



Pericardial effusions and sotatercept therapy in pulmonary arterial hypertension: a multicentre, real-world experience

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To the Editor:

Sotatercept, an activin signalling inhibitor (ASI), was recently approved to treat pulmonary arterial hypertension (PAH) [1, 2]. Sotatercept improves exercise capacity and reduces morbidity and mortality [3–5]. Four common side-effects found to be associated with sotatercept use in the pivotal clinical trials [4] include polycythaemia (6%), thrombocytopenia, (6%), telangiectasia (10%) and bleeding events (20%). Potentially related to telangiectasias, a rare but serious complication of severe hypoxaemia and intrapulmonary shunting was recently reported [6]. A phase 2 trial (TROPOS) of ciboterecept, another ASI, for the treatment of PAH, was recently halted due to multiple occurrences of unanticipated pericardial effusions in patients in the treatment arm [7]. However, development of pericardial effusions was not significantly higher with sotatercept therapy in the landmark trials [3–5]. In this multicentre case series, we report multiple instances of clinically significant moderate to large pericardial effusions in PAH patients treated with sotatercept.

Among 391 adults with PAH who were consecutively treated with sotatercept as add-on therapy at six comprehensive care centres in the South, Midwest and Northeast USA, we identified 20 cases of new-onset or worsening pericardial effusions. Of these 391 patients, 165 (42.2%) had idiopathic PAH (IPAH), 133 (34.0%) had PAH associated with connective tissue disease (CTD), 34 (8.7%) had drug- and toxin-associated PAH, 26 (6.6%) had heritable PAH (HPAH), 25 (6.4%) had PAH associated with congenital heart disease, five (1.3%) had portopulmonary hypertension, and three (0.8%) had PAH associated with HIV. 70.3% were on a prostacyclin pathway agent at the time of sotatercept start.

20 patients who were treated with sotatercept experienced either new-onset or worsening pericardial effusions, leading to an incidence of 5.1% (20/391 patients). Characteristics for these patients are summarised in table 1. 16 (84.0%) were female with mean±SD age of 62.6±12.8 years), 13 (65.0%) had CTD-PAH and 14 (70.0%) were on triple therapy at the time of sotatercept initiation. 95% of patients (19/20) were on a drug targeting the prostacyclin pathway. 14 (70.0%) patients were white, three (15.0%) were black, two (10.0%) were Hispanic, and one (5.0%) was Asian. All events occurred among patients on 0.7 mg·kg⁻¹ dose of sotatercept with a median exposure period of 136 days (interquartile range (IQR) 89, 207). Seven patients (35.0%) developed new-onset effusions, while 13 (65.0%) developed worsening of an existing pericardial effusion, defined as a clinically significant increase in the size of the effusion, or the development of features of increased pericardial pressure.

When evaluating the cumulative incidence of pericardial effusions across each PAH subgroup, aside from HIV-PAH which carried low representation in the overall population (resulting in a cumulative incidence of 33.3%; 1/3 patients), the group with the highest cumulative incidence was CTD-PAH (9.8%; 13/133 patients). Cumulative incidence was 3.9% in HPAH (1/26 patients), 2.9% in drug and toxin-associated PAH (1/34 patients), and 2.42% in IPAH (4/165 patients).

In all these instances, clinicians who managed these patients attributed the incidence or worsening of effusions to be connected to sotatercept, as the occurrences were associated with contemporaneous improvement in haemodynamics and/or right heart function, as opposed to the progression of cardiopulmonary vascular disease (*i.e.* PAH) (table 1). These patients experienced improvement in haemodynamics despite the development of pericardial effusion, as evidenced by a median change in

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Multicentre US case series identifies clinically significant pericardial effusions in 5.1% of patients with PAH after receiving sotatercept, highlighting a potential drug-related safety signal

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TABLE 1 Characteristics of patients who developed pericardial effusions after treatment with sotatercept

