Transitioning Stable Patients with Pulmonary Arterial Hypertension from Parenteral Prostanoids to Oral Selexipag

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Keywords
Pulmonary arterial hypertension · Pulmonary hypertension · Prostacyclin · Prostaglandins · Six-minute walk distance

Abstract

Introduction: Parenteral prostanoids are the most potent therapies for pulmonary arterial hypertension (PAH) but are associated with complications and lifestyle limitations. Carefully selected stable patients may be considered for a transition from parenteral prostanoids to a more convenient oral regimen. We present our experience transitioning patients on parenteral prostanoids to selexipag on an outpatient basis. Methods: This was a retrospective cohort study of all group 1 PAH patients on parenteral prostanoids who transitioned to selexipag using a standardized outpatient-based protocol. Hospitalization and routine prognostic data were recorded. Results: Fourteen patients were followed for a median of 1,240 (1,052–1,528) days; all were functional class (FC) II (n = 9) or III (n = 5). Thirteen patients completed the transition, including 11 who underwent catheterization 376 (321–735) days after discontinuing parenteral therapy. Three patients had unfavorable transitions requiring reinitiation of parenteral treatment. Overall, pulmonary vascular resistance increased (3.3–4.5 WU, \( p = 0.01 \)), cardiac index fell (4.0–2.8 L/min/m\(^2\), \( p = 0.01 \)), N-terminal pro-hormone of brain natriuretic peptide worsened (111–205 pg/dL, \( p = 0.03 \)), but PAH-related hospitalizations improved (27–8, \( p = 0.02 \)). Cardiac imaging, FC, and 6-min walk distance (6MWD) were unchanged. Patients who failed were older (64 vs. 56 years old) with shorter 6MWD (274 vs. 392 m) and higher REVEAL 2.0 scores (11 vs. 3). Conclusions: Transition from parenteral prostanoids to oral selexipag in carefully selected low-risk patients was well-tolerated in many patients, with up to 5 years of follow-up. Overall, the hemodynamic response to transition is unpredictable and close monitoring, particularly in the first year of follow-up, is recommended. Additional evaluation of potential predictors of success is necessary.

Introduction

Pulmonary arterial hypertension (PAH) is a severe progressive disease of the pulmonary vasculature associated with significant morbidity and mortality. Parenteral prostacyclins are the most potent therapies for PAH and are often used as rescue therapy, although this comes at a
cost: catheter-associated bloodstream infections, pump malfunctions, nausea, and diarrhea, among others [1, 2]. Subcutaneous (SC) formulations may also be associated with intolerable site pain. Use of a continuous pump also carries limitations to lifestyle and adds a layer of complexity to daily living including showering, sleeping, traveling, and even intimacy [2, 3]. Advances in treatment have allowed patients to live significantly longer, and PAH is becoming a chronic disease [4]. As with other chronic diseases, consideration of patient-centered outcomes has become increasingly important. With quality of life (QoL) in mind, a subset of stable patients may be considered for transition from parenteral prostacyclins to a more convenient oral regimen.

Selexipag, an oral selective prostacyclin receptor agonist, received FDA approval in 2015 and EMA approval in 2016 after the GRIPHON clinical trial demonstrated efficacy as a component of combination therapy [5]. Originally intended as an escalation of therapy for patients on oral regimens, it may also be useful for de-escalation from parenteral therapy. However, data on transitions from parenteral prostacyclins to selexipag are limited, with even less data on transitioning on an outpatient basis. We present our experience of transitioning patients with PAH on a stable dose of parenteral prostacyclins to oral selexipag on an outpatient basis, including up to 5 years of clinical and hemodynamic follow-up.

Methods

Participants
This was a retrospective cohort study; all patients with group 1 PAH who transitioned from intravenous (IV) epoprostenol or IV/SC treprostinil to oral selexipag from January 2016 to October 2019 at our PH referral center were included. Patients with PAH are treated in a multispecialty (cardiology and pulmonary) clinic with regular follow-up. Parenteral therapy patients are followed closely, with clinic visits approximately every 3 months to assess symptoms and volume status. Patients also had an assigned PH specialist nurse who stays in close contact with patients during medication initiation and up- or down-titration. Protocols are in place to manage expected prostacyclin side effects including pain, nausea, and diarrhea. At follow-up, risk stratification is performed on an ongoing basis, with right ventricular (RV) imaging consisting of echocardiogram (TTE) or cardiac MRI (CMR) performed every 6–12 months and right heart catheterization (RHC) performed before and after major changes in therapy.

