Right ventricular afterload predicts long-term transition from parenteral to oral treprostinil in pulmonary arterial hypertension

Travis Maestas[1], Lillian M. Hansen[2], Rebecca R. Vanderpool[3], Ankit A. Desai[3,4,5],
Sophia Airhart[4,5], Shannon M. Knapp[6], Adam Cohen[7], Jeremy Feldman[8] and
Franz P. Rischard[2,3,5]

[1]Department of Medicine, University of Arizona, Tucson, AZ, USA; [2]Division of Pulmonary, Critical Care, Sleep, and Allergy Medicine, University of Arizona,
Tucson, AZ, USA; [3]Division of Translational and Regenerative Medicine, University of Arizona, Tucson, AZ, USA; [4]Division of Cardiology, University of Arizona,
Tucson, AZ, USA; [5]Sarver Heart Center, University of Arizona, Tucson, AZ, USA; [6]BIO5 Institute, University of Arizona, Tucson, AZ, USA; [7]Creighton School of
Medicine, Phoenix, AZ, USA; [8]Arizona Pulmonary Specialists, Phoenix, AZ, USA

Abstract

Despite the increasing trends, reports on long-term follow-up are limited on transitioning from parenteral to oral treprostinil therapy in patients with pulmonary arterial hypertension (PAH). We investigated both the effectiveness of parenteral to oral treprostinil transition and the characteristics associated with transition failure over a duration of two years. The study included 37 Group I functional class I and II patients with PAH on combination therapy. Patients were excluded if cardiac index ≤ 2.2 L/min/m^2, right atrial pressure ≥ 11 mmHg, or 6-min walk distance ≤ 250 m. Patients were categorized as successful ($_s$Transition) or unsuccessful ($_u$Transition) transition based on clinical stability, or a parenteral comparator ($_c$Parenteral) if they remained on parenteral therapy (no transition). All patients underwent two right heart catheterizations, one at enrollment and a second post transition. Of 24 total transition patients, 46% were classified as $_u$Transition. $_u$Transition occurred on average 577 days post transition. Both $_u$Transition and $_s$Transition had similar hemodynamics at diagnosis and treprostinil dose before and after transition. Before transition, the pulmonary vascular resistance (PVR) was significantly higher in the $_u$Transition (6.7 ± 2 WU) vs. $_s$Transition group (3.5 ± 1.5 WU). At follow-up catheterization, the $_u$Transition group demonstrated further increases in PVR, greater than the $_c$Parenteral group, without recovery despite "rescue" therapy in the $_u$Transition group. A pre-transition PVR of 4.16 WU discriminated the $_u$Transition from the $_s$Transition group. While a subset of PAH patients on combination therapy may be safely transitioned from parenteral to oral treprostinil, caution should be exercised in patients with elevated baseline PVR to avoid irreversible destabilization.

Keywords

drug delivery, pulmonary arterial hypertension, right ventricle function and dysfunction

Background

Pulmonary arterial hypertension (PAH) is a serious and life-altering disease. Though not curable, available therapies help to alleviate symptoms and improve quality of life for patients. The treatment options for PAH are rapidly changing, as is the approach to management. Initial management can often include a monotherapy or combination of therapies. Previous work has demonstrated a lower risk of clinical decline with combination therapy in a subset of

Corresponding author:
Franz P. Rischard, Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine, Division of Translational and Regenerative Medicine, 1501 N. Campbell Avenue, Tucson, AZ 85724, USA.
Email: frischard@deptofmed.arizona.edu

patients than with monotherapy[1] and profound hemo-dynamic improvement even in severe cases.[2] Combination therapy with parenteral prostacyclin class agents is typically prescribed for the sickest patients but is associated with increased burden for patients with infusion-related side effects including the inconvenience of a pump and the risk of infection.

Treprostinil, a prostacyclin analog, infusion therapy is one of the cornerstones in PAH management that has shown success with improvement of hemodynamics and symptoms in many patients.[3,4] After development as a tablet formulation (known as Orenitram)® in 2013, recent data demonstrate successful transition from subcutaneous parenteral to oral treprostinil therapy for up to 24 weeks in PAH patients who are functional class (FC) I/II with normalized cardiac index (CI) and right atrial pressures (RAP), and have been on stable doses of parenteral treprostinil therapy.[5] With these findings, the transition from parenteral treprostinil to its oral form in more patients may be anticipated.

