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Title: Sotatercept for the Treatment of Portopulmonary Hypertension: A Case Report

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Abstract

Background

Portopulmonary Hypertension is a subtype of pulmonary arterial hypertension with high mortality. There are extremely few clinical trials to guide treatment in portopulmonary hypertension, which is typically based on the approach to treatment for other types of pulmonary arterial hypertension. Sotatercept, the newest pulmonary arterial hypertension approved therapeutic, is a novel activin signaling inhibitor which has been shown to significantly improve disease severity and enhance survival when added to background therapy in pulmonary arterial hypertension. Unfortunately, portopulmonary hypertension patients were excluded from the clinical trials that led to Sotatercept approval, and the efficacy, safety, and tolerability of Sotatercept in portopulmonary hypertension remains unclear.

Methods

Here we describe, to the best of our knowledge, a case report of the first use of Sotatercept in the treatment of portopulmonary hypertension, combined with single cell RNA sequencing and plasma proteomic analysis.

Results

We demonstrate that profiling the circulating leukocyte transcriptomic and circulating pulmonary artery proteomic signatures before and after Sotatercept treatment identifies changes in CD8+ T-Cell and Monocyte gene expression, and levels of proteins involved in inflammation and ubiquitination. Sotatercept appears well tolerated, effective in reducing pulmonary hypertension hemodynamic severity in a portopulmonary hypertension patient refractory to conventional pulmonary hypertension therapies, but may be associated with the development of hepatopulmonary syndrome.

Conclusions

This report demonstrates tolerability and efficacy of Sotatercept in portopulmonary hypertension, identifies candidate biomarkers of treatment response, but also suggests caution may be warranted. Findings from this work support further investigation of Sotatercept in the treatment of portopulmonary hypertension.

Plain Language Summary

Portopulmonary hypertension is disease of the blood vessels in the lungs, that occurs in people with underlying liver disease. It is very deadly, there is no cure, and there are limited treatments. A new treatment for pulmonary hypertension, Sotatercept, has shown benefit, but has not yet been tried in patients with portopulmonary hypertension. Here we report the results of using Sotatercept in a patient with portopulmonary hypertension, who hadn't fully responded to other pulmonary hypertension treatments. With Sotatercept, his disease improved, and he was able to get a liver transplant. He did develop low oxygen levels, that might have been related to Sotatercept treatment. This case highlights the possible risks and benefits of using Sotatercept in portopulmonary hypertension, and encourages further study of Sotatercept for treatment of portopulmonary hypertension.

Introduction

Pulmonary arterial hypertension (PAH) is a progressive and ultimately fatal disease of the pulmonary arterioles, characterized by elevations in the mean pulmonary artery pressure (mPAP) assessed by right heart catheterization (RHC)[1]. Sotatercept is an activin signaling inhibitor that has shown strong efficacy in treating PAH, reducing mPAP and improving functional capacity, even for patients already on background PAH treatment[2-3]. Portopulmonary Hypertension (PoPH) is a type of PAH that occurs in the context of underlying portal hypertension and liver disease, through mechanisms that are not well understood[4]. PoPH was excluded from all Sotatercept clinical trials, and the safety, tolerability, and efficacy of Sotatercept in PoPH remains unknown.

Here we present our experience using Sotatercept for the treatment of PoPH. Using a combination of proteomics techniques (proximity extension assay and liquid chromatography with mass spectrometry) and single cell RNA sequencing, we analyze the transcriptomic and circulating plasma protein changes in response to Sotatercept therapy. In this PoPH patient, Sotatercept therapy reduces the hemodynamic burden of PAH disease, but results in the development of hypoxemia and intrapulmonary shunting. Therapy also reduces levels of circulating proteins related to inflammation and protein degradation processes, and changes the transcriptomic profile of circulating leukocytes (CD8+ T-Cells and Monocytes). This case highlights both evidence of benefit but also possible risk with Sotatercept therapy in PoPH, and further reports and case series are required to better understand how Sotatercept might be useful in this PAH disease subtype.

Methods

Patient Details and Study Approach

Informed consent was obtained, and clinical data and sample acquisition were collected with institutional ethics approval from the University of Cincinnati IRB (UC IRB 2021-1109). Additional written consent was obtained from this patient to publish their information as part of this case. Whole blood was obtained from the pulmonary artery position during right heart catheterization for sequencing and proteomics. Blood samples for transcriptomics were collected immediately prior to start of Sotatercept therapy, and following six months of Sotatercept treatment. Blood was obtained from the pulmonary artery position during right heart catheterization in K2 EDTA tubes (Fisher Scientific 02-657-32). For proteomics samples, following processing into plasma, samples were stored at -80 degrees Celsius until analysis. For sequencing samples, following right heart catheterization blood was transported immediately to the lab for processing and sequencing. Samples were collected at five different timepoints pre-Sotatercept, with stable background PAH targeted therapy using tadalafil (20mg oral daily) and macitentan (10mg oral daily), and varying doses of daily selexipag (1000mcg, 1000mcg, 1600mcg, 400mcg, and 0mcg respectively). Samples were collected from two different timepoints post-Sotatercept, with stable PAH background targeted therapy using macitentan (10mg oral daily), and varying doses of daily tadalafil (20mg, 10mg).

