPR2 is a transmembrane receptor consisting of different domains such as the cytoplasmic, kinase, heterodimerization, and extracellular ligand binding domain (*Figure 1A*). Among patients with heritable PAH, there is a variety of disease-causing *BMPR2* variants. Depending on its exact type and localization, each mutation can cause a functional loss of single or multiple protein domains which may result in an inability to bind the ligands or prevent receptor proteins from reaching the cell surface. In other cases mRNA is degraded or function of the kinase domain is impaired or abolished. These different effects of the mutation can also affect downstream signaling in a different ways (6,7).
We hypothesized, that specific BMPR2 domains, if functionally affected by the underlying *BMPR2* variant, might correlate with the individual response to sotatercept.
In line with this hypothesis, we have observed differences in the in vitro response to sotatercept in induced pluripotent stem cell-derived smooth muscle cells from heritable PAH patients with *BMPR2* mutations affecting either the extracellular or the kinase domain. Depending on the specific type of mutation in the *BMPR2* gene, RNAseq analysis revealed variations in the regulation of certain genes and signaling pathways (unpublished). These findings also suggest additional unrecognized mechanisms of action of sotatercept resulting in varying drug responsiveness in patients carrying different *BMPR2* mutations.

All patients with *BMPR2*+ heritable PAH who received sotatercept at Hannover Medical School by the end of 2025 were included in this analysis. Functional attribution of *BMPR2* variants and affected protein domains was performed by an expert on molecular genetic diagnostics (CE). Clinical data including hemodynamic parameters were assessed at sotatercept initiation (baseline). Six-minute walk distance (6MWD), N-terminal fragment of brain natriuretic peptide (NT-proBNP) values, WHO functional class (WHO-FC), and established risk scores were determined at baseline and at 3, 6, and 12 months after sotatercept initiation. Patients were assigned into 5 groups according to which protein domains were functionally affected.

Statistical analysis was performed using GraphPad Prism version 9.5.2 for Mac, GraphPad Software, Boston, MA. Shapiro Wilk test was performed for normality testing and t-test as well as Kolmogorov Smirnov test for comparisons of treatment effects over time within groups as appropriate. All patients signed the German Centre of Lung Research broad

consent form (https://dzl.de/en/dzl-data-warehouse), which permits us to utilize data obtained during clinical routines for research purposes. This broad consent form has also been approved by the ethics committee of our institution (number 2923_2015).

A total of 16 patients were eligible for this analysis. Patient characteristics at time of sotatercept initiation as well as follow-up information on 6MWD, NT-proBNP, WHO-FC, and mortality risk as determined by the COMPERA 2.0 model (8) are shown in *Table 1*.

As shown in *Table 1* and *Figure 1B*, patients whose *BMPR2* mutation affected the extracellular or cytoplasmic domains showed a rapid and profound response to sotatercept initiation with normalizations or near-normalizations of NT-proBNP, 6MWD, WHO-FC values, and risk strata. Patients whose *BMPR2* mutation affected the kinase domain were more severely impaired at baseline and exhibited a blunted clinical response to sotatercept therapy. A mixed clinical response was observed in the two patients who carried mutations in the heterodimerization domain: one patient improved while the other had no clinical improvement and eventually died of progressive right heart failure.

Our observations support the notion that *BMPR2* mutation carriers are a heterogeneous population with varying clinical courses and varying responses to sotatercept treatment. A mechanistical explanation for the distinct treatment responses is not straightforward as sotatercept does not directly affect BMPR2 signaling. We therefore speculate that mutations affecting different functional domains of BMPR2 may exhibit distinct features of pulmonary vascular remodeling, which may affect the response to therapy. In line with this hypothesis, differences in the *in vitro* response to sotatercept were observed in induced pluripotent stem cell-derived smooth muscle cells from heritable PAH patients with *BMPR2* mutations affecting either the extracellular or the kinase domain (unpublished).

The major limitations of this study are the limited number of patients owing to the fact that heritable PAH is a rare disease and the reliance on non-invasive variables owing to the lack of hemodynamic follow-up assessments in some patients.

