Experience in Transitioning From Parenteral Prostacyclins to Selexipag in Pulmonary Arterial Hypertension

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Abstract: Parenteral prostacyclin therapies remain first-line therapy for patients with pulmonary arterial hypertension (PAH) with class IV symptoms. In selected patients who have been clinically stabilized, switching to selexipag, a chemically distinct prostacyclin receptor agonist, may alleviate risks associated with long-term parenteral therapy. We report our experience with transition of patients from parenteral prostacyclin therapy to selexipag. From January 2016 to July 2017, patients with PAH at the Duke University Pulmonary Vascular Disease Center with functional class II symptoms on stable parenteral prostacyclin therapy were offered the opportunity to transition to selexipag. A standardized protocol was developed to guide titration of therapies. Patients underwent pre- and post-transition assessments of hemodynamics, echocardiography, laboratory biomarkers, and functional status. We studied 14 patients with PAH (11 women; median age 53 years) in total. Overall, 13 patients tolerated the switch to selexipag and remained on the drug at study completion, and 1 patient passed away due to progressive liver failure. Surrogate markers including NT-proBNP, 6MWD, RV function, and TAPSE, and right heart catheterization hemodynamics were similar before and after transition. The transition from parenteral prostanoid therapy to oral selexipag was overall well-tolerated in patients with stable PAH and functional class II symptoms. Finally, doses of selexipag up to 3200 μg twice daily were well-tolerated in patients who had been treated with prior parenteral prostacyclins.

Key Words: pulmonary arterial hypertension, selexipag, parenteral prostanoid

(*J Cardiovasc Pharmacol*™ 2020;75:299–304)

INTRODUCTION

For 20 years, parenteral prostacyclins and its analogues have remained first-line therapy for pulmonary arterial hypertension (PAH) patients with advanced symptoms due to improvements in quality of life and long-term clinical outcomes including survival.[1,2] Prostacyclins are believed to benefit patients with PAH through potent pulmonary vasodilation and inhibition of vascular smooth muscle cell proliferation, 2 of the key pathophysiological derangements in the disease resulting in upstream right heart failure.[3] The biological effects of prostacyclins are likely to be derived from their actions at the prostacyclin (IP) receptor but may also include actions at other prostanoid receptors. Optimal management after clinical stabilization however is less clear, especially in the modern era of increased therapeutic options. Oral prostanoid and nonprostanoid prostacyclin (IP) receptor agnoists are available and include oral treprostinil and the selective IP receptor agonist selexipag. Successful transition from parenteral to oral treprostinil has been described with 5-day inpatient observation for safety with follow-up to 24 weeks,[4] although another group reported almost 50% of their experience with transitions to oral treprostinil as unsuccessful.[5] Selexipag was approved by the Food and Drug Administration for treatment of PAH in late 2015 after the pivotal Prostacyclin (PGI_2) Receptor Agonist in Pulmonary Arterial Hypertension (GRIPHON) trial reported delayed disease progression and reduced risk of PAH hospitalizations with selexipag versus placebo.[6] However, important caveats distinguish this population when considering transition from parenteral therapies to selexipag. The trial appropriately excluded patients taking prostacyclin analogues, and the majority of patients with naïve disease was not clear parenteral prostanoid candidates with only 11/1156 (1%) participants overall exhibit World Health Organization functional class IV symptoms at baseline. Thus, an evidence gap exists for those improved patients who are maintained on parenteral prostanoid therapy for prior severe disease. Given the improved clinical outcomes observed in GRIPHON, we believe a transition from parenteral prostanoid to oral prostacyclin receptor agonist may minimize or negate risks of possible treatment de-escalation. To understand safety, feasibility, and associated challenges with this transition, we aimed to systematically switch appropriate PAH patients from their parenteral prostanoid therapy to selexipag from 2016 to 2017 and observe longer-term outcomes associated with the switch.

Received for publication January 25, 2019; accepted December 2, 2019.

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This was an investigator-initiated study (S.R.) funded by Actelion.

K. S. Parikh reported consulting for United Therapeutics. S. Rajagopal reported consulting for United Therapeutics, Actelion, and Bayer Sciences; research funding by United Therapeutics and Actelion.