Single Cell RNA Sequencing

Following acquisition, blood was transported on wet ice in a 15cc conical tube to the lab for processing, and immediately processed into a single cell suspension using the 10X genomics

protocol “Start Option 1” (CG00392, Rev. B). Briefly, processing involved multiple rounds of red blood cell lysis, centrifugation, and supernatant removal. Cell viability >90% prior to sequencing was confirmed using Trypan Blue staining. Following processing, concentration was adjusted to ~1000 cell/ul and 14,500 cells were loaded into the 10X chromium controller for 10X single cell sequencing, generating gel beads in emulsion. cDNA libraries were prepared as per instructions provided in the 10X Genomics single cell GEM-X 3’v4 Reagent kit, and single cell libraries were sequenced. Single cell data was processed using the 10X Cell Ranger software version 9.0.0, mapping reads to a GrCh38 human genome version 2024-A. Using the *Seurat* package version 4.3.0, the *scrublet* package, and *R* version 4.1.2, data were processed[5]. We excluded cells with greater than 5% of UMIs mapped to the mitochondrial genome, fewer than 50 detected genes, and fewer than 300 unique expressed genes. Doublets were detected using *scrublet* based on predicted doublet scores, with an expected doublet rate of 6%, and removed[6]. Each sample was size-factor normalized to 10,000 UMI per cell, log base 2 transformed and scaled using *Seurat*. Using data from all samples together, integration anchors were identified across datasets, and samples were integrated together for analysis. The integrated dataset was then scaled, and the top 30 principal components were identified, with the top 18 principal components used for clustering using *Seurat’s* shared nearest neighbor (SNN)-Louvain clustering algorithm at a resolution of 0.2, yielding 10 unique clusters. Differentially expressed “marker” genes for a given cluster were identified using the *FindAllMarkers* function in *Seurat*, applying a likelihood ratio test and selecting upregulated genes expressed in a minimum of 25% of nuclei with a minimum log-fold difference in expression of 0.25 or greater between clusters. Previously described canonical marker genes[7] for peripheral blood leukocytes (T-Cells: *CD3D, CD3E, CD3G*; CD4 T-Cells: *CD4*; CD8 T-Cells:*CD8A, CD8B*; NK Cells: *NCAM1, KLRB1,*

NKG7; Monocytes: *CD14, CD68, FCGR3A*; Erythrocyte precursors: *HBB*; Polymorphonuclear neutrophils: *CSF3R, FCGR3B, CXCR2*) and the *sc_type* package in R[8] were used together to name clusters. Significant differentially expressed genes were identified for each cluster by comparing pre-treatment and post-treatment clusters using the *findMarkers* function in *Seurat*. Gene Ontology enrichment analysis was performed across clusters using Cytoscape version 3.10.3 and STRING enrichment[9]. Briefly, individual genes in a cluster were first scaled to the intensity of differential gene expression in pre-treatment relative to post-treatment (log-fold-change between groups), STRING networks were constructed based on protein queries, functional enrichment was obtained for the largest discrete network, and significantly affected KEGG, GO, and Disease pathways corresponding to this network were obtained.

Drug-target prediction

The list of significant differentially expressed genes for the NK Cell, CD8+ T-Cell, and Myeloid Lineage Granulocyte-like Cell were then input into the CMap/LINCS platform to identify similar perturbational signatures[10]. Briefly, for each cluster we input the top 150 up-regulated and down-regulated significantly expressed genes between the pre-treatment and post-treatment states into a L1000 query in CMap (clue.io/query). The resulting gene set enrichment analysis result was filtered, and perturbation compounds that had known mechanisms of action and known targets, a positive connectivity score (i.e. perturbation compounds whose effects were comparable to Sotatercept treatment on differentially expressed genes), and a false discovery rate q-value of 0.05 were retained.

Plasma Protein Quantitation

Plasma samples were prepared for liquid chromatography tandem mass spectrometry (LC-MS/MS) as previously described[11]. Briefly, plasma samples were subjected to protease/phosphatase inhibition, followed by albumin depletion, fractionation by SDS gel chromatography, in-gel tryptic digestion, and peptide extraction. Tryptic digests were subjected to LC-MS/MS with a mass analyzer setup for data-dependent acquisition using dynamic exclusion settings of: repeat count = 2, repeat duration = 10 seconds, exclusion list size = 100, exclusion duration = 30 seconds, and exclusion mass width = 1.5 amu. Collision-induced dissociation (CID) was used to fragment peptides, spectra were searched against a human fasta database using the Proteome Discoverer™ software version 2.4 (Thermo Fisher Scientific, Waltham, Massachusetts, USA). A reverse database decoy and percolator[12] was used to control for false discovery. Plasma proteins, that were measured in all of the pre-treatment samples (N=5) and decreased in post-treatment samples (N=2), or were absent from all the pre-treatment samples and increased in all post-treatment samples, were retained for further analysis. Plasma samples were also subjected to proximity extension assay analysis using the commercial Olink ® Explore HT platform (Olink Proteomics Inc, Waltham MA USA), which quantifies 5416 plasma proteins and reports values using a relative and logarithmic unit (the Normalized Protein Expression value, or NPX)[13]. Proximity extension assay technology employs polyclonal antibodies targeting specific proteins which, once bound, results in hybridization of two single-strand DNA probes which form a unique barcode corresponding to that protein.

Data Availability Statement

All single cell RNA sequencing data generated by this study have been deposited and are readily accessible in the NCBI Sequence Read Archive (PRJNA1322486, accessions SAMN51248041

and SAMN5124802). Proteomic data results are available in the Supplement. The source data for Table S1 is in Supplementary Data 1, the source data for Table S2 is in Supplementary Data 2, and the source data for Figure S3 is in Supplementary Data 3 and the NCBI Sequence Read Archive files. The source data for Table 1, and Figures 1, 2, and S1, S2 is in Supplementary Data 4. Additional data supporting the findings of this study are available from the corresponding author (AJ) upon reasonable request.

Statistics and Reproducibility

For single cell RNA sequencing data, significant differentially expressed genes were identified by selecting a Benjamini-Hochberg corrected Wilcoxon Rank Sum test threshold of $p<0.05$ for each cluster when comparing pre-treatment and post-treatment clusters. For Gene Ontology enrichment analysis and STRING enrichment network generation, significance of a pathway was ascertained by applying a two-sided Bonferroni false discovery rate corrected $p<0.05$. For plasma protein quantification using Olink Explore HT, groups were compared using a Welch 2-sample t-test, with correction for multiple testing using the Benjamini-Hochberg method, with a two-sided adjusted $p<0.05$ retained for significance.