	Age, gender, race/ethnicity	Type of PAH	Background therapy	ASI: number of doses or duration of therapy prior to pericardial effusion	Δ mPAP	Δ BNP/NTproBNP	Δ mRAP	Δ CO/CI	Δ 6MWD	Imaging characteristics at the time of the effusion	Change in RV size and function	Pericardial drainage performed?	Characteristics of pericardium/pericardial effusion	Dose reduction	Prior pericardial effusion?
Case 1	72, F, Hispanic	Drug- and toxin-induced PAH	Inhaled treprostinil, macitentan, riociguat	4 doses (0.7 mg·kg ⁻¹), 75 days	-21 mmHg (-44.7%)	NTproBNP +59 pg·mL ⁻¹ (+74.7%)	-8 mmHg (-88.9%)	CO -3.55 L·min ⁻¹ CI (-51.8%) -0.39 L·min ⁻¹ ·m ⁻² (-10.4%)	-8 m (-2.7%)	Increase in size of pericardial effusion with evidence of developing tamponade physiology	Pre-drug: mildly enlarged; systolic function is moderately depressed; TAPSE 1.7 cm Post-drug: RV size is mildly enlarged; RV systolic function is mildly to moderately depressed	Yes (window)	Serosanguinous fluid (500 mL) Cytology: low cellularity; mesothelial cells; macrophages; small mature lymphocytes; rare neutrophils; RBC	Yes	Yes
Case 2	35, M, Hispanic	HPAH (BMPR2)	<i>i.v.</i> treprostinil, macitentan, tadalafil	6 doses (0.7 mg·kg ⁻¹), 107 days	-14 mmHg (-25%)	NTproBNP -1090 pg·mL ⁻¹ (-89.3%)	-10 mmHg (-66.7%)	CO +0.07 L·min ⁻¹ CI (+1.74%) +0.05 L·min ⁻¹ ·m ⁻² (+2.27%)	+77 m (+19.6%)	Enlargement of pericardial effusion from previous echo and some evidence of tamponade physiology; pericardial enhancement in CMR suggestive of pericarditis	Pre-drug: severely enlarged; systolic function is severely depressed; TAPSE 0.8 cm Post-drug: severely enlarged; systolic function is severely depressed	Yes (window)	Serous (700 mL) LDH: 222 U·L ⁻¹ Protein: 2.3 g·dL ⁻¹ RBC: 28 000 per mm ³ Nucleated cells: 150 per mm ³ Neutrophils: 34% Lymphocytes: 40% Macrophages: 26%	No	Yes
Case 3	47, F, Asian	IPAH	<i>i.v.</i> epoprostenol, macitentan, tadalafil	15 doses (0.7 mg·kg ⁻¹), 319 days	-17 mmHg (-29.8%)	NTproBNP -806 pg·mL ⁻¹ (-51.3%)	-5 mmHg (-35.7%)	CO -3.55 L·min ⁻¹ CI (-45.4%) -1.73 L·min ⁻¹ ·m ⁻² (-44.9%)	+40 m (+10.9%)	New onset, small to moderate posterolateral pericardial effusion; no signs of tamponade	Pre-drug: severely enlarged; systolic function is severely/moderately depressed; TAPSE 1.5 cm Post-drug: enlarged; systolic function is normal; TAPSE 2.3 cm	No, close monitoring	NA	Yes	No
Case 4	54, F, black	CTD-PAH (lupus)	<i>i.v.</i> treprostinil, macitentan, tadalafil	4 doses (0.7 mg·kg ⁻¹), 87 days	-3 mmHg (-7.3%)	NTproBNP -1381 pg·mL ⁻¹ (-30%)	+1 mmHg (+14.3%)	CO +0.37 L·min ⁻¹ CI (+9%) +0.34 L·min ⁻¹ ·m ⁻² (+11.6%)	+3 m (+0.9%)	Large circumferential pericardial effusion, largest (3.8 cm) around posterolateral and infero-posterior walls; right atrial systolic collapse is present however <1/3 of cardiac cycle; findings are suggestive of increased intrapericardial pressure	Pre-drug: RV size is severely enlarged; RV function is severely depressed Post-drug: RV size is enlarged; RV systolic function is moderately to severely depressed	Yes (window)	Serous (750 mL) Biopsy of pericardium: pericardial tissue with reactive mesothelial cell hyperplasia; mature fibrous tissue with patchy mild mononuclear inflammatory cell infiltrate including mature plasma cells	No	Yes
Case 5	80, F, white	IPAH	Selexipag, macitentan, riociguat	5 doses (0.7 mg·kg ⁻¹), 91 days	NA	NTproBNP -408 pg·mL ⁻¹ (-61.4%)	NA	NA	-40 m (-15.8%) [#]	New appearance of trace posterior pericardial effusion in the presence of clinical improvement by symptoms and biomarker improvement	Pre-drug: TAPSE 1.4 cm, RV size severely dilated, right atrial volume index 38.9 mL·m ⁻² , PA systolic pressure 65 mmHg Post-drug: TAPSE 1.8 cm, right ventricular size moderate to severely dilated, right atrial volume index 35.8 mL·m ⁻² , PA systolic pressure 47 mmHg	No, close monitoring	NA	No	No

