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CASE SERIES
Congenital heart disease

Contemporary use of Selexipag in pulmonary arterial hypertension associated with congenital heart disease: a case series

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Background There are significant risks of parenteral prostacyclin use in patients with pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD), which may limit their use. Selexipag is an oral, selective prostacyclin analogue that has been shown to reduce disease progression and improve exercise capacity in patients with PAH-CHD. Administering Selexipag in patients with PAH-CHD could potentially overcome some of the risks of parenteral therapy while improving clinical outcomes.

Case summary We report five cases highlighting the clinical uses of Selexipag in patients with PAH-CHD. In the first two cases, Selexipag was initiated as part of a Treat-to-close strategy. In the third case, initiation of Selexipag improved symptoms and objective exercise capacity in a patient with Eisenmenger syndrome. In the fourth and fifth cases, rapid cross-titration protocols were used to transition from parenteral prostacyclins to Selexipag. In the fourth case, Selexipag was initiated in the context of significant side effects limiting parenteral prostacyclin use. In the fifth case, Selexipag was used to down-titrate from parenteral prostacyclins following closure of a sinus venosus atrial septal defect and redirection of anomalous pulmonary veins.

Discussion Selexipag is a promising oral therapy for patients with at various stages of the spectrum of PAH-CHD to improve symptoms, exercise capacity and, in some cases, haemodynamics. Our cases also highlight practical aspects of Selexipag use including targeting the individualized maximally tolerated dose for each patient, managing side effects and managing dose interruptions.

Keywords Case series • Congenital heart disease • Pulmonary arterial hypertension • Prostacyclin analogues

Learning points

- The oral route of administration of Selexipag overcomes some of the challenges of using parenteral prostacyclins in patients with congenital heart disease.
- Patients at various stages of the spectrum of pulmonary arterial hypertension associated with congenital heart disease can benefit from Selexipag.
- Titration of Selexipag should focus on achieving the individualized maximally tolerated dose for each patient.

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Introduction

Pulmonary arterial hypertension associated with congenital heart disease (PAH-CHD) encompasses 10–20% of all PAH cases.[1,2] While some goals of treating PAH-CHD are similar to treating other aetiologies of PAH, there are some unique considerations in PAH-CHD.

Monotherapy or combination therapy with endothelin antagonists, phosphodiesterase-5 inhibitors, and prostacyclins[3,4] is recommended. While parenteral prostacyclins have clinical and mortality benefits in PAH,[5] use in patients with PAH-CHD is limited by the challenges relating to intravenous (IV) or subcutaneous (SC) administration, the impact on quality of life, the risk of infection and the risk of systemic embolism from catheter-related thrombi in patients with unrepaired shunts.

Selexipag is an oral, selective prostacyclin receptor agonist. In a randomized, placebo controlled substudy of 110 well-matched PAH-CHD patients with repaired shunts, Selexipag decreased the composite primary outcome (disease progression, hospitalization, progression to parenteral therapy, death, need for transplant/atrial septostomy), increased objective exercise capacity, and decreased N-terminal pro B-type natriuretic peptide (NT-proBNP) levels.[6]

Herein, we report five cases where Selexipag was used across the spectrum of PAH-CHD (*Table 1*), including patients with unrepaired shunts.

Timeline

Patient 1

Date	Event
Childhood	Diagnosed with atrial septal defect (ASD)
March 2016	Re-established care with congenital cardiology clinic
April 2016	Heart catheterization: severely elevated mean pulmonary arterial pressure (mPAP), severely elevated pulmonary vascular resistance (PVR), net right-to-left shunt
	Tadalafil and Macitentan initiated
December 2016	Heart catheterization: moderately elevated mPAP, mildly elevated PVR, net left-to-right shunt
	Selexipag initiated
September 2017	Heart catheterization: haemodynamics suitable for ASD closure
	ASD closed
February 2018	Heart catheterization: mildly elevated mPAP, normal PVR
	Selexipag wean started
June 2018	Heart catheterization: mildly elevated mPAP, normal PVR
	Macitentan weaned
December 2018	Tadalafil weaned
Follow-up	Heart catheterization: borderline elevated mPAP, normal PVR

Continued

Continued

Patient 2

Date	Event
1987	Diagnosed with aortopulmonary window
2013	Tadalafil started
January 2017	Immigrated to USA
May 2017	Established care with primary care provider
December 2017	Heart catheterization: Eisenmenger physiology
	Macitentan started
February 2018	Selexipag started
July 2018	Heart catheterization: haemodynamics suitable for fenestrated closure
Follow-up	Patient declined surgical closure