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METHODS

Participants

All participants included in the study had PAH (World Health Organization group 1 PH), were on constant dose of any parenteral prostanoid (ie, intravenous epoprostenol, intravenous treprostinil, or subcutaneous tresprostinil), and

were followed up at the Duke University Pulmonary Vascular Disease Clinic. Possible risks and benefits of transitioning from parenteral to oral prostacyclin therapy were explained, including risk of clinical decompensation, side effects, drug–drug interactions, and dosing/titration of selexipag. Specific criteria listed in Table 1 were prespecified to ensure only clinically stable patients were selected for transition to selexipag. Study data were entered into the Duke Pulmonary Hypertension Database and managed using Research Electronic Data Capture (REDCap) tools hosted at Duke University.[7] REDCap is a secure, web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for importing data from external sources.

Before selexipag initiation, all subjects underwent right heart catheterization as part of their routine care to assess hemodynamic improvement on parenteral prostanoid therapy. PAH disease biomarkers including 6MWD, N-terminal pro-brain natriuretic peptide (NT-proBNP), and transthoracic echocardiography were obtained as part of the routine clinic visit before switch. Transthoracic echocardiography parameters of interest described RV function, including categorical RV systolic function (0 = normal; 1 = mild dysfunction; 2 = moderate dysfunction; and 3 = severe dysfunction) and tricuspid annulus plane systolic excursion (TAPSE), assessed by an experienced, blinded echocardiographer. In addition, demographics and concomitant PAH medications were recorded in the database.

Switch Protocol

Because the clinically optimal dose of parenteral therapy varies by participant, conversion was individualized for each participant but followed the same general principles (Fig. 1). We used the general approach to uptitration of selexipag from the GRIPHON trial, namely initiation at 200 μg twice daily followed by weekly dose increases in twice-daily increments of 200 μg. This step-wise process allowed us to assess whether patients were tolerating the transition. The dose of parenteral drug was decreased by ≥1 ng/kg/min with initiation of selexipag based on participants' prior tolerability with prostanoid titration. With every uptitration of selexipag, 3 days were allowed for steady state and then the dose of parenteral therapy was reduced by 1/8 over that week. For example, for a patient on 40 ng/kg/min of intravenous epoprostenol, initiation of selexipag 200 μg twice daily was accompanied by an intravenous dose reduction to 35 ng/kg/min that week (Table 2). The rationale behind this approach was that differences in half-life and dosing frequency required significant overlap between the 2 therapies. Clinical visits during the switch period were based on the participant's response as part of routine care. If a patient had increased symptoms of PAH before the next scheduled increase of selexipag, the dose of parenteral prostanoid therapy was increased by 1–3 ng/kg/min per day depending on clinical judgment. If the patient was still experiencing PAH symptoms at a dose of selexipag 1600 μg BID, further titration up to 3200 μg BID was considered. Once subjects completed the transition to oral selexipag at a stable dose, repeat right heart catheterization, biomarkers collection, and concomitant medication assessments were performed.

Data Analysis

Baseline and pre- versus post-differences were analyzed using JMP, Version <13.1>, SAS Institute Inc, Cary, NC, 1989–2018. Statistical differences in pre- and post-switch hemodynamic parameters, 6MWD, NT-proBNP, qualitative RV function, and TAPSE were assessed for significance using the Wilcoxon signed-rank test or Fisher exact test. Subjects provided informed consent before enrollment. All procedures were performed for routine care. The Duke University Institutional Review Board determined that the study protocol adheres to ethical principles, and its approval was granted to this study before data collection. Actelion funded the chart review and data abstraction only; all medications and procedures were part of routine clinical care.

RESULTS

Over the study duration, 14 participants (11 women; 4 non-Caucasian) with clinically stable PAH and functional class II symptoms at the Duke University Medical Center attempted to switch from parenteral prostanoid therapy to selexipag. At the time of the switch, participants had a median age of 53.5 years (Q1: 48.5 years, Q3: 59.0 years) and body mass index of 30.1 kg/m^2 (Q1: 26.9 kg/m^2, Q3: 33.2 kg/m^2) (Table 3). The median time from diagnosis of PAH to initiation of parenteral therapy was 1.3 months (Q1: 0 months, Q3: 14.5 months) and from initiation of parenteral therapy to

TABLE 1. Key Eligibility Criteria for Participants' Inclusion in Switch From Intravenous Prostacyclin to Selexipag for PAH

1. No worse than functional class II symptoms
2. On additional oral therapy such as endothelin receptor antagonist, phosphodiesterase-5 inhibitor, or calcium channel antagonist
3. No or mild right ventricular enlargement on transthoracic echocardiography
4. 6-min walk distance >350 meters
5. Prior demonstration of adherence to prior therapies
6. No contraindications to selexipag including concomitant medical therapies (ie, gemfibrozil)
7. No change in PAH therapies in previous 3 mo
8. No evidence of pulmonary veno-occlusive disease
9. Agree to switch after discussion of risks and benefits