Patient selection for transition to selexipag in our cohort was highly individualized based on each patient’s complications, side effects, and preferences. General principles included fair functional status (WHO functional class [WHO-FC] I-III), stable hemodynamics and parenteral dose, and pulmonary vascular resistance (PVR) ≤ 5 WU with no signs of RV failure by RHC, TTE, or CMR. Patients on parenteral doses of >40 ng/kg/min of epoprostenol or >80 ng/kg/min of treprostinil were generally excluded from consideration for transition. However, in order to provide a more complete picture, all patients transitioning during the study period including one who transitioned against medical advice and without medical supervision during the initial cessation of parenteral therapy were also included. Decisions on continuation of oral therapy were based on subjective assessment of symptom burden, readmissions, and QoL along with cardiac imaging and hemodynamics, where possible, similar to previously published transition studies [6–8]. Transition failure was defined as reintroduction of parenteral therapy. Institutional review board approval was obtained from the University of Texas Southwestern Medical Center Human Research Protection Program, including a waiver of informed consent, for the retrospective review of patient data.

Suggested Transition Protocol
Patients on IV epoprostenol were down-titrated by 1 ng/kg/min every 3–7 days to a goal of 10 ng/kg/min. Patients on IV/SC treprostinil were down-titrated by 2 ng/kg/min every 3–7 days to a goal of 20 ng/kg/min. Once at goal, patients were re-evaluated for clinical stability based on symptoms and exam; if indicated, a repeat RHC, TTE, or CMR was performed. Stable patients proceeded with the overlap period by initiating oral selexipag at 200 µg twice daily (b.i.d.) while decreasing parenteral doses. At the time of selexipag initiation and with each weekly selexipag increase of 200 µg b.i.d., epoprostenol was decreased by 2 ng/kg/min and treprostinil by 4 ng/kg/min. By day 28, patients were expected to be on selexipag 1,000 µg b.i.d., at which point parenteral therapy was halted and central access was removed. The selexipag dose increases then continued in 200-µg b.i.d. increments to a maximum of 1,600 µg b.i.d., as tolerated. As per usual selexipag dosing, the dose could also be decreased by 200 µg b.i.d. for excessive side effects. Online supplementary eTable 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000526190) depicts our suggested transition protocol.

Data Acquisition
Hospitalization data for PH-related complications were abstracted from the electronic medical record beginning at the point of parenteral prostacyclin initiation. If a patient was referred to our PH center already on triple therapy, then hospitalization data were recorded from the point of establishing care. PH-related complications included acute decompensated RV failure, central line complications (including associated local or bloodstream infections and displaced catheters requiring replacement), pump malfunctions, and admissions for side effect management. Unrelated hospitalizations were excluded from analysis.

Results from routine prognostic studies obtained prior to down-titration of parenteral therapy, during the overlap period, and during follow-up were abstracted from the electronic medical record. These studies included N-terminal pro-hormone of brain natriuretic peptide (NT-proBNP) level, 6-min walk distance (6MWD), WHO-FC, RHC, TTE, and CMR. Hemodynamic measures included right atrial pressure, mean pulmonary artery pressure, pulmonary artery oxygen saturation, PVR, and cardiac index (CI). TTE measurements included RA area, RV end-diastolic diameter, degree of tricuspid regurgitation, the presence of septal flattening, RV systolic pressure (RVSP), and tricuspid annular plane systolic excursion. CMR measures included RV end-diastol-
ic volume, LV end-diastolic volume, RV ejection fraction, and LV ejection fraction. REVEAL 2.0 scores were also calculated, which includes additional parameters such as recent pulmonary function tests, vital signs, and comorbidities.

**Statistical Analysis**

Continuous variables were described as median (1st–3rd interquartile range). Changes in variables between baseline (at full-dose parenteral therapy), during the overlap period (at a reduced-dose of parenteral therapy) and at follow-up closest to 1-year after the discontinuation of parenteral therapy were compared using the Wilcoxon signed-rank test. The NT-proBNP was log-transformed to approximate a normal distribution. Categorical variables such as the qualitative severity of tricuspid regurgitation and right atrial dilation were assigned numerical values such that 0 = none, 1 = trivial, 2 = mild, 3 = moderate, and 4 = severe. The absence or presence of septal flattening was assigned 0 = absent and 1 = present. Kaplan-Meier curves were created for overall survival and survival free from parenteral therapy. Patients were censored at the point of last access of their medical record or at the point of resuming parenteral therapy. To minimize selection bias related to loss to follow-up, listwise deletion was used to account for missing data. Statistical analyses were conducted using R version 3.6.2 (2019-12-12) – “Dark and Stormy Night” © 2019 The R Foundation for Statistical Computing.