Patient 3

Date	Event
1969 (birth)	Diagnosed with patent ductus arteriosus
2010	Started Bosentan
2018	Bosentan changed to Tadalafil
	Started Macitentan
September 2018	Referral for consideration of escalation of pulmonary vasodilators
October 2018	Selexipag initiated
Follow-up	Patient reports improved symptoms

Patient 4

Date	Event
1988	Diagnosed with ventricular septal defect
December 2019	Established care in USA
	Admitted to hospital, Tadalafil and Epoprostenol started. Macitentan not tolerated
February 2020	Two hospitalizations for severe local skin reactions at catheter site
	Rapid cross-titration of Selexipag
Follow-up	Tolerating Selexipag and Tadalafil

Patient 5

Date	Event
2016	Diagnosed with sinus venosus ASD and pulmonary arterial hypertension
September 2018	Heart catheterization on Treprostinil (subcutaneous), Macitentan and Tadalafil: haemodynamics suitable for closure
January 2019	Surgical repair of sinus venosus ASD and partial anomalous pulmonary veins
	Complicated by vasodilatory state and renal dysfunction requiring dialysis
	Heart catheterization on Treprostinil, Macitentan, and Sildenafil: mild elevation in mPAP, normal PVR
June 2019	Heart catheterization on Treprostinil, Macitentan, and Sildenafil: borderline elevation in mPAP
	Treprostinil wean started
July 2019	Admitted for rapid cross-titration from Treprostinil to Selexipag
Follow-up	Tolerating oral triple therapy

Table 1 Summary of uses of Selexipag in our case series

	Congenital diagnosis	Stage of PAH-CHD	Baseline WHO FC status	Baseline systemic saturation	Indication for Selexipag	Maximally tolerated dose	Clinical status following Selexipag initiation
Patient 1	Secundum atrial septal defect	Eisenmenger physiology	II	90% RA	Treat-to-close	1600 μg twice daily	Haemodynamics suitable for closure on oral triple therapy Improved symptoms (WHO FC I) Improved 6MWD
Patient 2	Aortopulmonary window	Eisenmenger physiology	II–III	84% RA	Treat-to-close	1600 μg twice daily	Haemodynamics suitable for closure on oral triple therapy Improved symptoms (WHO FC I)
Patient 3	Patent ductus arteriosus	Eisenmenger physiology	III	81% RA	Symptomatic improvement in Eisenmenger syndrome	600 μg in the morning, 800 μg in the evening	Improved symptoms (WHO FC II) Improved 6MWD
Patient 4	Ventricular septal defect	Severe pulmonary arterial hypertension due to systemic to pulmonary shunt	III	93% RA	Cross-titration parenteral prostacyclin not tolerated	1400 μg twice daily	Maintained WHO FC III symptoms and saturation No further skin reactions
Patient 5	Repaired sinus venosus atrial septal defect	PAH after defect correction	II	98% 4 L O_2	Cross-titration parenteral prostacyclin no longer required following Treat-to-close	1000 μg twice daily	Maintained WHO FC II symptoms and saturation Subclinical decline in cardiac index

6MWD, 6-min walk distance; O_2, oxygen; PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; RA, room air; WHO FC, World Health Organization Functional Class.

Case presentation

Patient 1

A 31-year-old woman [body mass index (BMI) = 21 kg/m^2] with a large unrepaired secundum atrial septal defect (ASD), normal pulmonary venous drainage and severe pulmonary artery (PA) dilation (49 mm) was referred for evaluation after a lapse in care. Baseline haemodynamics were consistent with Eisenmenger physiology (*Table 2*). Repeat catheterization on Macitentan 10 mg daily and Tadalafil 40 mg daily demonstrated improvements in haemodynamics; however, the haemodynamics remained borderline for ASD closure (*Table 2*). Given the risks of systemic embolism, the risks of line-related infection and the patient's preference to avoid parenteral therapy, Selexipag was subsequently uptitrated to the maximally tolerated dose of 1600 μg b.i.d. with bothersome, yet tolerable, side effects (myalgias, headaches, jaw pain, nausea, vomiting, and diarrhoea). Repeat haemodynamics after 3 months of therapy were suitable for closure (*Table 2*). The ASD was closed percutaneously with a 36 mm Amplatzer septal occluder. Starting 4 months following closure, she underwent serial right heart catheterizations to guide down-titration of oral pulmonary vasodilators. Selexipag was weaned first, followed by Macitentan and then Tadalafil over the course of 12 months. The mean PA pressure was borderline elevated with a normal pulmonary vascular resistance (PVR) following discontinuation of all pulmonary vasodilators (*Table 2*). Improvements in her functional capacity and in her 6-min walk distance (6MWD) were also observed (*Table 2*).