Despite these limitations, we believe that our findings provide a first signal that the response to sotatercept treatment in *BMPR2* mutation carriers may be determined by the location of the pathogenetic variant. Patients carrying *BMPR2* mutations affecting the cytoplasmatic or extracellular domain appear to have a more profound response to sotatercept treatment than patients who carry mutations in the kinase and the heterodimerization domain. If confirmed by future studies, a better understanding of the specific location of *BMPR2* mutations may provide prognostic information and may help predicting the likelihood of therapeutic success. Given the limited number of patients and the high variability of *BMPR2* mutations, our observations should be considered hypothesis-generating and future studies involving larger cohorts are required to corroborate and further refine these results.

Conflicts of interest

JCK received funding for research from Volkswagen Stiftung, Else Kröner Fresenius Stiftung, and Deutsches Zentrum für Lungenforschung, all outside this work. CAE acknowledges payments of honoraria or lecture fees from MSD, OMT, and Ferrer. RO received funding

from Deutsche Forschungsgesellschaft and Deutsches Zentrum für Lungenforschung, all outside this work. UM received funding for research from Federal Ministry of Education and Research (BMBF), European Union Horizon Europe program, and Deutsches Zentrum für Lungenforschung, all outside this work. KMO acknowledges payments of honoraria or lecture fees or support for clinical research from Acceleron, Actelion, AOP Health, Bayer, Ferrer, Gossamer, Inhibikase, Janssen, and MSD. MMH acknowledges payments of honoraria or lecture fees from 35pharma, Acceleron, Actelion, Aerovate, AOP Health, Bayer, Ferrer, Gossamer, Inhibikase, Janssen, Keros, MSD, and Novartis. All other authors do not have any real or perceived conflicts.

Authors contributions

Study design: JCK, RO, and MMH. Resources: JR. In depth genetic work-up of all cases: CE. Writing of the original draft: JCK and MMH. Critical review and final approval: all authors.

Tables

Table 1. Patient characteristics and clinical follow-up data.

	Baseline	3 months follow-up	p-value	6 months follow-up	p-value	12 months follow-up	p-value
Age at sotatercept initiation (years)	44 ± 10.9						
Female (%)	69						
BMI	24.5 ± 5.5						
Affected BMPR2 domain(s) (n)							
extracellular	2						
cytoplasmic	4						
cytoplasmic + kinase	4						
kinase	4						
kinase + heterodimerization + cytoplasmic	1						
kinase + heterodimerization	1						
Time from PAH diagnosis to start of sotatercept therapy (years)	7 ± 5.1						
RA (mmHg)[#]	9 ± 3.6						
mPAP (mmHg) [#]	56.5 ± 12.6						
PAWP (mmHg) [#]	9 ± 2.6						
PVR (WU) [#]	12.4 ± 6.4						
Cardiac indec ($L*min^{-1}*m^{-2}$) [#]	2.2 ± 0.5						
SvO2 (%)[#]	58 ± 9						
WHO-FC (I, n / II, n / III, n)	0 / 4 / 12	0 / 9 / 7	n/s	2 / 5 / 7	n/s	1 / 9 / 4	n/s
extracellular	0 / 1 / 1	0 / 2 / 0	n/s	0 / 2 / 0	n/s	0 / 2 / 0	n/s
cytoplasmic	0 / 1 / 3	0 / 3 / 1	n/s	1 / 2 / 1	n/s	1 / 2 / 1	n/s
cytoplasmic + kinase	0 / 1 / 3	0 / 2 / 2	n/s	1 / 2 / 1	n/s	0 / 3 / 1	n/s
kinase	0 / 0 / 4	0 / 1 / 3	n/s	0 / 0 / 4	n/s	0 / 2 / 2	n/s
Kinase + heterodimerization + cytoplasmic	0 / 1 / 0	0 / 1 / 0	n/s	0 / 1 / 0	n/s	n/a*	n/a
Kinase + heterodimerization (I, n / II, n / III, n)	0 / 0 / 1	0 / 0 / 1	n/s	0 / 0 / 1	n/s	n/a**	n/a
6MWD (m)	432 ± 105	462 ± 85	n/s	468 ± 88	n/s	466 ± 78	n/s
extracellular	520 ± 13	504 ± 4	n/s	518 ±7	n/s	516 ± 5	n/s
cytoplasmic	432 ± 71	464 ± 57	n/s	476 ± 55	n/s	488 ± 55	n/s
cytoplasmic + kinase	391 ± 137	454 ± 97	n/s	459 ± 104	n/s	444 ± 92	n/s
kinase	339 ± 27	359 ± 73	n/s	366 ± 78	n/s	382 ± 53	n/s
kinase + heterodimerization + cytoplasmic	609 ± 0	582 ± 0	n/s	n/a*	n/a	n/a*	n/a
kinase + heterodimerization	403 ± 0	401 ± 0	n/s	397 ± 0	n/s	n/a**	n/a
NT-proBNP ($ng*L^{-1}$)	803 ± 1208	173 ± 824	**0.02**	310 ± 590	**0.02**	235 ± 600	**0.02**
extracellular	458 ± 418	71 ± 31	n/s	48 ± 8	n/s	48 ± 8	n/s
cytoplasmic	526 ± 59	73 ± 42	**0.03**	76 ± 34	**0.03**	65 ± 40	**0.03**
cytoplasmic + kinase	1605 ± 1755	561 ± 837	n/s	615 ± 356	n/s	755 ± 564	n/s