**Results**

**Patient Characteristics**

The study population included 14 patients with group 1 PAH on a stable dose of parenteral prostanoylds. Thirteen patients were female (93%), median age was 57.5 years (range 30–78), and the most common etiology was idiopathic PAH (Table 1). All patients were WHO-FC II (n = 9) or III (n = 5). At the time of transition, 13 patients were receiving triple therapy with a parenteral prostanoyld, an ERA, and either PDE5i or riociguat, while only 1 patient was on a parenteral prostanoyld plus an ERA alone, due to prior issues with tolerability with PDE5i. Patients transitioned from IV epoprostenol (n = 10), IV treprostinil (n = 3), or SC treprostinil (n = 1). Median IV epoprostenol and IV/SC treprostinil doses were 23.5 (19.3–28.5) ng/kg/min and 40.5 (34.0–72.5) ng/kg/min, respectively. Median duration of parenteral therapy prior to transition was 1,258 (794–2,091) days, and transitions were completed over a median of 68 (32–96) days. Complete patient characteristics are provided in Table 1.

**T tolerability of Transition (Short-Term)**

Transitions were completed via slow outpatient down- titration of the parenteral prostanoyld except in 1 patient who self-discontinued abruptly, against medical advice, after reporting intolerable site pain associated with SC

| No. | Age | Sex | Diagnosis | Transition | 6MWD, m | WHO-FC | FC | Transition duration, days | Survival, days | Reinitiation, days | Baseline | 1 year | 2 years | 3 years |
|-----|-----|-----|-----------|------------|---------|--------|----|------------------------|-------------|------------------|----------|--------|---------|---------|
| 1   | 78  | F   | PoPH III | 457        | 78      | 1,303  | D  | 13                     | 239          | 262              | 3.5      | 4.2    | 3.5     | 4.2     |
| 2   | 35  | F   | IPAH II  | 653        | 107     | 1,810  | A  | 1                      | 437          | 262              | 6.9      | 14.6   | 4.3     | 3.9     |
| 3   | 43  | F   | IPAH II  | 2,196      | 124     | 1,773  | A  | 1                      | 57           | 262              | 8.2      | 14.6   | 4.3     | 3.9     |
| 4   | 30  | F   | HPAP III | 523        | 92      | 1,223  | A  | 5                      | 193          | 262              | 2.5      | 3.9    | 2.6     | 3.9     |
| 5   | 56  | F   | RA-APAH II| 2,440     | 150     | 1,253  | A  | 3                      | 258          | 262              | 5.4      | 14.6   | 4.3     | 3.9     |
| 6   | 51  | F   | D-PAH    | 2,179      | 0       | 1,250  | A  | 4                      | 151          | 262              | 5.4      | 14.6   | 4.3     | 3.9     |
| 7   | 58  | M   | SSc-APAH II| 803       | 63      | 579    | A  | 9                      | 421          | 262              | 5.4      | 14.6   | 4.3     | 3.9     |

**Table 1. Patient characteristics of successful and unsuccessful transitions to oral selexipag.**

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treprostinil. Thirteen of 14 patients tolerated short-term cessation of parenteral therapy with no immediate evidence of rebound vasoconstriction or worsening symptoms. One patient had a marked increase in PVR during down-titration and required up-titration of epoprostenol to her original treatment dose. Typical prostanoid-associated side effects were reported during selexipag up-titration in 6 of 14 patients, including nausea (21%), diarrhea (14%), headaches (14%), flushing (14%), and jaw pain (14%). In all instances, these side effects were either tolerated or improved by reducing the selexipag dose. For the final maintenance doses, no patients were on low doses (200–400 µg b.i.d.), 4 (29%) remained on intermediate doses (600–1,000 µg b.i.d.), and 10 (71%) were on high doses (1,200–1,600 µg b.i.d.), with 8 of these 10 on the maximum dose of 1,600 µg b.i.d.