Continued

TABLE 1 Continued

	Age, gender, race/ethnicity	Type of PAH	Background therapy	ASI: number of doses or duration of therapy prior to pericardial effusion	Δ mPAP	Δ BNP/NTproBNP	Δ mRAP	Δ CO/CI	Δ 6MWD	Imaging characteristics at the time of the effusion	Change in RV size and function	Pericardial drainage performed?	Characteristics of pericardium/pericardial effusion	Dose reduction	Prior pericardial effusion?
Case 6	61, F, white	IPAH	<i>i.v.</i> treprostinil and sildenafil	7 doses (0.7 mg·kg ⁻¹), 149 days	-16 mmHg (-30.8%)	NTproBNP -4 pg·mL ⁻¹ (-3%)	+4 mmHg (+66.7%)	NA	-19 m (-5.89%)	New moderate circumferential pericardial effusion present with no indication of cardiac tamponade	Pre-drug: mild RV dilation and dysfunction Post-drug: normal RV size and function	No	NA	Stopped sotatercept	No
Case 7	77, F, white	CTD-PAH (scleroderma)	Sildenafil, ambrisentan	12 doses (0.7 mg·kg ⁻¹), 171 days	+1 mmHg (+2.9%)	BNP -39 pg·mL ⁻¹ (-2.5%)	+2 mmHg (+25%)	CO -0.4 L·min ⁻¹ (-9.5%) CI +0.4 L·min ⁻¹ ·m ⁻² (+17.4%)	NA	Pre-drug: small circumferential pericardial effusion without evidence of increased pericardial pressure Post-drug: large circumferential pericardial effusion with early cardiac tamponade physiology	Pre-drug: non-dilated RV with hypertrophy and normal function Post-drug: non-dilated RV with normal function and without hypertrophy	Yes	Serous (595 mL) LDH: 250 U·L ⁻¹ RBC: 6063 Nucleated cells: 740 Neutrophils: 49% Lymphocytes: 3% Monocytes: 2% Mononuclear: 46% Protein: 4.3 g·dL ⁻¹ pH: 8.3 Glucose: 90 mg·dL ⁻¹ Cytology: atypical cells, mesothelial cells, numerous macrophages; repeat pericardiocentesis required	Yes (continued dosing after first pericardiocentesis but discontinued after second pericardiocentesis)	Yes
Case 8	79, M, white	CTD-PAH (scleroderma)	Selexipag, sildenafil	10 doses (0.7 mg·kg ⁻¹), 175 days	+3 mmHg (+8.8%)	BNP -77 pg·mL ⁻¹ (-19%)	-3 mmHg (-37.5%)	CO -2.7 L·min ⁻¹ (-39.7%) CI -1.3 L·min ⁻¹ ·m ⁻² (-34.2%)	NA	Pre-drug: small circumferential pericardial effusion without evidence of increased pericardial pressure Post-drug: moderate-to-large circumferential pericardial effusion with increased pericardial pressure but no tamponade	Pre-drug: mildly dilated RV without hypertrophy and normal function Post-drug: mildly dilated RV with hypertrophy and normal function	Yes	Serous (770 mL) LDH: 183 U·L ⁻¹ RBC: 6612 Nucleated cells: 144 Neutrophils: 9% Lymphocytes: 1% Monocytes: 5% Mononuclear: 84% Protein: 45.1 g·dL ⁻¹ pH: 7.8 TG: 20 Glucose: 87 mg·dL ⁻¹ Cytology: atypical epithelioid cells, reactive mesothelial cells, macrophages	Yes	Yes
Case 9	57, F, white	CTD-PAH (scleroderma)	Oral treprostinil, tadalafil, macitentan	10 doses (0.7 mg·kg ⁻¹), 223 days	-10 mmHg (-27.8%)	BNP -126 pg·mL ⁻¹ (-71%)	-4 mmHg (-28.6%)	CO -2 L·min ⁻¹ (-35.7%) CI -1.2 L·min ⁻¹ ·m ⁻² (-38.7%)	NA	Pre-drug: small circumferential pericardial effusion without evidence of increased pericardial pressure Post-drug: moderate circumferential pericardial effusion with possible increased pericardial pressure	Pre-drug: normal RV size and function Post-drug: normal RV size and function	Yes	Serous (585 mL) LDH: 164 U·L ⁻¹ RBC: 304 Nucleated cells: 204 Lymphocytes: 10% Mononuclear: 90% Glucose: 90 mg·dL ⁻¹ Cytology: reactive mesothelial cells, histiocytes	Yes	Yes