Results

Clinical Course

Patient is a 44-year-old White male with a past medical history of cryptogenic liver cirrhosis who first presented to our clinic in 2021 after a one-year history of dyspnea on exertion. He was diagnosed with liver cirrhosis in 2009, with a liver ultrasound notable for nodular liver contour and coarse echotexture of the hepatic parenchyma. Liver biopsy demonstrated extensive fibrous

septae and multiple regenerative nodules but no histological features of autoimmune hepatitis, Wilson's disease, or fat droplets, and in light of a negative workup for alternative etiologies of liver cirrhosis he was given a diagnosis of cryptogenic cirrhosis. He was obese on presentation, with a body mass index (BMI) of 36.96 kg/m^2, with but normal vital signs (blood pressure 108/52, pulse 61, saturating 95% on room air). He underwent a transthoracic echocardiogram (TTE), notable for an elevated tricuspid regurgitant velocity of 4.4 meters per second, concerning for pulmonary hypertension. RHC testing confirmed a diagnosis of severe pulmonary arterial hypertension (PAH), with a mPAP of 65 mmHg, a left-ventricular end-diastolic pressure of 8mmHg, and a cardiac output by indirect Fick measurement of 5.5 Liters/minute, yielding a pulmonary vascular resistance (PVR) of 10.4 Wood Units. An exhaustive workup (ventilation-perfusion scan, pulmonary function testing, laboratory testing for autoimmune disease, thyroid abnormalities, and human immunodeficiency virus infection) for alternative etiologies of PAH was negative, and the patient was diagnosed with Portopulmonary Hypertension (PoPH). He was promptly initiated on dual PAH therapy with a phosphodiesterase-5 inhibitor (sildenafil transitioned to tadalafil) and endothelin receptor antagonist (macitentan), with some improvement in his PAH (mPAP 52 mmHg, PVR 3.7 Wood Units). Despite treatment escalation (parenteral prostacyclin treprostinil, later transitioned to oral prostacyclin receptor agonist selexipag) and three years of targeted PAH therapy, his mPAP and PVR remained elevated (April 2024 RHC with mPAP 65 mmHg, PVR 6.1 Wood Units), with persistent dilation of the right ventricle (internal diameter 4.5cm) on TTE, and the patient was unable to achieve acceptable hemodynamics to facilitate liver transplantation. Given the desire to pursue liver transplantation, he was ultimately trialed on the activin signaling inhibitor Sotatercept in June

2024. During treatment with Sotatercept, only one change in PAH background therapy (tadalafil 20mg to 10mg daily) was made.

After tolerating Sotatercept at a dose of 0.3 mg/kg for several weeks, a dose escalation to 0.7 mg/kg was attempted in September of 2024. This was followed by a hospitalization due to acute anemia (hemoglobin of 7.6 g/dL) later that month, prompting a hold of medication. An extensive work-up for sources of bleeding was negative, including a colonoscopy with only minor mucosal bleeding in the setting of thrombocytopenia, an upper endoscopy with portal hypertensive gastropathy and small non-bleeding <5mm esophageal varices without red wale signs or stigmata of recent bleeding, and a peripheral blood smear without dysplasia, circulating blasts, or increased schistocytes. Anemia was ultimately attributed to dietary iron deficiency, treated with intravenous iron repletion with improvement, and Sotatercept was resumed at 0.3 mg/kg dosing. Following treatment with Sotatercept for six months, the patient had an increase in platelet count (41,000/ul to 59,000/ul) and stable hemoglobin (14.4 g/dL). (**Figure S1, Figure S2) (Table 1) (Supplementary Data 4).** The patient also showed marked improvement in the burden of PAH on both RHC (mPAP decreased to 40 mmHg, PVR decreased to 3.5 Wood Units) and TTE (right ventricular diameter decreased to 3.7 cm, tricuspid regurgitant velocity decreased to 3.4 m/s), exhibited a robust functional capacity (World Health Organization functional class of I, six-minute walk test distance of 536 meters), and maintained a low-risk status (REVEAL 2.0 risk score of 3). (**Figure 1, Figure 2**) The presence of a right-to-left shunt was noted on the six-month TTE, raising concern for underlying Hepatopulmonary Syndrome (HPS), but the patient had normal oxygen saturation both at rest and with exertion. A subsequent RHC after nine months of Sotatercept therapy at 0.3 mg/kg showed further improvements in burden of PAH on

RHC (mPAP of 35 mmHg, PVR of 2.08 Wood Units) and platelet count (65,000/ul). At nine months the patient did demonstrate transient exertional hypoxemia (though none at rest), and further workup was pursued. A cardiac magnetic resonance imaging scan showed evidence of PoPH (mild right ventricular dilation, hypertrophy, and right ventricular insertion point late gadolinium enhancement) but was negative for interatrial/interventricular septal defects or anomalous pulmonary venous return. An Arterial Blood Gas measurement conducted at room air showed hypoxemia (PaO2 of 58 mmHg). Pulmonary Function Testing was repeated, without obstruction or restriction, but with a reduced diffusion capacity for carbon monoxide (18.94 ml/mmHg-sec, 60% of predicted). Genetic testing for vascular Ehlers-Danlos Syndrome, Marfan Syndrome, and Loeys-Deitz Syndrome were negative. In the presence of liver cirrhosis, a right-to-left shunt on TTE, and hypoxemia, the patient was diagnosed with HPS. Given the marked response to Sotatercept and improvement in PAH, the patient also qualified for PoPH MELD exception points and was reconsidered for liver transplant. After two months on the waitlist (almost eleven months after first starting Sotatercept), he underwent a successful orthotopic liver transplantation with well-controlled PAH on intraoperative hemodynamics (mPAP 35mmHg, PVR 1.5 Wood Units). Following surgery, he was extubated the next day, and was discharged to home after two weeks on dual oral therapy (macitentan and tadalafil) with supplemental oxygen via nasal cannula.