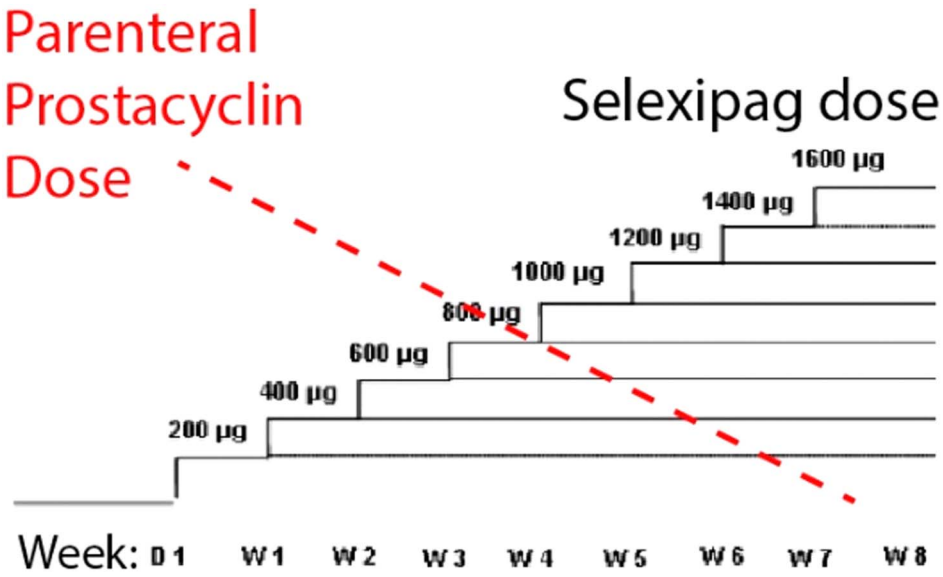

FIGURE 1. Algorithm for switch from intravenous prostanoid therapy to selexipag. The amount of overlap between selexipag titration and parenteral prostanoid taper balanced risk of clinical decompensation with excessive side effects. Figure adapted from selexipag titration schedule used in the prostacyclin (PGI2) receptor agonist in pulmonary arterial hypertension (GRIPHON) study.[6] Doses shown in figure are twice daily.

initiation of selexipag was 5.6 years (Q1: 3.0 years; Q3: 8.8 years). Before selexipag start (median 43 days, Q1: 30 days, Q3: 62 days), the median mean pulmonary artery pressure was 39 mm Hg (Q1: 31.8 mm Hg; Q3: 50.3 mm Hg); cardiac index was 3.25 L/min/m^2 (Q1: 2.7 L/min/m^2; Q3: 3.7 L/min/m^2); and pulmonary vascular resistance (PVR) was 4.4 Wood units (Q1: 3.5 Wood units; Q3: 7.5 Wood units). The cohort overall had good functional capacity as indicated by median baseline 6MWD (498.9 m; Q1: 422.2 m; Q3: 541.1 m), and most patients (12/14; 86%) had either no or mild right ventricular dysfunction observed on echocardiogram.

Participants transitioned from parenteral prostanoid therapy to stable selexipag dose using a protocol implemented by the Duke PAH care team involving clinic visits every 3 months and phone calls in between visits to assess clinical stability and provide guidance for titrations (Fig. 1). The switch occurred over a median time period of 5.5 months (Q1: 4.1 months; Q3: 6.4 months) from selexipag start to post-right heart catheterization assessment. The median total daily selexipag dose achieved was 3200 µg (Q1: 3200 µg; Q3: 4800 µg), and 6/15 patients were taking >3200 µg total daily dose. Two patients required an additional oral agent (PDE-5 inhibitor and/or endothelin receptor antagonist) during this period. Repeat assessments of PAH severity and functional capacity revealed stability in hemodynamics, NT-proBNP, and functional capacity (Table 4). RV function remained stable except in one patient who only could tolerate 1200 µg total daily dose of selexipag. This patient's RV function worsened from normal to mild dysfunction in the setting of stable symptoms and other assessed surrogate markers (Fig. 2: subject 4). At the time of this publication, all but one subject survived and remained on selexipag, and none required reinitiation of parenteral therapy (median 23.7 months; Q1: 20.3 months; Q3: 28.6 months). The death occurred in a subject with portopulmonary hypertension (Fig. 2: subject 14), who died from worsening liver failure