Continued

TABLE 1 Continued

	Age, gender, race/ethnicity	Type of PAH	Background therapy	ASI: number of doses or duration of therapy prior to pericardial effusion	Δ mPAP	Δ BNP/NTproBNP	Δ mRAP	Δ CO/CI	Δ 6MWD	Imaging characteristics at the time of the effusion	Change in RV size and function	Pericardial drainage performed?	Characteristics of pericardium/pericardial effusion	Dose reduction	Prior pericardial effusion?
Case 10	61, F, white	CTD-PAH (dcSSc)	Selexipag, tadalafil, ambrisentan	11 doses (0.7 mg·kg ⁻¹), 206 days	+1 mmHg (+5.6%)	NA	+4 mmHg (+80%)	CO -3.9 L·min ⁻¹ (-33.6%) CI -1.4 L·min ⁻¹ ·m ⁻² (-25.9%)	NA	Pre-drug: no pericardial effusion Post-drug: moderate pericardial effusion with possible increased pericardial pressure; CMR suggestive of pericarditis and constrictive physiology after second pericardiocentesis	Pre-drug: mildly dilated RV without hypertrophy and normal function Post-drug: normal RV size and function	Yes	Serous (550 mL) LDH: 201 U·L ⁻¹ RBC: 1830 Nucleated cells: 60 Neutrophils: 28% Lymphocytes: 20% Monocytes: 28% Mononuclear: 24% Protein: 4 g·dL ⁻¹ pH: 7.8 TG: 25 Glucose: 92 mg·dL ⁻¹ Cytology: atypical cells, reactive mesothelial cells, macrophages; repeat pericardiocentesis required	Yes (discontinued dosing after first pericardiocentesis)	No
Case 11	69, F, white	CTD-PAH (suspected anti-synthetase syndrome versus MCTD versus scleroderma)	<i>i.v.</i> treprostinil, tadalafil	5 doses (0.7 mg·kg ⁻¹), 122 days	NA	BNP -320 pg·mL ⁻¹ (-78%)	NA	NA	NA	Pre-drug: small circumferential pericardial effusion without evidence of increased pericardial pressure Post-drug: moderate circumferential pericardial effusion without tamponade physiology	Pre-drug: moderately dilated RV with hypertrophy and normal function Post-drug: normal RV size with hypertrophy and normal function	No	NA	No	Yes
Case 12	45, F, white	CTD-PAH (positive antibodies for scleroderma and RA)	<i>i.v.</i> treprostinil, macitentan, sildenafil	6 doses (0.7 mg·kg ⁻¹), 210 days	NA	BNP -887 pg·mL ⁻¹ (-98%)	NA	NA	NA	Pre-drug: circumferential pericardial effusion without evidence of increased pericardial pressure Post-drug: large circumferential pericardial effusion without tamponade physiology	Pre-drug: severely dilated RV with hypertrophy and mildly reduced function Post-drug: severely dilated RV without hypertrophy and mildly reduced function	No	NA	Yes	Yes
Case 13	71, F, white	IPAH	Selexipag, riociguat, ambrisentan	13 doses (0.7 mg·kg ⁻¹), 295 days	-12 mmHg (-21%)	NTproBNP -3277 pg·mL ⁻¹ (-99%)	+1 mmHg (+10%)	CO +0.57 L·min ⁻¹ (+15.0%) CI +0.35 L·min ⁻¹ ·m ⁻² (+15.0%)	NA	Pre-drug: small circumferential pericardial effusion without evidence of increased pericardial pressure Post-drug: moderate-to-large pericardial effusion without tamponade physiology	Pre-drug: non-dilated RV with hypertrophy and normal function Post-drug: NA	No	NA	No	Yes