**Long-Term Transition and Survival Analysis**

Three of 14 patients failed long-term transition to selexipag, all within the first year of follow-up. This included 1 patient with failure during down-titration (never came off parenteral therapy), as discussed above, and 2 who were restarted on parenteral therapy 54 and 357 days after transition, respectively (Fig. 1). Three patients died over a median follow-up of 1,240 (1,052–1,528) days. This included 2 patients who failed transition: one responded poorly to the reinitiation of IV therapy and developed progressive RV failure, while the other developed COVID-19-related acute respiratory distress syndrome several years later. One additional patient who remained on selexipag throughout follow-up died at home more than 3.5 years after transitioning.

Compared to those who transitioned successfully, patients failing to transition were slightly older (64 compared to 56 years old) with a shorter 6MWD (274 compared to 392 m) and a higher REVEAL 2.0 score (11 compared to 3). Otherwise, baseline characteristics, doses, and durations on parenteral therapies were grossly similar between the groups. Statistical analyses were deferred due to the limited number of patients failing the transition.
Hospitalization Analysis

A total of 102 patient-years of follow-up was recorded, including 53.3 patient-years prior to the transition and 48.5 patient-years after the transition. Prior to transition, there were 27 hospitalizations, including 19 related to pump or line complications, 7 related to PAH (volume or otherwise), and 1 for significant prostanoid side effects. Following transition, there were 8 hospitalizations related to RV failure or to initiation of parenteral therapy (N = 5 and 3, respectively), all in the 3 patients who reinitiated parenteral therapy. The number of hospitalizations was significantly reduced in the post-transition period (N = 27 vs. 8, p = 0.02).

Hemodynamics: Intra-Transition and after 1 Year off of Parenteral Therapy

Nine patients had a RHC during the overlap period to assist with guiding the transition. Among these 9, PVR (3.3–4.7 WU, p = 0.04) and mean pulmonary artery pressure (30–31 mm Hg, p = 0.05) worsened, and CI trended toward worsening (4.0–2.9 L/min/m², p = 0.09). One patient had markedly worse hemodynamics, and her transi-
tion was subsequently aborted. Otherwise, 8 of 9 (89%) patients with an intra-transition RHC proceeded with the transition and discontinuation of their parenteral therapy (Fig. 2).

Thirteen patients underwent an RHC after a median of 376 (321–735) days since initial cessation of parenteral therapy. Compared with full-dose parenteral prostacyclin, PVR increased (3.3–4.5 WU, \( p = 0.01 \)), CI fell (4.0–2.8 L/min/m\(^2\), \( p = 0.01 \)), and there was a trend toward worsening pulmonary artery pressures (30–31 mm Hg, \( p = 0.14 \)), with significant variability (Fig. 2). NT-proBNP also worsened (111–205 pg/dL, \( p = 0.03 \)), and REVEAL 2.0 score at 1 year was significantly higher (3.5–6.5, \( p = 0.04 \)). There was no significant change in FC or 6MWD. Thirteen patients also had a TTE, and 8 patients had a CMR, and there were no significant changes in any parameters derived from these studies. A minority of patients also had follow-up TTEs and RHCs at years 2, 3, and 4; although statistical tests were not run, they grossly appear to suggest stability compared to the first follow-up results. Results are summarized in Table 2.

### Discussion

In this study, we found that 13 of 14 patients tolerated transition from parenteral therapy to oral regimens including selexipag and that 11 of 14 patients remained free of parenteral therapy after an average of 41 months of follow-up. These results suggest that successful transition is possible in some patients but that caution and further investigation is needed.