TABLE 2. Example of Dose Adjustments Made During Switch From Parenteral Prostanoid to Selexipag

Week	Selexipag Total Daily Dose (µg)	Intravenous Prostacyclin (ng/kg/min)*
1	0	40
2	400	35
3	800	30
4	1200	25
5	1600	20
6	2000	15
7	2400	10
8	2800	5
9	3200	0

Note that titration schedule was individualized according to tolerability.
*Parenteral prostanoid dose adjustment made 3 days after selexipag dose adjustment to allow for steady state concentration to be achieved. Each decrease in intravenous prostacyclin dose was divided into 1–3 ng/kg/min increments daily over the following 4 day period.

TABLE 3. Baseline Characteristics of Participants With PAH (N = 14) Included in Selexipag Switch Study

Characteristics	
Demographics	
Age, yr	53.5 (48.5–59.0)
Women, N (%)	11 (79%)
Ethnicity, N (%)	
Caucasian	10 (71%)
African American	4 (29%)
Body mass index, kg/m^2	30.1 (26.9–33.2)
PAH history	
Etiology, N (%)	
Idiopathic	8 (57%)
Familial	1 (7%)
Connective tissue disease	2 (14%)
Congenital	1 (7%)
Portopulmonary	1 (7%)
Drugs/toxins	1 (7%)
Duration since diagnosis, yr	5.7 (3.5–12.5)
Duration on parenteral therapy, yr	5.6 (3.0–8.8)
Parenteral therapy dose, ng/kg/mL	
Intravenous (N = 9)	30.8 (28.4–37.0)
Subcutaneous (N = 5)	79 (76–119)
Additional PAH therapies, N (%)	
1	6 (43%)
2	8 (57%)
PAH assessments	
N-terminal brain natriuretic peptide, ρg/mL	136 (55.3–404.3)
Right ventricular dysfunction, N (%)	
None	7 (50%)
Mild	5 (36%)
Moderate	1 (7%)
Severe	1 (7%)
Tricuspid annular plane systolic excursion, cm	2.0 (1.75–2.5)
6-min walk distance, m	499 (422–541)
Right atrial pressure, mm Hg	6 (4–10)
Mean pulmonary artery pressure, mm Hg	37 (32–47)
Pulmonary vascular resistance, wood units	4.3 (3.5–6.3)
Pulmonary capillary wedge pressure, mm Hg	10 (8, 13)
Cardiac index, L/min/m^2	3.3 (2.7–3.7)

Data are presented as median (Q1, Q3) or N (%).

after the switch. No other subjects experienced hospitalization or death.

DISCUSSION

In this observational, prospective study, we found that a systematic approach to clinically stable PAH patients with functional class II symptoms on parenteral prostanoids allowed for successful transition to selexipag. Participants had been on parenteral therapy soon after their diagnosis of PAH, for approximately 5–6 years, and over 80% were on combination therapy. Given possible side effects with increases in prostacyclin and previously observed decompensation with interruption of intravenous prostanoid therapies,[2,8] we designed our protocol to minimize clinical manifestations related to changes in levels of prostacyclin pathway therapies. In addition, the pharmacokinetics of selexipag is favorable for the tolerability of a switch in appropriate patients. Treatment interruptions in GRIPHON participants during selexipag titration were found to be safe and without deleterious effects, likely due to the longer half-life of selexipag (0.5–2.5 hours) and its active metabolite (6.2–13.5 hours),[9–11] as previously noted by Preston et al.[12] In our study, most patients were on combination therapy (and 2 patients had additional oral agents added during the switch) which may have prevented deterioration during the transition. The high rate of combination therapy may also partially explain our results in contrast to the 46% unsuccessful transition rate to oral treprostinil from parenteral therapy recently reported by Maestas et al[5] In that study, multivariate analysis was performed and found baseline PVR >4.2 Wood units most predictive of transition failure. The median baseline PVR in our study was 4.4 Wood units however, which suggests that transition from parenteral to oral prostanoid therapy is safe and feasible even in this previously recognized high-risk group. At 2-year follow-up, patients continued on selexipag therapy without reverting to parenteral therapy, except for one subject who died from a non-PAH cause. Importantly, serial assessment of routinely used surrogate markers including RV function on echocardiography, 6MWD, hemodynamics, and NT-proBNP showed no significant worsening of PAH severity postswitch.