Patient 2

A 29-year-old woman was referred when cyanosis was noted on a visit to establish care with a primary care provider. She reported she

Table 2 Summary of haemodynamic and clinical data at various timepoints for patients receiving Selexipag in a Treat-to-close strategy

Therapy	Systemic saturation on room air (%)	mPAP (mmHg; normal <20–25)	PASP (mmHg; normal <35)	SBP (mmHg; normal 120–130)	PCWP/direct LA pressure (mmHg; normal 4–12)	PVR (WU; normal <3)	Qp:Qs (normal = 1)	WHO FC	6MWD (m)
Patient 1: Secundum ASD									
None	90	60	97	110	4	11	0.7	II	127
Macitentan and Tadalafil	95	44	69	90	9	4.5	2.7	II	NM
Macitentan, Tadalafil, Selexipag	94	27	48	90	5	1.7	3.8	I	500
Percutaneous ASD closure performed									
Macitentan, Tadalafil, Selexipag	100	20	27	98	7	2.3	1.1	I	580
Macitentan, Tadalafil	99	26	35	99	13	2.3	0.92	I	NM
No therapy	99	23	31	103	9	2.8	1	I	NM
Patient 2: Aortopulmonary window									
Tadalafil	84	72	101	98	5	19	0.7	II-III	180
Tadalafil, Macitentan, Selexipag	91	70	89	97	5	6.2	2.3	I	NM

LA, left atrial; mPAP, mean pulmonary arterial pressure; NM, not measured; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SBP, systolic blood pressure; WHO FC, World Health Organization Functional Class; WU, Wood Units.

Table 3 Summary of haemodynamic and clinical data for a patient receiving Selexipag to improve symptoms in Eisenmenger syndrome

Therapy	Lower extremity saturation (%)	mPAP (mmHg; normal <20–25)	PASP (mmHg; normal <35)	SBP (mmHg; normal 120–130)	PCWP/direct LA pressure (mmHg; normal 4–12)	PVR (WU; normal <3)	Qp:Qs (normal = 1)	WHO FC	6MWD (m)
Patient 3: Patent ductus arteriosus									
None	81	102	140	115	12	23	0.6	III	NM
Tadalafil and Macitentan	NM	NM	NM	NM	NM	NM	NM	III	360
Tadalafil, Macitentan, Selexipag	80	76	122	110	12	24	0.8	II	485

LA, left atrial; mPAP, mean pulmonary arterial pressure; NM, not measured; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SBP, systolic blood pressure; WHO FC, World Health Organization Functional Class; WU, Wood Units.

was diagnosed with a hole in her heart and prescribed Tadalafil 20 mg daily for years prior to immigrating to the USA. She was experiencing World Health Organization Functional Class (WHO FC) II–III symptoms and had a resting systemic saturation of 84%. Subsequent imaging demonstrated a large aortopulmonary window. Haemodynamic catheterization on Tadalafil 20 mg daily identified Eisenmenger physiology (*Table 2*). Macitentan 10 mg daily was started followed by Selexipag. She transiently experienced tolerable nausea, vomiting, and headaches with each increase in dosing to a maximum dose of 1600 µg b.i.d. Repeat cardiac catheterization after 3 months of oral triple therapy revealed improvements with haemodynamics suitable for fenestrated closure. Notably, the minimal change in PA pressures despite significant reversal of the direction of the shunt and reduction in the PVR was expected given the large size of the defect. Although fenestrated closure was recommended, she made an informed decision not to proceed with surgical repair.

Patient 3

A 48-year-old woman with an unrepaired patent ductus arteriosus associated with Eisenmenger physiology (*Table 3*) was referred for consideration of escalation in pulmonary vasodilators. She was continuing to experience WHO FC III symptoms on Tadalafil 20 mg daily and Macitentan 10 mg daily. She declined parenteral prostacyclin therapy. Selexipag was initiated at 200 µg b.i.d. and increased by 400 µg a day every week with the intention of improving symptoms and functional capacity. She intermittently stopped taking Selexipag for a week when the dose was increased from 600 to 800 µg b.i.d.

due to intolerable headaches and nausea. The dosage was then resumed at 200 μg b.i.d. and uptitrated to 600/800 μg b.i.d. which has been well tolerated. Although her haemodynamics on oral triple therapy remained consistent with Eisenmenger physiology, subjective and objective improvements in symptoms and functional class were noted (*Table 3*).