| Table 2. Hemodynamics and other test results at baseline and 1-year follow-up |
|---------------------------------------------------------------|
| **Test parameter** | **Baseline** | **1-year follow-up** | **\( p \) value** |
| RHC (\( N = 13 \)) | | | |
| RAP, mm Hg | 2.0 (2.0–3.0) | 4.0 (0.0–5.0) | 0.50 |
| PAP, mm Hg | 30 (22–35) | 31 (22–45) | 0.14 |
| PVR, Wood Units | 3.3 (2.9–4.3) | 4.5 (3.3–7.3) | \( \textbf{0.01} \) |
| PA saturation, % | 71 (65–72) | 68 (63–72) | 0.35 |
| CI, L/min/m\(^2\) | 3.8 (3.1–4.4) | 2.8 (2.7–3.0) | \( \textbf{0.01} \) |
| TTE (\( N = 13 \)) | | | |
| RVSP, mm Hg | 64 (50–69) | 60 (52–115) | 0.14 |
| RVDD, cm | 3.6 (3.5–3.9) | 3.6 (3.6–4.4) | 0.24 |
| TAPSE, cm | 2.2 (2.0–2.3) | 2.2 (1.7–2.3) | 0.20 |
| \(^1\)RA Area (cm\(^2\)) | 1 (0–2) | 1 (0–2) | 0.83 |
| \(^1\)Tricuspid Regurg | 2 (1–2) | 1 (1–2) | 0.41 |
| \(^2\)Septal Flattening | 0 (0–1) | 0 (0–1) | 0.77 |
| cMRI (\( N = 8 \)) | | | |
| RVEDV, mL | 137 (125–168) | 134 (124–157) | 0.50 |
| LVEDV, mL | 116 (98–123) | 116 (97–126) | 1.0 |
| RVEF, % | 54 (44–55) | 54 (48–57) | 0.81 |
| LVEF, % | 63 (58–65) | 64 (60–66) | 1.0 |
| \( N = 13 \) | | | |
| \(^3\)NT-proBNP, pg/dL | 132 (69–388) | 205 (97–342) | \( \textbf{0.03} \) |
| 6MWD, m | 399 (369–534) | 421 (373–488) | 0.63 |

Data are presented as median (interquartile range). Bolded values have reached statistical significance based on having a \( p \) value of <0.05. "Baseline" represents full-dose parenteral therapy and "1-year follow-up" represents 1 year after discontinuation of parenteral therapy. In addition, 8 patients had a TTE at 2 years, and 4 patients had a TTE at 3 years; statistical tests were not run although they appear to suggest stability: RVSP was 43 mm Hg (36–79) at 2 years and 42 mm Hg (40–46) at 3 years. RAP, right atrial pressure; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; PA, pulmonary artery; CI, cardiac index; RVSP, right ventricular systolic pressure; RVDD, right ventricular end-diastolic diameter; TAPSE, tricuspid annular plane systolic excursion; Regurg, regurgitation; RVEDV, right ventricular end-diastolic volume; LVEDV, left ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal-pro-hormone of the brain natriuretic peptide; 6MWD, 6-min walk distance. \(^1\)0 = normal; 1 = trivial; 2 = mild; 3 = moderate; 4 = severe. \(^2\)0 = absent; 1 = present. \(^3\)\( p \) value reflects the difference in the log (NT-proBNP).
### Table 3. Summary of the transition studies from parenteral prostanoids to oral selexipag

| Study                        | N       | Inpatient/outpatient | Duration | Age (year)/sex | WHO-FC Follow-up, month | Background treatment | RHC before | RHC after | Prostanoid decrement, ng/kg/min | Selexipag increment, µg | Outcome | Comments |
|------------------------------|---------|----------------------|----------|----------------|--------------------------|----------------------|-------------|-----------|--------------------------------|--------------------------|----------|----------|
| Mims et al. [25] (2017)      | 12      | −                    | −        | −              | II–IV                    | All were on background therapy | PA 38.5     | CI 3.3    | PVR 4.3                          | −                       | −        | Success 11/12 Only 6 patients had post-transition hemodynamics measured |
| Fanous and Janmohamed [23] (2018) | 4       | Inpt: 10.5 days, Outpt: 22 weeks | 51.5     | 3 F, 1 M       | II–IV                    | All 4 on PDE5i + ERA | Outpatient: RA 4.5, PA 21, PVR 2.5, CO 6, PCW 5.5 | −                       | Inpt: 1.5–2 q6h-q12h, Outpt: 1–2.5 q2–4d | −                       | Success 4/4 Outpatients received RHC during transition to guide the transition |
| Holthaus et al. [24] (2019)  | 5       | Inpatient           | 8 days   | 36; 5 F, 0 M  | I–II                     | PDE5i + ERA alone: 1 None  | RA 4, PA 32, PVR 3.7, PCW 10  | CO 5.1      | RA 6, PA 27, PVR 4, PCW 10, CO 4.6   | 1/8 fraction daily | 400 daily | Success 5/5 Hemodynamics mostly stable with trend toward worsened CO |
| Parikh et al. [26] (2020)   | 14      | Outpatient          | 22 weeks | 53.5; 11 F, 3 M| II                        | 8 and 6 patients were on 1 and 2 background therapies, respectively | PA 39, CI 3.25, PVR 4.4 | PA 40, CI 3.1, PVR 4.4 | 1/8 fraction weekly | 200 µg b.i.d. weekly | Success 13/14 6 patients (43%) were on a final dose greater than 1,600 µg BID. Stable NT-proBNP, 6MWD, RV function, TAPSE, and hemodynamics before and after transition |
| Yanaka et al. [27] (2020)   | 8       | −                    | −        | −              | −                        | All were on PDE5i and ERA | −                     | −                       | −                       | 200 µg b.i.d. over 3–5 days | Success 8/8 Stable 6MWD and NT-proBNP but trend toward worsened CI, French invasive and noninvasive risk |
| Aldweib et al. [22] (2021)  | 5       | Outpatient          | 8 weeks  | 51.4; 4 F, 1 M| II–III                   | 4/5: PDE5i, ERA: 1: Riociguat | RA 46, PA 29, CI 3.8, PVR 2.8 | RA 2.7, PA 28, CI 3.7, PVR 2.3 | 2 ng/kg/min twice weekly | 200 µg b.i.d. weekly | Success 4/5 For 2/5, transition monitored with CardioMEMS in real-time rather than serial RHC |