Continued

TABLE 1 Continued

	Age, gender, race/ethnicity	Type of PAH	Background therapy	ASI: number of doses or duration of therapy prior to pericardial effusion	Δ mPAP	Δ BNP/NTproBNP	Δ mRAP	Δ CO/CI	Δ 6MWD	Imaging characteristics at the time of the effusion	Change in RV size and function	Pericardial drainage performed?	Characteristics of pericardium/pericardial effusion	Dose reduction	Prior pericardial effusion?
Case 14	53, M, white	HIV-PAH	<i>i.v.</i> epoprostenol, ambrisentan, riociguat	5 doses (0.7 mg·kg ⁻¹), 5 months	NA	NTproBNP –294 pg·mL ⁻¹ (–62%)	NA	NA	+9 m (+1.7%)	Pre-drug: small circumferential pericardial effusion Post-drug: moderate circumferential pericardial effusion	Pre-drug: severely enlarged and dysfunctional RV Post-drug: normal size with moderate enlargement	No	NA	No	Yes
Case 15	47, F, black	CTD-PAH (SSc)	Selexipag, ambrisentan, riociguat	4 doses (0.7 mg·kg ⁻¹), 2 months	–10 mmHg (–25%)	BNP –68 pg·mL ⁻¹ (–24%)	–1 mmHg (–14.3%)	CO –0.10 L·min ⁻¹ (–2.8%) CI –0.08 L·min ⁻¹ ·m ⁻² (–3.8%)	–163 m (–52%)	Pre-drug: large circumferential pericardial effusion without evidence of tamponade Post-drug: (worsening within 1–2 months) very large circumferential pericardial effusion with no evidence of tamponade	Pre-drug: RV normal in size and function Post-drug: RV normal in size and function	Yes (drain)	Serous (800 mL) Cytology: mild chronic inflammation and amorphous debris, negative for malignancy LDH fluid 157 U·L ⁻¹ LDH serum 369 U·L ⁻¹ Protein 4.1 g·dL ⁻¹ Serum 6.1 g·dL ⁻¹ 33% polys, 6% lymphocytes, 59% macrophages, 47 absolute WBC, 40 ANC	Yes	Yes
Case 16	67, F, white	CTD-PAH (SSc)	Sildenafil, ambrisentan, <i>i.v.</i> treprostinil	5 doses (0.7 mg·kg ⁻¹), 3 months	NA	BNP –94 pg·mL ⁻¹ (–70%)	NA	NA	+38 m (+9%)	Pre-drug: small pericardial effusion without evidence of tamponade Post-drug: large circumferential pericardial effusion with no evidence of tamponade	Pre-drug: RV moderately dilated with reduced function (TAPSE 15 mm) Post-drug: (11 months) mildly dilated RV with normal function (TAPSE 25 mm)	No	NA	No	Yes
Case 17	76, F, white	CTD-PAH (SSc)	Selexipag, macitentan, riociguat	4 doses (0.7 mg·kg ⁻¹), 4 months	NA	BNP –52 pg·mL ⁻¹ (–42%)	NA	NA	+9 m (+2.3%)	Pre-drug: no effusion Post-drug: moderate circumferential pericardial effusion with no evidence of tamponade	Pre-drug: RV moderately dilated with normal function (TAPSE NA) Post-drug: (8 months) mildly dilated RV with normal function (TAPSE 22 mm)	No	NA	No	No