We also showed that the use of doses greater than 1600 μg twice daily (>3200 μg total daily dose), the maximum allowed dose in the Phase 3 study of selexipag,[6] was safe and overall well tolerated in patients previously on parenteral prostacyclin therapy. Of the 14 subjects included in the study, 6 saw continued benefit of increasing selexipag doses >1600 μg twice daily. This is consistent with GRIPHON post hoc analyses suggesting the optimal dose of selexipag is the one that is maximally tolerated.[13] Because parenteral therapy dose does not convert to optimal selexipag dosing in a straightforward, quantifiable way, a personalized approach to PAH symptoms versus side effects and knowledge of their prior tolerability to parenteral therapy guided our uptitration of selexipag.

Limited published case reports with N = 1 subject have documented prior attempts to transition from parenteral to oral selexipag therapy with mixed results.[14,15] In contrast to one example, in which a stable patient on combination PAH therapy was successfully transitioned,[14] another report highlighted the potential risks. In this case, a rapid transition over 6 days occurred from intravenous treprostinil to selexipag in a patient with chronic thromboembolic pulmonary hypertension and functional class IV symptoms out of necessity due to the patient's circumstances.[15] He required readmission for worsening PAH and went back onto parenteral therapy after 4 months. Another case series published in 2008, before availability of oral prostacyclin pathway therapies, documented a single center's experience with transitioning from

TABLE 4. Change in Pre- and Postswitch Assessments of PAH Severity and Functional Capacity

Parameter	Days From End of Switch to Postassessment	Change With Switch	*P*	Postswitch Value
N-terminal brain natriuretic peptide, ρg/mL	25 (3.2 to 73.3)	24 (−31 to 101)	0.50	129.5 (85.8 to 216.0)
Echocardiography	105 (−14 to 197)			
Right ventricular dysfunction, N (%)			1.0	
Stable/improved		13 (93%)		—
Worse		1 (7%)		—
Tricuspid annular plane systolic excursion, cm		−0.2 (−0.5 to 0.3)	0.37	2.1 (1.9 to 2.4)
6-min walk distance, m	38 (−15 to 74)	2 (−20 to 13)	0.75	508.5 (409.2 to 550.0)
Hemodynamics	0			
Right atrial pressure, mm Hg		2 (−2 to 3)	0.48	7 (6 to 11)
Mean pulmonary artery pressure, mm Hg		2 (−2 to 9)	0.48	40 (34 to 51)
Pulmonary vascular resistance, wood units		−0.1 (−1.2 to 1.1)	0.87	4.4 (3.3 to 7.3)
Pulmonary capillary wedge pressure, mm Hg		2 (0 to 3)	0.15	11 (10 to 14)
Cardiac index, L/min/m^2		0.1 (−0.5 to 0.4)	0.98	3.1 (2.8 to 3.8)

Switch occurred over a median time period of 5.5 months (Q1: 4.1 months; Q3: 6.4 months) from selexipag start to post-right heart catheterization assessment. After end of switch, natriuretic peptide and 6-minute walk distance were assessed within 3 months, and echocardiography was performed within 6 months. Numerical data are presented as median (Q1, Q3).

parenteral prostanoid therapy to other PAH therapies. Of 21 attempts, 15 were successful; the 6 who failed the transition did not share any characteristics that could be identified as potential predictors of failure.[16] The only characteristic associated with successful transition was concomitant sildenafil use as background therapy, either alone or in combination with bosentan. The 6 transition failures were able to regain baseline clinical status with return to parenteral therapy at 2-year follow-up. Our study and the 2-year success of the surviving participants shows that the availability of an oral prostacyclin IP receptor agonist may allow for a "cleaner" exchange without compromise in PAH treatment and