Single Cell RNA Sequencing

Following processing, quality control, and filtering, 3506 pre-treatment and 8092 post-treatment cells remained for analysis, which clustered into major circulating leukocyte cell types (**Figure S3**) (**Supplementary Data 3**). Pathway analysis of differentially expressed genes between pre-

treatment and post-treatment states for several of the largest clusters predicted several significantly enriched pathways. (**Supplementary Data 6**) These included suppressed cellular response to chemical stimulus/stress (GO:0062197 and GO:0070887; PMN, Myeloid Lineage Granulocyte-like Cell, NK Cell), suppressed smooth muscle cell proliferation (GO:004860, Myeloid Lineage Granulocyte-like Cell, CD8+ T-Cell), and suppressed leukocyte transendothelial cell migration (hsa04670; PMN, NK Cell, Myeloid Lineage Granulocyte-like Cell, Monocyte, CD8+ T-Cell, CD8+ T-Cell).

Pathway Analysis

Focusing on three specific clusters highly represented in pathway analysis (CD8+ T-Cell, NK Cell, Myeloid Lineage Granulocyte-like Cell), we then examined drugs predicted to result in similar gene expression changes as Sotatercept treatment (**Supplementary Data 5**). Predicted pathways included mTOR inhibition, NF-kB inhibition, PI3K inhibition, and protein kinase C activation. Several PAH specific therapeutics were also predicted from this analysis, including Phosphodiesterase-5 inhibitors (sildenafil, tadalafil), endothelin receptor antagonists (ambrisentan), prostacyclin receptor agonists (dinoprostone), and guanylate cyclase activators (riociguat), predominantly in the CD8+ T-Cell cluster.

Circulating Plasma Proteomic Analysis

We then examined the changes in circulating proteins pre-treatment and post-treatment using LC-MS/MS (**Supplementary Data 1**). The resulting list included 46 unique proteins which decreased, and 101 unique proteins which increased, following Sotatercept treatment. Sotatercept treatment increased circulating levels of hemoglobin alpha, beta, and delta subunits. Increases in

the ubiquitin ligase proteins RNF213 and RNF130, absent in circulation pre-treatment, were observed. The GTPase activating RABGAP1 protein was increased following treatment. Levels of circulating HPS1 and ASH1L proteins were decreased following Sotatercept treatment. Changes in circulating proteins were also examined using the Olink ® Explore HT platform (**Supplementary Data 2**), which additionally identified significant increases in circulating BBX and SELE proteins following Sotatercept treatment. Several proteins decreased (such as NTproBNP and INHBB), however these decreases were not significant following correction for multiple comparisons. Cross-referencing these proteins with transcriptomic data following Sotatercept treatment identified corresponding differential gene expression changes, particularly in Monocytes (**Table S1, S2**).

Discussion

To the best of our knowledge, this is the first report describing the successful use of Sotatercept in the treatment of PoPH. In this patient with longstanding PoPH and a persistently elevated mPAP refractory to traditional PAH targeted therapeutics, six months of Sotatercept resulted in a significant and sustained decrease in mPAP, a corresponding reduction in PVR, and an overall improvement in the burden of PAH. Response persisted after nine months of Sotatercept therapy, and enabled the patient to finally meet PoPH MELD exception criteria and successfully tolerate orthotopic liver transplantation after eleven months of Sotatercept therapy. Therapy was well tolerated, with improved hemoglobin levels and platelet counts. Analyses of circulating leukocyte transcriptomics and plasma proteomics identified several therapeutic targets that may be effective in PoPH treatment, and suggested that CD8+ T-Cells, Monocytes, and both

inflammation and protein degradation processes may be involved in Sotatercept therapeutic response in PoPH.

Although known to demonstrate poor survival even with traditional PAH targeted therapy and often exhibiting a “hyperdynamic” circulation that can complicate efforts to escalate targeted PAH therapy[14-15], PoPH patients were excluded from the STELLAR and PULSAR randomized controlled trials that led to approval of Sotatercept as a treatment for PAH[2-3]. Sotatercept therapy, associated with a number of side-effects (thrombocytopenia, epistaxis, telangiectasias) that may be poorly tolerated in patients with underlying portal hypertension and liver cirrhosis, has also been linked to serious gastrointestinal bleeding events[16-17]. We did not observe evidence of significant gastrointestinal bleeding in our patient while on Sotatercept, however the presence of iron deficiency anemia with a substantial drop in hemoglobin, and the possibility that Sotatercept (particularly at higher doses) may result in new or worsening occult gastrointestinal bleeding, cannot be ruled out. In this context, our case demonstrates that treatment with Sotatercept is associated with hemodynamic improvement of PAH disease severity (in a PoPH patient exhibiting hyperdynamic circulation refractory to standard PAH targeted therapy), with the caveat that this is a single case report and our patient may have had an increase in occult gastrointestinal bleeding and iron deficiency anemia as a result of Sotatercept. To clarify the safety profile of Sotatercept as a PoPH therapeutic, further investigation into the association between Sotatercept and gastrointestinal bleeding (both major and occult) will be necessary.