Continued

TABLE 1 Continued

	Age, gender, race/ethnicity	Type of PAH	Background therapy	ASI: number of doses or duration of therapy prior to pericardial effusion	Δ mPAP	Δ BNP/NTproBNP	Δ mRAP	Δ CO/CI	Δ 6MWD	Imaging characteristics at the time of the effusion	Change in RV size and function	Pericardial drainage performed?	Characteristics of pericardium/pericardial effusion	Dose reduction	Prior pericardial effusion?
Case 18	80, F, white	CTD-PAH (SSc)	Selexipag, ambrisentan	8 doses (0.7 mg·kg ⁻¹), 11 months	NA	BNP −62 pg·mL ⁻¹ (−42%)	NA	NA	−29 m (−11%)	Pre-drug: no effusion Post-drug: small circumferential pericardial effusion with no evidence of tamponade	Pre-drug: RV mildly dilated with normal function (TAPSE 20 mm) Post-drug: (6 months) normal sized RV with normal function (TAPSE 20 mm)	No	NA	Stopped	No
Case 19	56, M, black	CTD-PAH (SSc)	<i>i.v.</i> treprostinil	4 doses (0.7 mg·kg ⁻¹), 12 weeks	−7 mmHg (−20%)	−5165 pg·mL ⁻¹ (−74.3%)	−6 mmHg (−54.6%)	CO +0.70 L·min ⁻¹ (+38%) CI +0.48 L·min ⁻¹ ·m ⁻² (+36.4%)	NA	Pre-drug: moderate size, circumferential pericardial effusion. Post-drug: large circumferential pericardial effusion with no tamponade physiology	Pre-drug: severe RV enlargement and systolic dysfunction, underfilled left ventricle Post-drug: normal size RV with moderate RV systolic dysfunction, elevated left-sided filling pressures	No	NA	No change	Yes
Case 20	64, F, white	CTD-PAH (SSc)	<i>i.v.</i> treprostinil, sildenafil, macitentan	4 doses (0.7 mg·kg ⁻¹), 12 weeks	−9 mmHg (−20%)	−240 pg·mL ⁻¹ (−17.5%)	−4 mmHg (−30.8%)	CO +0.80 L·min ⁻¹ (+17.4%) CI +0.6 L·min ⁻¹ ·m ⁻² (+23.1%)	NA	Pre-drug: no pericardial effusion Post-drug: normal size RV with hyperdynamic RV function; elevated left-sided filling pressures	Pre-drug: moderate RV dilation with moderate RV systolic dysfunction Post-drug: moderate size pericardial effusion	No	NA	No change	No

References to increased pericardial pressure were based on established sonographic indicators of elevated intrapericardial pressure such as right atrial and ventricular collapse across diastole and/or systole; altered mitral and tricuspid valve inflow velocities, and dilated inferior vena cava with minimal collapse. #: subject complained of back pain at the time of the 6-min walk test. PAH: pulmonary arterial hypertension; ASI: activin signalling inhibitors; mPAP: mean pulmonary artery pressure; BNP: brain natriuretic peptide; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; mRAP: mean right atrial pressure; CO: cardiac output; CI: cardiac index; 6MWD: 6-min walk distance; RV: right ventricle; F: female; M: male; HPAH: heritable pulmonary arterial hypertension; BMPR2: bone morphogenetic protein receptor II; IPAH: idiopathic pulmonary arterial hypertension; CTD: connective tissue disease; dcSSc: diffuse cutaneous systemic sclerosis; MCTD: mixed connective tissue disease; RA: rheumatoid arthritis; SSc: systemic sclerosis; CMR: cardiac magnetic resonance; TAPSE: tricuspid annular plane systolic excursion; PA: pulmonary artery; LDH: lactate dehydrogenase; RBC: red blood cells; TG: triglycerides; ANC: absolute neutrophil count.