The literature on transitioning from parenteral prostacyclins to selexipag is limited and heterogeneous in methodology with variability in inpatient versus outpatient transition, frequency and duration of follow-up, duration of oral and parental overlap, maximum selexipag dose, and reporting of risk stratification. Length, age and hemodynamics presented as median values. WHO-FC, World Health Organization functional class; RHC, right heart catheterization; PDE5i, phosphodiesterase 5 inhibitor; ERA, endothelin receptor antagonist; PA, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; RA, right atrial pressure; PCW, pulmonary capillary wedge pressure; CO, cardiac output; Inpt, inpatient; Outpt, outpatient; bid, twice daily.
Parenteral prostacyclins are the most potent guideline recommended therapy for PAH patients, conferring a clear mortality benefit [9–14]. The most recent society-endorsed treatment algorithm utilizes multiparametric risk stratification and proposes upfront triple combination therapy, including a parenteral prostacyclin, in high-risk patients [15]. Further, recent observational studies suggest that early triple therapy in intermediate-risk patients may be beneficial as well, providing a possible mortality benefit as well as the best chance at reverse RV remodeling [16–19]. Although the current treatment algorithm also recommends continuing existing treatment with structured follow-up, even when treatment results in low-risk status, many patients favor transitioning to oral regimens. [15, 20] A lack of large series describing predictors and outcomes with de-escalation makes advising these patients difficult, and may even contribute to underutilization [21], as patients may be more likely to consider an invasive therapy if a route toward potential de-escalation is better defined. To best inform this, structured studies including clinical trials will be necessary. One clinical trial (NCT05203510) is planned to attempt to address whether mean PA pressure can be used to guide de-escalation from parenteral to oral treprostinil.

In the interim, at least 6 prior case series in addition to our current study have described outcomes for patients transitioning from parenteral therapy to oral therapy including selexipag (Table 3) [22–27]. Out of N = 48 patients in these prior studies, only 3 patients failed to successfully transition to oral therapies. These series also reported stability in most risk measures, though with some variability [24, 27]. Our results, therefore, are not as positive, with 3 patients requiring reintroduction of parenteral therapy, 2 of whom subsequently died, and with worsening PVR, CI, and NT-proBNP levels. The cause for this discordance is unclear but could relate to patient selection, small sample sizes, publication bias, or shorter follow-up time in most prior series. Nevertheless, a majority of carefully selected patients in both our study as well as all published series to date were able to successfully transition.

Our ability to identify predictors of transition failure was limited by our cohort size, but we did make several observations. First, hemodynamics obtained during the transition were not very useful in predicting later hemodynamic results. It therefore seems plausible that some benefits from parenteral prostacyclin may continue for weeks or months following dose decrease or discontinuation [28, 29]. The reverse has previously been shown during epoprostenol initiation, where the acute hemodynamic changes have failed to predict long-term hemodynamic response [30]. Second, the 3 patients failing transition had higher REVEAL 2.0 scores compared to those transitioning successfully. Although REVEAL 2.0 was designed to predict long-term outcomes in PAH in general, it seems plausible that REVEAL 2.0 may have utility in informing which patients are at greater risk of failing transition to oral selexipag, particularly among those who otherwise meet traditional low/intermediate-risk criteria [31, 32]. Third, 2 of 3 patients failing transition had scleroderma-associated PAH, which is generally associated with worse outcomes than idiopathic PAH [33–37].