While being treated with Sotatercept, which improved the burden of PoPH, our patient also developed HPS. Recent reports have implicated Sotatercept in the development of

intrapulmonary vascular dilatations in PAH patients with veno-occlusive disease, congenital heart disease, and connective tissue disease, potentially through a bone morphogenetic protein type-9 dependent mechanism[18-20]. As HPS is known to afflict 5-10% of patients with chronic liver disease (including some with PoPH), and in our case transcriptomic and proteomic analysis did not identify *GDF2* expression or circulating bone morphogenetic protein type 9 as significantly affected by Sotatercept treatment, it is possible the development of hypoxemia with intrapulmonary shunting in this patient was not related to HPS, but instead reflected intrapulmonary shunting from a high-flow state, or the effects of Sotatercept creating incomplete pulmonary vascular units that consequently resulted in intrapulmonary shunting, ventilation-perfusion mismatch, and hypoxemia [4,21]. However, this remains a concerning possibility, particularly as there is growing evidence linking bone morphogenetic protein type 9 deficiency with development of HPS in animal models and human epidemiologic studies[22-23], and we did not directly compare bone morphogenetic protein 9 levels post-Sotatercept in this patient with other PoPH patients not treated with Sotatercept. It is important to note that, compared to healthy individuals and those with other types of PAH, patients with underlying liver disease (such as those with PoPH) typically have lower baseline circulating bone morphogenetic protein 9 and 10 levels as a consequence of the hepatic disease[23], and further reductions following Sotatercept exposure (though not statistically significant) may still cumulatively influence development of HPS through a bone morphogenetic protein dependent mechanism. Thus, extreme caution and extensive counseling should be undertaken when considering the possible use of Sotatercept in PoPH, given the potential for development of an additional serious pulmonary vascular disease due to liver disease (HPS). Further, larger, and more comprehensive data clarifying the potential clinical and mechanistic links between PoPH, Sotatercept, circulating bone morphogenetic

protein levels, and HPS will be necessary before this therapy could be considered safe for wider use.

When examining transcriptomic data, gene expression of CD8+ T-Cells and Monocytes appeared to change following Sotatercept treatment. Levels of several proteins, known to enhance protein degradation (RNF130, RNF213, RABGAP1), or whose suppression may have anti-proliferative and pro-apoptotic effects (ASH1L), also changed following Sotatercept treatment and corresponded to Monocyte gene expression changes[24-26]. The mTOR and NF-kB inhibitor classes of drugs, which have anti-inflammatory effects and also affect ubiquitination and protein degradation, were predicted to result in similar gene expression changes to Sotatercept treatment[27-28]. Sotatercept also increased the presence of several hemoglobin subunit proteins, expected given its effectiveness in treating anemia with beta-thalassemia, which supports the premise that the proteomic changes observed reflect Sotatercept therapy rather than being spurious[29]. Together, this suggests Sotatercept may improve disease severity in PoPH through an anti-inflammatory and pro-ubiquitination effect on the pulmonary vasculature, presumably mediated by circulating CD8+ T-Cells and Monocytes through RING finger, GTPase-activator, and histone methyltransferase proteins. Further investigation of circulating leukocyte transcriptome and proteome changes in PoPH patients, in larger cohorts and recognizing the differences in plasma proteomic coverage with different techniques (LC-MS/MS and proximity extension assay), following Sotatercept therapy will be required to validate these findings.

Although our patient's improvement was temporally related to the addition of Sotatercept to stable background PAH therapy (tadalafil and macitentan), we cannot exclude the possibility that

this response was a result of the combination of Sotatercept and specific background therapy, rather than the result of Sotatercept alone. We also cannot exclude the possibility that the proteomic and transcriptomic changes observed in this case were confounded by the patient's underlying liver disease or other external factors, and the challenges in drawing conclusions from a single case report should not be understated. It is known that iron deficiency anemia is deleterious in PAH, and we cannot exclude the possibility that correction of iron deficiency anemia contributed to the improvement in PAH experienced by this patient, their beneficial hemodynamic response to Sotatercept, or both[30]. Prior experience using Sotatercept in PAH patients (non-PoPH) suggests effectiveness regardless of background PAH therapy[2,3,16], but whether this finding extends to PoPH patients, or if the effectiveness of Sotatercept in PoPH is dependent on the particular type of PAH background therapy used or specific liver disease afflicting the patient, remains to be determined. The increasing cardiac output in this patient treated with Sotatercept raises concern that, in a PoPH patient with chronic therapy, this medication may exacerbate hyperdynamic circulation, and the efficacy and tolerability profile of Sotatercept in PoPH may be dependent upon length of exposure to medication.

In summary, we report the use of Sotatercept in the treatment of PoPH, describing both efficacy and tolerability in this PAH subtype. Our data suggests that Sotatercept may be beneficial in carefully selected patients with PoPH, particularly those with hyperdynamic circulation refractory to conventional therapy, and further exploration of this treatment in PoPH is warranted. The potential link between PoPH, Sotatercept, and HPS will need to be further examined to better understand the safety profile of Sotatercept in PoPH. Investigation of Monocytes, CD8+ T-cells, and proteins involved in inflammatory and ubiquitination, which may

be involved in treatment response to Sotatercept in PoPH, may help clarify PoPH molecular pathogenesis and help identify therapeutics that could be repurposed for PoPH treatment.