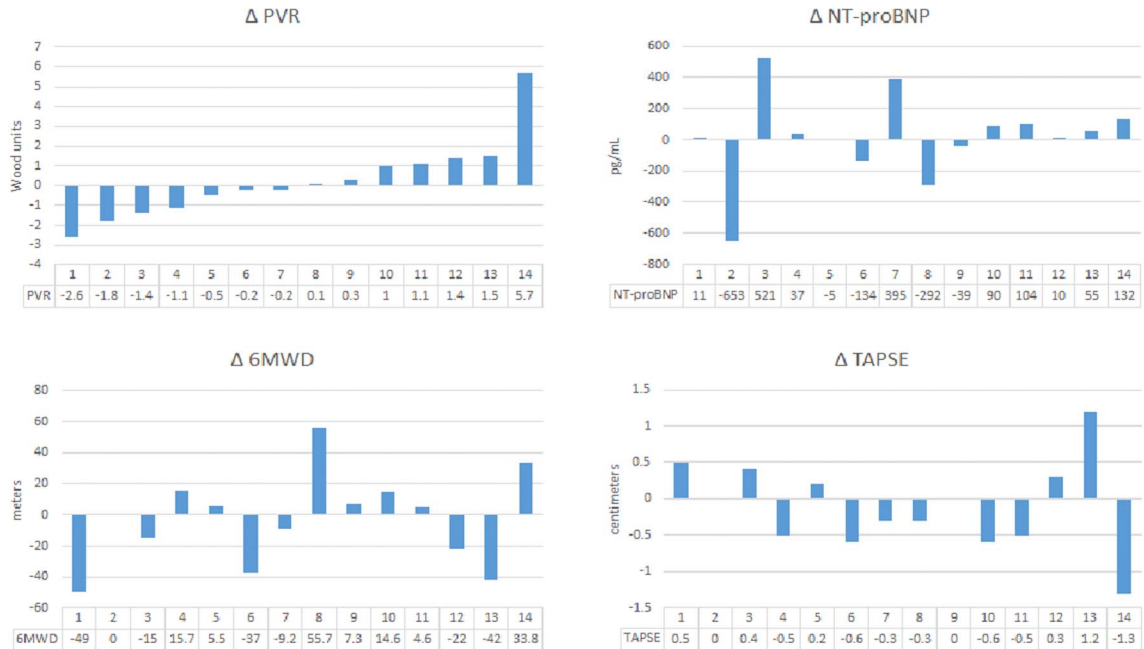

FIGURE 2. Panels depict change in parameters of interest. Subjects ranked 1–14 by change in PVR for each panel. Top left, change in PVR: Median −0.05 WU (−1.2, 1.1 WU). Top right, change in NT-proBNP: Median 24 pg/mL (−30, 100 pg/mL). Bottom left, change in 6MWD: Median 2.3 m (−20, 13 m). Bottom right, change in TAPSE: Median −0.2 cm (−0.5, 0.3 cm).

potentially change prior considerations for switching from parenteral to oral PAH therapies. A systematic approach to this switch, especially in the absence of a larger, multicenter study, is important for safety at the patient level to allow for standardized monitoring and adjustment of protocol.

Comparative efficacy for epoprostenol (ie, parenteral prostacyclin therapy) versus selexipag in clinically stabilized patients is not well understood; prior clinical trials of respective therapies are significantly confounded by heterogeneous study populations and a changed standard of care. However, selexipag is a selective IP receptor agonist and may have different clinical efficacy from prostacyclin therapy regardless of route of administration. Although the GRIPHON trial showed significant clinical benefit with selexipag, breakdown of its composite endpoint did not show reduction in mortality. This contrasts with the survival advantage with parenteral prostacyclin therapy (albeit premodern era background therapy), as well as preliminary results suggesting lower overall mortality with oral treprostinil versus background monotherapy in the recently completed FREEDOM EV trial (NCT01560624).[17]

Furthermore, whether decompensation during an attempt to transition from parenteral to oral therapy increases longer-term risk of worse outcomes is unknown and needs further study. Side effect profile may vary by the administration route, including possibly more diarrhea with selexipag.[18] Potential benefits of switching from parenteral to oral therapy also need further characterization including decreased risk of indwelling catheter complications, patient convenience, and reduced resource burden. Forthcoming data from the SPHERE registry for selexipag (SelexiPag: tHe usErs dRug rEgistry NCT NCT03278002) will provide helpful real-world data to further characterize transitions and will be complementary to the phenotyping and hemodynamics provided in this study.[19]

Although limited by small sample size and single-center experience, our study serves as an example that a similar approach could be developed and utilized to provide consistency in patient selection and transitioning therapies at other PAH centers, with adjustments for site- and patient-specific needs. Our study lacked assessments of quality of life and ascertainment of challenges faced by patients during the transition. Finally, although we saw disease stability at 2 years, a longer follow-up period would be useful to better characterize potential associations with change in disease severity and/or need for additional PAH therapies.

CONCLUSION

Our findings suggest that an appropriately selected, clinically stable PAH patient maintained on parenteral therapy may be successfully transitioned to selexipag with close monitoring. We report a novel standardized protocol for transitioning selected patients from parenteral prostanoid therapy to selexipag that can be used to guide this transition process at other PAH treatment centers. Selexipag doses >1600 μg twice daily were used for subjects still symptomatic during the transition and were well tolerated.

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