mean pulmonary artery pressure of -10 mmHg (IQR -15 , -2), and a median change in mean right atrial pressure (mRAP) of -4 mmHg (IQR -5 , -1) (haemodynamic data available from 12/20 patients). Cardiac output displayed a median change of -1.2 L·min $^{-1}$ (IQR -3.3 , $+0.3$) and cardiac index changed by a median of -0.8 L·min $^{-1}$ ·m $^{-2}$ (IQR -1.3 , $+0.1$). Biomarkers also improved, with brain natriuretic peptide (BNP) and N-terminal prohormone of BNP levels having a median change of -77 pg·mL $^{-1}$ (IQR: -153 , -62) and -607 pg·mL $^{-1}$ (IQR -1308 , -254), respectively. 6-min walk distance was largely stable, with a median change of -3 m (IQR -24 , $+24$).

Due to symptoms of fatigue or exercise intolerance, or echocardiographic indications of increased intrapericardial pressures, 11 patients (48%) required intervention either by pericardiocentesis or by the creation of a pericardial window. From these interventions, pericardial fluid was serous or serosanguinous without evidence of infection or frank haemorrhage but with occasional accumulation of atypical mesothelial and myeloid reactive cells. There was no periprocedural mortality observed in these patients.

Overall, the incidence of pericardial effusions in patients with group 1 PAH was 5.1% (20/391). Since all events of pericardial effusion did not occur within a calendar year, it is difficult to estimate the annual incidence rate. However, if we assume the incidence rate of 5.1% in patients on sotatercept treatment as the total eventual risk and assume a median time to onset of 136 days, we estimate approximately 43 events per 1000 patient-years.

Among 275 patients on background therapy with a prostacyclin pathway agent, 19 (6.9%) developed new onset or worsening effusions, compared to one of 116 patients (0.9%) not on prostacyclin. Although our interpretation is limited by the lack of control patients not treated with sotatercept, this corresponded to an eight-fold increased risk of effusion (RR 8.0, 95% CI 1.1–59.2) in the prostacyclin group and an absolute risk difference of 6.0% (95% CI 2.6–9.5), a finding that was statistically significant ($p=0.011$).

In this case series of patients managed at six PAH comprehensive care centres in the USA, we report clinically significant pericardial effusions in 5.1% of PAH patients treated with sotatercept. The exact mechanism of pericardial effusion development with sotatercept therapy is unclear. Historically, pericardial effusions in PAH have been attributed to worsening right heart failure [8]. Representing a poor prognostic PAH biomarker [9], pericardial effusions tend to develop when a higher mRAP due to right heart failure impairs fluid reabsorption of pericardial fluid *via* the venous or lymphatic channels draining into the right atrium [8, 10]. However, in this series, patients developed pericardial effusion despite mostly improved and/or stable right ventricular function. This argues against worsening right heart failure as a predominant mechanism of development of pericardial effusion.