Table 1: Change in Testing with Sotatercept Therapy over 9 Months

Variable	Baseline Pre-Sotatercept	6-months Post-Sotatercept	9-months Post-Sotatercept	11-months Post-Sotatercept	Change (Baseline to last timepoint)
RHC Hemodynamics					
RA (mmHg)	8	6	5	12	+4
PAS (mmHg)	102	60	57	52	-50
mPAP (mmHg)	65	40	35	35	-30
PAWP (mmHg)	11	7	9	13	+2
CO (L/min)	8.8	9.3	12.5	14.4	+5.6
CI (L/min/m2)	3.87	4.15	5.68	6.8	+2.93
PVR (Wood Units)	6.13	3.5	2.08	1.53	-4.6
Transthoracic Echocardiography					
LVEF (%)	60	55	---	60	0
LVIDD (cm)	5.4	5	---	5.4	0
RVIDD (cm)	4.5	3.7	---	---	-0.8
TAPSE (cm)	2.3	2.7	---	2.6	+0.3
TRV (m/s)	3.9	3.4	---	4.1	+0.2
Laboratory Values					
Creatinine (mg/dL)	0.77	0.75	0.75	0.73	-0.04
Hemoglobin (g/dL)	13.3	14.4	14.5	15.9	+2.6
Hematocrit (%)	37.9	42.1	43.4	44.7	+6.8
Platelet Count	41,000	59,000	61,000	66,000	+25,000
Bilirubin (mg/dL)	2.4	2.5	2.9	3.8	+1.4
INR	1.7	1.5	1.5	1.6	-0.1
MELD 3.0 Score	16	14	16	17	+1

Abbreviations: RHC - right heart catheterization; RA - right atrial pressure; RVS - right ventricular systolic pressure; PAS - pulmonary artery systolic pressure; mPAP - mean pulmonary artery pressure; PAWP - pulmonary artery wedge pressure; CO - cardiac output by indirect Fick ; CI - cardiac index by indirect Fick; PVR - pulmonary vascular resistance; LVEF - left ventricular ejection fraction; LVIDD - left ventricular internal diameter in diastole; RIVDD - right ventricular internal diameter in diastole; TAPSE - tricuspid annular plane systolic excursion; TRV - tricuspid valve regurgitant jet velocity; INR - international normalized ratio; MELD - model for end-stage liver disease

Figure Legends

Figure 1: Mean Pulmonary Artery Pressure Trend Over Time with Different PAH Targeted Therapies

Plot showing mean pulmonary artery pressure (mPAP, mmHg) on right heart catheterization versus time. Specific pulmonary hypertension targeted therapy (agent, dose, route) is specified at the bottom of the figure and in the colored bars across the bottom of the figure.

Figure 2: Pulmonary Vascular Resistance Trend Over Time with Different PAH Targeted Therapies

Plot showing pulmonary vascular resistance (PVR, Wood units) versus time. Specific pulmonary hypertension targeted therapy (agent, dose, route) is specified at the bottom of the figure and in the colored bars across the bottom of the figure.

References

1. Kovacs G, Bartolome S, Denton CP, et al. Definition, classification, and diagnosis of pulmonary hypertension. Eur Respir J 2024;64(4):2401324.
2. Hoeper MM, Badesch DB, Ghofrani HA, et al. Phase 3 trial of sotatercept for treatment of pulmonary arterial hypertension. N Engl J Med 2023;388:1478-1490.
3. Humbert M, McLaughlin V, Gibbs JSR, et al. Sotatercept for the treatment of pulmonary arterial hypertension. N Engl J Med 2021;384:1204-1215.
4. Krowka MJ. Hepatopulmonary Syndrome and Portopulmonary Hypertension: the pulmonary vascular enigmas of liver disease. Clin Liver Dis (Hoboken) 2020;15(S1):S13-S24.
5. Hao Y, Hao S, Andersen-Nissen E, et al. Integrated analysis of multimodal single-cell data. Cell 2021;184(13):3573-3587.e29.
6. Wolock SL, Lopez R, Klein AM. Scrublet: computational identification of cell doublets in single-cell transcriptomic data. Cell Sys 2019;8:281-291.e9
7. Wang Z, Xie L, Ding G, et al. Single-cell RNA sequencing of peripheral blood mononuclear cells from acute Kawasaki disease patients. Nat Commun 2021;12:5444.
8. Ianevski A, Giri AK, Aittokallio T. Fully automated and ultra-fast cell-type identification using specific marker combinations from single-cell transcriptomic data. Nat Commun 2022;13:1246.
9. Shannon P, Markiel A, Ozier O, et al. Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome Res* 2003;13:2498-2505.
10. Subramanian A, Narayan R, Corsello SM, et al. A next generation connectivity map: L1000 platform and the first 1,000,000 profiles. Cell 2017;171(6):1437-1452.e17

11. Ziady AG, Kinter M. Protein sequencing with tandem mass spectrometry. Methods Mol Biol 2009;544:325-341.
12. Kall L, Canterbury JD, Weston J, et al. Semi-supervised learning for peptide identification from shotgun proteomics datasets. Nat Methods 2007;4(11):923-925.
13. van der Burgt YEM, de Meijer E, Palmblad M. Brief evaluation of Olink reveal proximity extension assay for high-throughput proteomics: a case study using NIST SRM 1950 and two spike-in protein standards. J Proteome Res 2025;10.1021/acs.jproteom.5c00571.
14. Krowka MJ, Miller DP, Barst RJ, et al. Portopulmonary hypertension: a report from the US-based REVEAL registry. Chest 2012;141(4):906-915.
15. Jose A, Rahman N, Opotowsky AR, et al. Association of cardiopulmonary hemodynamics and mortality in veterans with liver cirrhosis: a retrospective cohort study. JAHA 2024;13(8):e033847.
16. Preston IR, Badesch D, Ghofrani HA, et al. A long-term follow-up study of Sotatercept for treatment of pulmonary arterial hypertension: interim results of SOTERIA. Eur Respir J 2025;20:2401435.
17. Hakim A, Fricker ZP, Feuerstein JD, et al. Recurrent gastrointestinal bleeding in a patient with pulmonary arterial hypertension treated with Sotatercept. Ann Intern Med 2024;177(1):115-117.
18. Olsson KM, Savale L, Guignabert C, et al. Severe hypoxemia and pulmonary capillary dilatations in PAH patients treated with Sotatercept. Am J Respir Crit Care med 2025;doi:10.1164/rccm/202502-0344RL.