Patient 4

A 37-year-old woman with severe PAH secondary due to an unrepaired doubly committed ventricular septal defect (VSD) experienced improvement from WHO FC IV to WHO FC III symptoms following initiating and uptitration of medical therapy (Tadalafil 40 mg daily, epoprostenol 12 ng/kg/min, lasix 20 mg daily, and spironolactone 50 mg daily). She experienced pulmonary oedema limiting the use of Macitentan. She required admission to hospital twice for evaluation of significant local skin reactions to multiple dressings, adhesives and cleaning solutions limiting further uptitration of epoprostenol. She also expressed a need to travel overseas. The team undertook a shared decision-making approach with the patient in assessing the risks and benefits of transitioning to oral Selexipag. Following a repeat right heart catheterization demonstrating severe pre-capillary pulmonary hypertension with haemodynamics borderline for VSD closure (*Table 4*), the patient underwent rapid cross-titration from epoprostenol to Selexipag as an inpatient. The dose of epoprostenol was decreased by 1 ng/kg/min three times a day (0900, 1500, and 2100). The Selexipag dose started at 200 μg and was increased by 200 μg every 12 h to a maximally tolerated dose of 1400 μg. Vital signs were monitored every 4 h without hypotension or worsening hypoxia noted. The cross-titration was completed in 5 days. She experienced tolerable headaches and muscle aches while taking Selexipag, which improved with Tylenol and tramadol.

Patient 5

A 59-year-old woman with PAH-CHD secondary to a sinus venosus ASD and partial anomalous pulmonary venous return underwent surgical correction following a successful Treat-to-close strategy with Tadalafil 40 mg daily, Macitentan 10 mg daily, and Treprostinil 60 ng/kg/min SC. Her surgical course was complicated by a prolonged vasodilatory state and renal dysfunction requiring dialysis. She was discharged on sildenafil 40 mg t.i.d., Macitentan 10 mg t.i.d., and Treprostinil 28 ng/kg/min SC. Cross-titration from Treprostinil to Selexipag was planned on the basis of continued clinical and haemodynamic improvements. The dose of Treprostinil was then weaned to 20 ng/kg/min as an outpatient in anticipation of an inpatient admission for rapid cross-titration to Selexipag. Throughout the 5-day admission, the Selexipag dose was increased from 200 μg b.i.d. to 1000 μg b.i.d. (increases of 200–400 μg daily) and the Treprostinil dose was weaned by 2 ng/kg/min three times a day (0600, 1200, and 1800). Vitals were monitored every 4 hours without hypotension or hypoxia noted. Invasive haemodynamics immediately following transition to Selexipag 1000 μg b.i.d. in addition to sildenafil 40 mg t.i.d. and Macitentan 10 mg daily revealed similar PVR however there was a decline in cardiac index (CI) from 2.9 L/min/m^2 prior to the cross-titration to 1.8 L/min/m^2 (normal 2.5–4 L/min/m^2). Despite the decrease in CI, she did not experience worsening of symptoms or functional capacity.

Table 4 Summary of cross-titration protocols, clinical data and haemodynamic data for patients who received Selexipag to cross-titrate from parenteral prostacyclins

	Indication for cross-titration	Parenteral infusion dose and route prior to transition	Parenteral infusion dose and route at Selexipag initiation	Decrement in parenteral dose	Increment in Selexipag	Maximal dose of selexipag	Worsening of symptoms	Notable haemodynamic changes following cross-titration
Patient 4 VSD	Recurrent local skin reactions	Epoprostenol 12 ng/kg/min intravenously	Epoprostenol 12 ng/kg/min intravenously	1 ng/kg three times a day	200 μg every 12 h	1400 μg twice daily	No	NM
Patient 5 Repaired sinus venosus ASD	Improved haemodynamics following shunt closure, parenteral agents no longer required	Treprostinil 28 ng/kg/min subcutaneously	Treprostinil 20 ng/kg/min subcutaneously	2 ng/kg/min three times a day	200 μg every 12 h	1000 μg twice daily	No	Similar PVR (2.7 vs. 2.8 WU, normal <3 WU) Reduced cardiac index (normal 2.5–4 L/min/m^2, pre-titration 2.9 L/min/m^2 vs. post-titration 1.8 L/min/m^2)

ASD, atrial septal defect; NM, not measured; PVR, pulmonary vascular resistance; VSD, ventricular septal defect; WU, Wood units.