Rather, the temporal association of sotatercept therapy prompts the serious consideration of a drug effect. Sotatercept, apart from acting as an activin ligand trap, also decreases levels of bone morphogenetic proteins (BMP) 9 and 10 [11], which are the ligands for BMP type II receptors [12]. Similarly, dalantercept [13], a fusion protein that blocks BMP9 and BMP10, and cibotercept [14], which selectively blocks only BMP10, have both been linked to increased incidence of pericardial effusions. BMP and activin signalling perform known roles in maintenance of vascular structure and integrity [15, 16], thus offering a potential mechanism that could explain the development of new telangiectasias and potentially new arteriovenous malformations [6] with sotatercept treatment. Notably, loss of BMP9 has been reported to exacerbate lymphatic drainage dysfunction and cardiac inflammation after myocardial infarction in mice [15]. Whether similar effects occur in humans during sotatercept therapy is an unknown and merits further investigation. The putative ability of sotatercept to alter venous or lymphatic wall integrity similarly could constitute a viable mechanism underlying an increased risk of pericardial effusion. Moreover, it is tempting to speculate that blockade of BMP9 and BMP10 signalling may represent a unifying explanation for an apparent consequence of not only sotatercept but a class effect of ASIs.

Numerous questions remain. Development of pericardial effusions was seen only in a minority of PAH patients, and predisposing factors are unclear. All patients in our series were on a 0.7 mg·kg $^{-1}$ dose, thus raising concern of a dose-dependent phenomenon. Yet, whether it is advisable to continue sotatercept even at a lower dose in patients requiring pericardial intervention remains to be seen. Patients on background therapy with a prostacyclin pathway agent had an eight-fold increased risk of effusion in our cohort. When considered with prior clinical observations of adverse events when both drug classes are used in combination, this anecdotal observation warrants further investigation.




Furthermore, the highest cumulative incidence for pericardial effusions was seen in CTD contexts (9.8%; 13/133 patients), a group comprising the majority of cases in this series (65%; 13/20), suggesting a

potential predisposing immune or inflammatory component. While there was evidence in some cases of inflammatory processes in the pericardium, the majority of cases where pericardial fluid analysis was available demonstrated transudative qualities, without significant acute inflammatory cellularity. Furthermore, in two patients who underwent pericardial biopsy at the time of window creation, histopathology suggested only reactive mesothelial cells. Two patients experienced two sequential episodes of pericardial effusion, each necessitating drainage. During the second event, cardiac magnetic resonance imaging (cMRI) in both showed pericardial inflammation consistent with pericarditis. While one had documented CTD-PAH, the other also tested weakly positive for antinuclear antibodies, despite a diagnosis of HPAH. An additional scleroderma PAH patient also exhibited the signs of pericarditis on the cMRI (case 10) (table 1). These findings suggest a possible autoimmune process related to these associations.

The PULSAR, STELLAR and ZENITH trials did not report significant occurrence of pericardial effusions [3–5]. This could stem from several possibilities, including relative underrepresentation of CTD-PAH patients in these studies or a potentially longer length of treatment that may be needed to develop effusions. Alternatively, based on the TROPOS trial [7], awareness to screen for pericardial effusions in this drug class has only recently been emphasised, suggesting the possibility of detection bias in the earlier studies. The open-label study of sotatercept (SOTERIA) should be able to offer more detail on the incidence of pericardial effusions in patients with a longer-term exposure to this drug [17].

Our real-world, retrospective series is limited by non-standardised data collection and variable follow-up duration. While interpreting these findings one must caution the limitation of real-world analysis and absence of a control arm. Since development of a pericardial effusion is already a known consequence of PAH progression, definitive causative attribution of new or existing effusions solely to sotatercept is not possible. In fact, cohort studies [18] have reported development of pericardial effusion in as high as 44% of patients, which is associated with poor survival. However, independent observation of the same safety signal across all six centres reinforces the plausibility, causal association and clinical relevance of at least a partial drug effect. Each individual clinician across the expert pulmonary hypertension care centres determined if these pericardial effusions were temporally associated with sotatercept therapy, if they occurred in the absence of any other obvious cause, and/or if there was disease improvement based on imaging or haemodynamics.

Further basic and translational research will be essential to better delineate the mechanism and risk factors for pericardial effusion with ASIs. Importantly, it is not clear whether these effusions should be classified as an off-target or on-target side-effect of this drug or drug class, thus carrying broad implications on how to maximise therapeutic value while minimising adverse clinical outcomes. Meanwhile, this evolving clinical scenario calls for heightened vigilance and timely intervention from treating clinicians.

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