19. Mitchell S, Gomez R, Mathavan A, et al. Development of new intrapulmonary shunts in pulmonary arterial hypertension treated with sotatercept. Am J Respir Crit Care Med 2025;doi:10/1164/rccm.202501-0056RL.
20. Savale L, Tu L, Normand C, et al. Effect of sotatercept on circulating proteomics in pulmonary arterial hypertension. Eur Respir J 2024;64(4):2401483.
21. Pham DM, Subramanian R, Parekh S. Coexisting hepatopulmonary syndrome and portopulmonary hypertension: implications for liver transplantation. J Clin Gastroenterol 2010;44(7):e136-140.
22. Robert F, Certain MC, Baron A, et al. Disrupted BMP-9 Signaling impairs pulmonary vascular integrity in hepatopulmonary syndrome. Am J Respir Crit Care Med 2024;210(5):648-661.
23. Owen NE, Alexander GJ, Sen S, et al. Reduced circulating BMP10 and BMP9 and elevated endoglin are associated with disease severity, decompensation, and pulmonary vascular syndromes in patients with cirrhosis. eBioMedicine 2020;56:102794.
24. Yin H, Qian G, Wang Y, et al. Rab1 GTPase regulates phenotypic modulation of pulmonary artery smooth muscle cells by mediating the transport of angiotensin II type 1 receptor under hypoxia. Int J Biochem Cell Biol 2011;43(3):401-408.
25. Rogawski DS, Deng J, Li H, et al. Discovery of first-in-class inhibitors of ASH1L histone methyltransferase with anti-leukemic activity. Nature Communications 2021;12:2792.
26. Cai C, Tang YD, Zhai J, et al. The RING finger protein family in health and disease. Signal Transduction and Targeted Therapy 2022;7:300.

27. Zhao J, Zhai B, Gygi SP, et al. mTOR inhibition activates overall protein degradation by the ubiquitin proteasome system as well as by autophagy. Proc Natl Acad Sci USA 2015;112(52):15790-7.

28. Yu H, Lin L, Zhang Z, et al. Targeting NF-kB pathway for the therapy of diseases: mechanism and clinical study. Signal Transduct Target Ther 2020;5(1):209.

29. Cappellini MD, Porter J, Origa R, et al. Sotatercept, a novel transforming growth factor B ligand trap, improves anemia in B-thalassemia: a phase II, open-label, dose-finding study. Haematologica 2019;104(3):477-484.

30. Howard LSG, He J, Watson GMJ, et al. Supplementation with iron in pulmonary arterial hypertension. Two randomized crossover trials. Ann Am Thorac Soc 2021;18(6):981-988.

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ED SUMMARY:
Jose et al. report their experience treating a portopulmonary hypertension patient with the activin signalling inhibitor Sotatercept. Treatment resulted in improvement in the burden of pulmonary hypertension, as well as changes in the circulating plasma proteome and pulmonary artery circulating leukocyte transcriptome, demonstrating benefit and supporting further investigation of this therapeutic in the management of portopulmonary hypertension.