kinase	1798 ± 437	590 ± 644	n/s	790 ± 682	n/s	536 ± 622	n/s
Kinase + heterodimerization, cytoplasmic	125 ± 0	114 ± 0	n/s	24 ± 0	n/s	n/a*	n/a
Kinase + heterodimerization	1750 ± 0	2729 ± 0	n/s	1616 ± 0	n/s	n/a**	n/a
Mortality risk[##] (low, n / intermediate-low, n / intermediate-high, n)	5 / 6 / 5	9 / 3 / 4	n/s	8 / 4 / 2	n/s	8 / 4 / 2	n/s
extracellular	1 / 1 / 0	2 / 0 / 0	n/s	2 / 0 / 0	n/s	2 / 0 / 0	n/s
cytoplasmic	1 / 3 / 0	4 / 0 / 0	n/s	4 / 0 / 0	n/s	4 / 0 / 0	n/s
cytoplasmic + kinase	1 / 1 / 2	2 / 0 / 2	n/s	1 / 1 / 2	n/s	1 / 2 / 1	n/s
kinase	1 / 1 / 2	1 / 2 / 1	n/s	1 / 3 / 0	n/s	1 / 2 / 1	n/s
Kinase + heterodimerization + cytoplasmic	1 / 0 / 0	0 / 1 / 0	n/s	1 / 0 / 0	n/a	n/a*	n/a
Kinase + heterodimerization	0 / 0 / 1	0 / 0 / 1	n/s	0 / 0 / 1	n/s	n/a **	n/a

*incomplete follow-up of this patient; **sotatercept therapy was terminated in this patient due to progressive deterioration; patient deceased approximately 11 months after sotatercept initiation; [#]hemodynamic follow-up via right heart catheterization was available only for a subset of patients not allowing a reasonable statistical comparison; [##]assessed via the COMPERA 2.0 model; n/a, not applicable; n/s, not significant; BMI, body mass index; BMPR2, bone morphogenetic protein receptor type II; PAH, pulmonary arterial hypertension; RA, right atrial pressure; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; SvO2, mixed-venous oxygen saturation; WHO-FC, World Health Organization functional class; 6MWD, 6 minute walking distance; NT-proBNP, N-terminal fragment of brain natriuretic peptide.