Discussion

These five patients highlight the varied uses, clinical effects and haemodynamic changes with Selexipag in adults with PAH-CHD with unrepaired and repaired shunts (*Table 1*).

Clinical uses of Selexipag

Treat-to-close is an emerging strategy for patients with PAH-CHD with pre- and post-tricuspid shunts. In both Patient 1 and Patient 2, Eisenmenger physiology was reversed with oral triple therapy. Robust parameters to predict whether a patient's haemodynamics will respond to triple therapy are currently lacking. Bradley *et al.*[7] identified lower BMI as potential predictor of response to pulmonary vasodilators in patients with PAH-CHD and unrepaired ASDs, also noting trends suggesting smaller PA diameters (<30 mm), younger age (<34 years) and less tricuspid regurgitation as potential predictors. Although Patient 1 had a large PA, all other clinical features suggested that she would respond to pulmonary vasodilators.

The limited data on Selexipag use in patients with Eisenmenger syndrome demonstrates that it is well tolerated[8] and that it can improve clinical and haemodynamic status.[9]

As seen with Patients 4 and 5, cross-titration from parenteral therapy may be considered when parenteral therapy is not well tolerated or is no longer necessary from a haemodynamic perspective. Most patients undergoing rapid[10,11] or outpatient[10,12]cross-titration maintain or improve their subjective functional class,[10,11,13] their objective exercise capacity[11–13] and the levels of NT-proBNP.[11,12] In the two case series reporting comprehensive invasive haemodynamics following cross-titration,[11,14] PA pressures, right atrial pressures, and PVR were similar however reductions in the CI within the first 6 months persisting to 17 months post-transition were also noted. A subclinical decline in CI was also noted in Patient 5. These subclinical changes in haemodynamics highlight the need for haemodynamic follow-up, particularly in cases where a re-trial of parenteral prostacyclins is possible.

Practical aspects of using Selexipag

Most of our patients experienced manageable side effects with Selexipag. The majority of patients receiving Selexipag or placebo in the GRIPHON substudy of patients with PAH-CHD experienced side effects (95% vs. 98%). The most common side effects include headaches, myalgias, arthralgias, fatigue, nausea, vomiting, diarrhoea, jaw pain, dizziness, and flushing. However, side effects only warranted discontinuation of Selexipag in 8% of patients.[6]

Patients 3, 4, and 5 achieved maximally tolerated doses lower than the maximal possible dose on the product monograph. The findings from the overall GRIPHON study[15] emphasize achieving the individualized maximally tolerated dose as the effect of Selexipag on the primary composite endpoint was consistent across low, medium, and high doses of Selexipag. A potential explanation for the similar clinical benefit with varying doses is that the density of prostacyclin receptors may also vary amongst patients.[16]

Treatment interruptions are common, occurring in 15% of patients in the GRIPHON trial.[17] Treatment interruptions are most common in the titration phase and are most commonly due to adverse events or administrative issues.[17] There was no evidence of haemodynamic decompensation noted during periods of treatment interruption, possibly because the half-life of Selexipag is relatively long and patients were on background therapy. If the interruption is less than 3 days, the product monograph recommends resuming Selexipag at the current dose. If the interruption is longer than 3 days, then the patient should resume Selexipag 200 µg b.i.d. and uptitrate by 400 µg daily on a weekly basis. Most patients are able to return to a similar dose of selexipag, however if the interruption occurs during the maintenance phase the highest tolerated dose was lower than prior to the interruption in nearly a third of patients.[17]

While the product monograph recommends weekly uptitration by 400 µg daily every week, cross-titration can occur rapidly over days in the inpatient setting. Selexipag doses can be increased by 200–400 µg daily while the parenteral therapy is down-titrated.[10,11,14]

Future directions

Identifying clinical predictors of patients likely to have suitable haemodynamics for closure with oral triple therapy may guide our use of Selexipag and parenteral therapies in a Treat-to-close strategy. Furthermore, initiating oral triple therapy may become the initial strategy for PAH-CHD if studies investigating this strategy upfront for patients with WHO FC II-III symptoms identify a clinical benefit. Future studies on specific subgroups of CHD, such as those with Eisenmenger Syndrome or Fontan physiology, may guide its use in these populations. Further understanding of the factors that influence the individualized maximal dose could guide uptitration strategies and minimize treatment interruptions.