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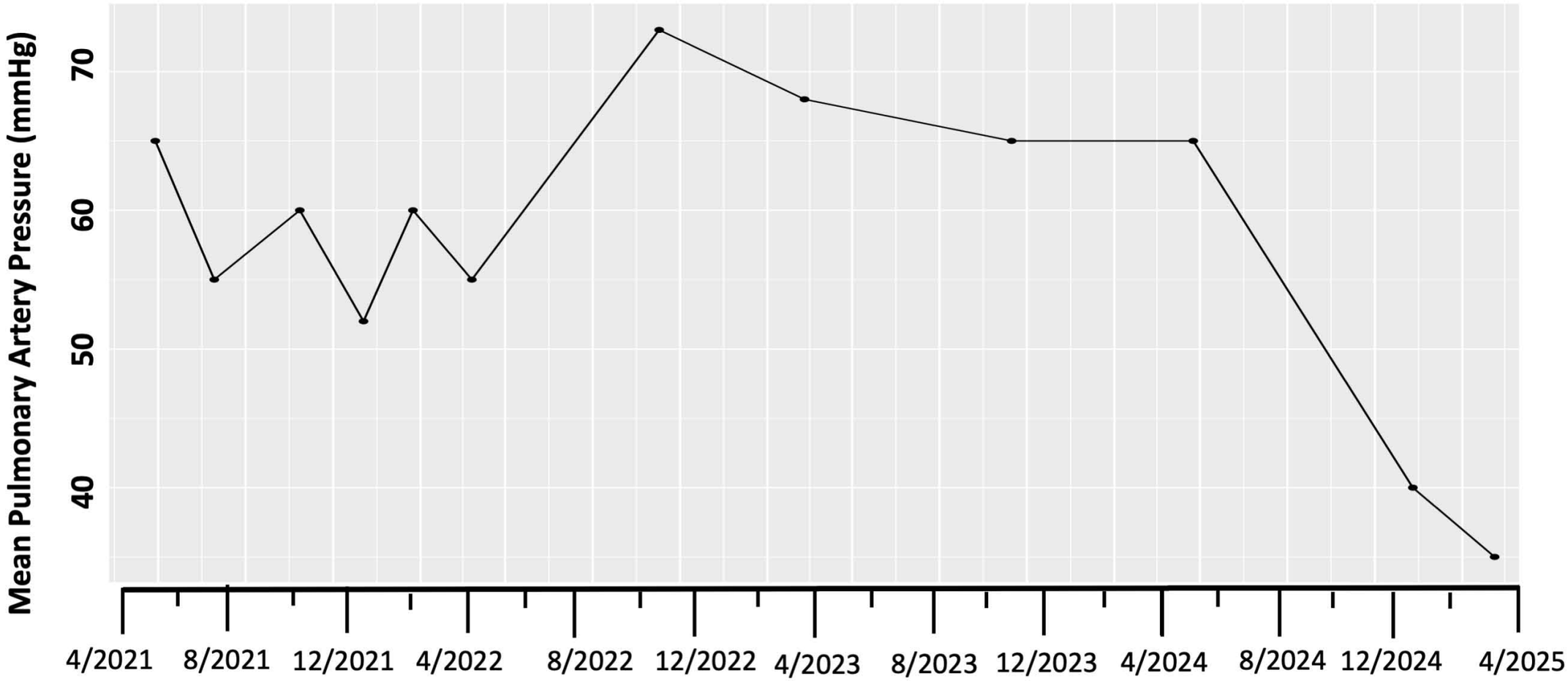
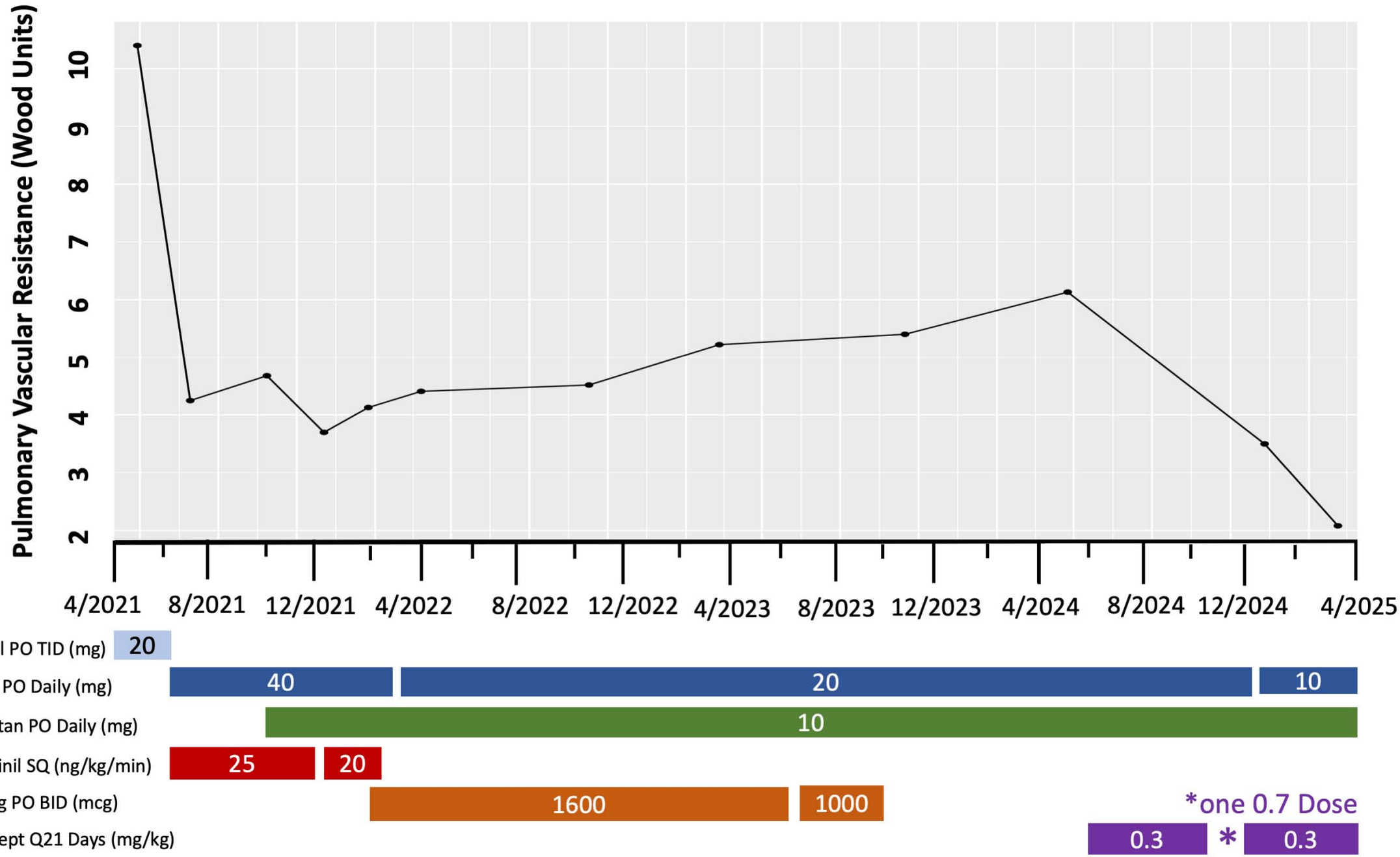

Mean Pulmonary Artery Pressure (mmHg)
70
60
50
40
4/2021
8/2021
12/2021
4/2022
8/2022
12/2022
4/2023
8/2023
12/2023
4/2024
8/2024
12/2024
4/2025


Sildenafil PO TID (mg)
20
Tadalafil PO Daily (mg)
40
20
10
Macitentan PO Daily (mg)
10
Treprostinil SQ (ng/kg/min)
25
20
Selexipag PO BID (mcg)
1600
1000
Sotatercept Q21 Days (mg/kg)
0.3
*
0.3
*one 0.7 Dose


Pulmonary Vascular Resistance (Wood Units)
2
3
4
5
6
7
8
9
10
4/2021
8/2021
12/2021
4/2022
8/2022
12/2022
4/2023
8/2023
12/2023
4/2024
8/2024
12/2024
4/2025
Sildenafil PO TID (mg)
20
Tadalafil PO Daily (mg)
40
20
10
Macitentan PO Daily (mg)
10
Treprostinil SQ (ng/kg/min)
25
20
Selexipag PO BID (mcg)
1600
1000
Sotatercept Q21 Days (mg/kg)
0.3
*
0.3
*one 0.7 Dose