Figure legends

Figure 1. Response to sotatercept in heritable PAH patients with specific BMPR2 variants

A) Pictogram illustrating the bone morphogenetic protein receptor type II (*BMPR2*) and its specific receptor domains; B) Important clinical parameters assessed at the timepoint of sotatercept initiation (baseline) and at 3, 6, and 12 months follow-up. NT-proBNP, N-terminal fragment of brain natriuretic peptide; 6MWD, 6-minute walk distance; WHO-FC, World Health Organization functional class; Risk Score: individual risk assessment using the COMPERA 2.0 model.

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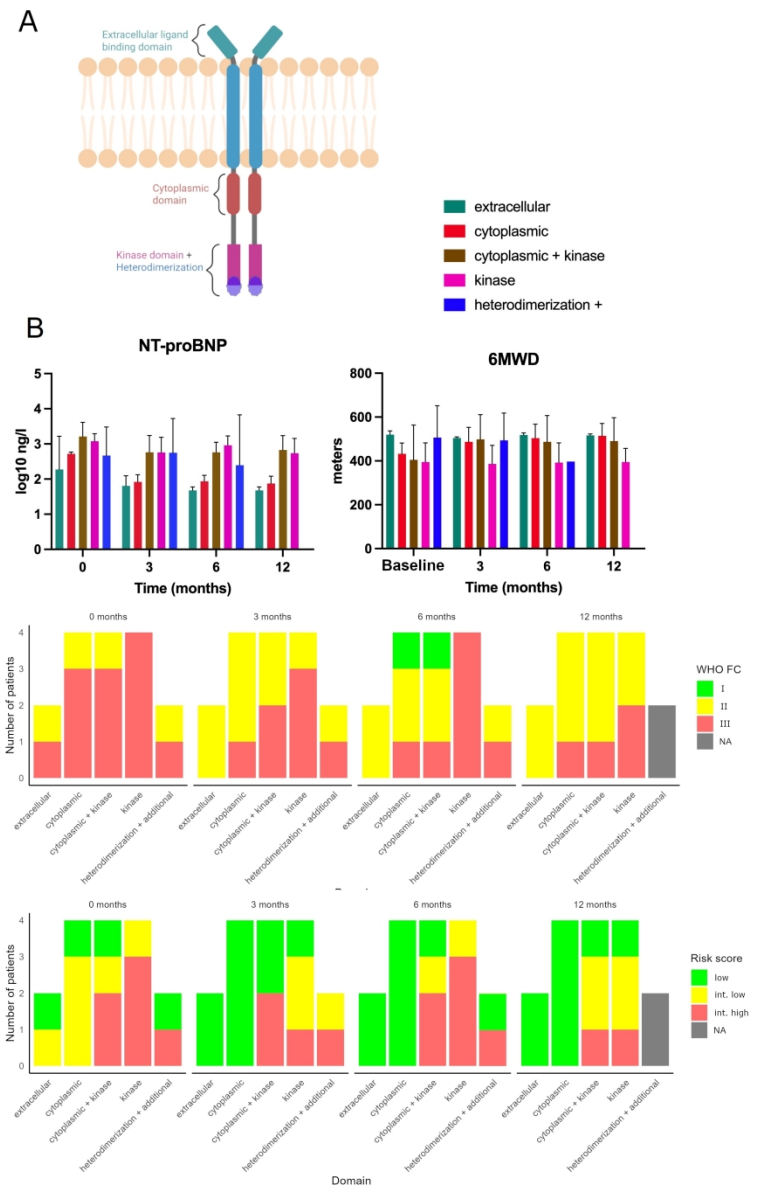

Figure 1. Response to sotatercept in heritable PAH patients with specific BMPR2 variants. A) Pictogram illustrating the bone morphogenetic protein receptor type II (BMPR2) and its specific receptor domains; B) Important clinical parameters assessed at the timepoint of sotatercept initiation (baseline) and at 3, 6, and 12 months follow-up. NT-proBNP, N-terminal fragment of brain natriuretic peptide; 6MWD, 6-minute walk distance; WHO-FC, World Health Organization functional class; Risk Score: individual risk assessment using the COMPERA 2.0 model.

219x347mm (300 x 300 DPI)