Summary

In summary, Selexipag is a promising oral therapy particularly in patients with PAH-CHD.

Lead author biography

Dr Sarah Blissett was an Adult Congenital Heart Disease Fellow at University of California San Francisco when this article was written. She is now an Assistant Professor of Medicine in the Division of Cardiology at Western University in London, Ontario, Canada. She is interested in advancing medical education within Cardiology.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patients in line with COPE guidance.

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References

1. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V *et al.* Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med* 2006;**173**:1023–1030.
2. Jansa P, Jarkovsky J, Al-Hiti H, Popelova J, Ambroz D, Zatocil T *et al.* Epidemiology and long-term survival of pulmonary arterial hypertension in the Czech Republic: a retrospective analysis of a nationwide registry. *BMC Pulm Med* 2014;**14**:45.
3. Galie N, Manes A, Palazzini M, Negro L, Marinelli A, Gambetti S *et al.* Management of pulmonary arterial hypertension associated with congenital systemic-to-pulmonary shunts and Eisenmenger's syndrome. *Drugs* 2008;**68**: 1049–1066.
4. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A *et al.* 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Rev Esp Cardiol (Engl Ed)* 2016;**69**:177.
5. Simonneau G, Barst RJ, Galie N, Naeije R, Rich S, Bourge RC *et al.* Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2002;**165**:800–804.
6. Beghetti M, Channick RN, Chin KM, Di Scala L, Gaine S, Ghofrani HA *et al.* Selexipag treatment for pulmonary arterial hypertension associated with congenital heart disease after defect correction: insights from the randomised controlled GRIPHON study. *Eur J Heart Fail* 2019;**21**:352–359.
7. Bradley EA, Chakinala M, Billadello JJ. Usefulness of medical therapy for pulmonary hypertension and delayed atrial septal defect closure. *Am J Cardiol* 2013;**112**: 1471–1476.
8. El-Kersh K, Suliman S, Smith JS. Selexipag in congenital heart disease-associated pulmonary arterial hypertension and Eisenmenger syndrome: first report. *Am J Ther* 2018;**25**:E714–E715.
9. Barnikel M, Kneidinger N, Klenner F, Waelde A, Arnold P, Sonneck T *et al.* Real-life data on Selexipag for the treatment of pulmonary hypertension. *Pulm Circ* 2019;**9**:204589401983219.
10. Fanous SM, Janmohamed M. Transition from treprostinil to selexipag in patients with pulmonary arterial hypertension: Case series. *Am J Heal Pharm* 2018;**75**: 1877–1881.
11. Yanaka K, Guillien A, Soumagne T, Benet J, Piliero N, Picard F *et al.* Transition from intravenous epoprostenol to selexipag in pulmonary arterial hypertension: a word of caution. *Eur Respir J* 2020;**55**:1902418.
12. Frost A, Janmohamed M, Fritz JS, McConnell JW, Poch D, Fortin TA *et al.* Safety and tolerability of transition from inhaled treprostinil to oral selexipag in pulmonary arterial hypertension: results from the TRANSIT-1 study. *J Hear Lung Transplant* 2019;**38**:43–50.
13. Furukawa A, Tamura Y, Iwahori H, Goto M, Ohashi N, Okabe T *et al.* Successful transition from Treprostinil to Selexipag in patient with severe pulmonary arterial hypertension. *BMC Pulm Med* 2017;**17**:1–3.
14. Holthaus N, Prins KW, Rose L, Prisco S, Pritzker M, Thenappan T. Transition from parental prostacyclin to selexipag: a case series of five pulmonary arterial hypertension patients. *Pulm Circ* 2019;**9**:2045894019862167.
15. Sitbon O, Channick R, Chin KM, Frey A, Gaine S, Galiè N *et al.* Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2015;**373**: 2522–2533.
16. Rajkumar R, Konishi K, Richards TJ, Ishizawar DC, Wiechert AC, Kaminski N *et al.* Genomewide RNA expression profiling in lung identifies distinct signatures in idiopathic pulmonary arterial hypertension and secondary pulmonary hypertension. *Am J Physiol Heart Circ Physiol* 2010;**298**:H1235–H1248.
17. Preston IR, Channick RN, Chin K, Di Scala L, Farber HW, Gaine S *et al.* Temporary treatment interruptions with oral selexipag in pulmonary arterial hypertension: insights from the Prostacyclin (PGI2) Receptor Agonist in Pulmonary Arterial Hypertension (GRIPHON) study. *J Hear Lung Transplant* 2018;**37**:401–408.