We also found the “intra-transition” catheterization, performed at 10 ng/kg/min of epoprostenol or 20 ng/kg/min of treprostinil, less informative than we anticipated. On the other hand, many patients who have completely stopped a parenteral prostacyclin and removed their central access are reluctant to consider reintiation compared to those who have only down-titrated. We would therefore consider continuing to perform a catheterization while on a low-dose parenteral prostacyclin but would consider doing so at a lower dose.

Finally, although the approved dose of selexipag ranges from 200 µg b.i.d. to 1,600 µg b.i.d., a higher maximum dose was utilized in the transition series by Parikh et al. [26] (N = 14) where selexipag doses of up to 3,200 µg twice daily were permitted. That series had a 93% transition success at 2 years along with stability in biomarkers and hemodynamics, raising the question of whether additional study is warranted. In our series, 8 (57.1%) of the patients transitioning tolerated the maximum selexipag dose of 1,600 µg b.i.d. and would potentially have been candidates for even higher doses if efficacy were established.

In summary, here, we describe our experience transitioning 14 patients from parenteral prostacyclin to oral selexipag, with 79% success over a median of 3.5 years of follow-up. From the clinician’s standpoint, hemodynamics and biomarkers significantly worsened; however, these results were heterogeneous, with much of the effects driven by a small number of patients. Further, from the patient’s perspective, functional status and exercise capacity were unchanged, and the rate of hospitalization was reduced. As patients live longer and PAH shifts toward becoming a chronic disease, many patients’ priorities shift toward quality of life and convenience. Our cohort reflected this with nine (64%) patients requesting to transition due to lifestyle limitations associated with parenteral therapy rather than side effects or complications.
**Limitations**

As a single-center study with only 14 patients and 3 failures, our ability to assess factors that predict the success or failure of transition was limited. Our results are not generalizable to all patients on parenteral therapy because we selected patients with lower risk features who were experiencing significant side effects or impairment of QoL. Patients were on various background therapies, and 1 patient who discontinued parenteral therapy against medical advice was also included in our analysis, which may both be confounding factors. There are some missing data, especially in late follow-up, which may contribute to selection bias as sicker patients are more likely to die prior to follow-up testing. Also, while we report among the longest follow-up periods in the literature to date with up to 5 years of follow-up available for some patients, the median follow-up was just under 3.5 years and thus long-term failure may still occur.

**Conclusions**

Transition from parenteral prostanoids to oral selexipag in carefully selected low-risk patients was well-tolerated in many patients with no significant change in functional status or exercise capacity, with up to 5 years of follow-up. Transitioned patients also had a lower rate of hospitalization. However, 3 of 14 patients did require re-initiation of parenteral therapies, 2 of whom died years after resuming parenteral therapy. Overall, the hemodynamic response to transition can be unpredictable and close monitoring, particularly in the first year of follow-up, is recommended. These findings need to be confirmed in larger studies, and additional evaluation of potential predictors of success is needed.

**Statement of Ethics**

Institutional review board approval was obtained from the University of Texas Southwestern Medical Center Human Research Protection Program (#052015-041), including a waiver of informed consent, for the retrospective review of patient data.

**Conflict of Interest Statement**

Colin Hinkamp has no competing financial interests or personal relationships to disclose. Sonja Bartolome and Edward Mims contributed to the concept and design of the work and revised the article critically for intellectual content. Kelly Chin and Trushil Shah contributed to the concept and design of the work, drafted the article, and revised the article critically for intellectual content. All the authors approved the version to be published and participated sufficiently in the article to take public responsibility for its content.

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**Author Contributions**

Colin Hinkamp contributed to the acquisition, analysis, and interpretation of data; drafted the article; and revised it critically for intellectual content. Sonja Bartolome and Edward Mims contributed to the concept and design of the work and revised the article critically for intellectual content. Kelly Chin and Trushil Shah contributed to the concept and design of the work, drafted the article, and revised the article critically for intellectual content. All the authors approved the version to be published and participated sufficiently in the article to take public responsibility for its content.

**Data Availability Statement**

All data generated or analyzed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.

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