Given pharmacokinetic data indicate that the area under the curve (AUC) is similar between parenteral and oral formulations of treprostinil,[5] it is possible that clinicians may attempt transition in patients with advanced disease, such as high right ventricular (RV) afterload. Despite similar overall AUC, serum peaks/troughs may be poorly tolerated in a patient with high afterload state and a marginally adapted RV, as opposed to parenteral delivery. This scenario may explain why our anecdotal long-term observations indicate that a subset of patients with initially compensated RV function fail transition after the 24-week period. Although it is understood that some patients can be successfully transitioned to oral therapy, we do not know which subset of patients can be safely targeted for transition. As hemodynamics are important markers of disease severity in PAH patients,[6] our aim was to compare resting hemodynamics in patients who have been successfully and unsuccessfully transitioned to long-term oral treprostinil in an effort to identify safe candidates for transition.

Methods

Study design and patient selection

Thirty-seven patients with Group I PAH provided written informed consent to participate in the study, which was approved by the institutional review board at the University of Arizona (Tucson, AZ, USA) and St. Joseph's Medical Center (Phoenix, AZ, USA) (Fig. 1). The diagnosis of PAH was established by dedicated PAH providers with invasive confirmation (based on right heart catheterization [RHC]) based on updated guidelines.[7] All patients included in the study were FC IV at diagnosis (Table 3) and therefore were initiated on parenteral therapy. All patients were eventually treated with combination therapy by adding a phosphodiesteras-5 (PDE5) inhibitor and/or endothelin receptor (ERA) antagonist within the first month. All enrolled patients were administered combination
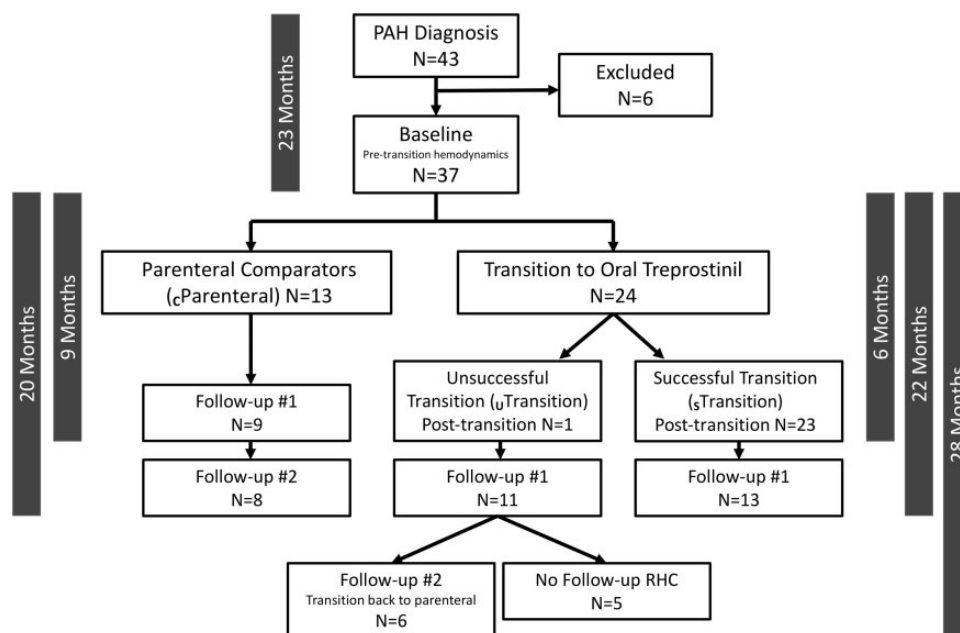
Fig. 1. Disposition of study cohorts relative to transition group. Of the patients initially screened, six were excluded due to protocol deviation, poor drug adherence, and/or clinical instability. Timescales in the margins represent mean months between assessments by parenteral comparator (cParenteral), left margin, and successful transition (sTransition)/unsuccessful transition (uTransition), right margin. Patients are assigned here to sTransition or uTransition here based on assessment at each visit (as opposed to final assignment at last assessment). All patients had a RHC at enrollment and at least one follow-up RHC. A subset had more than one follow-up RHC.

therapy for >90 days and on a stable dose for >30 days. All individuals were WHO FC I–II. Participants with FC III–IV, a CI $\leq 2.2\,L/min/m^2$, a RAP $\geq 11\,mmHg$, and/or a 6-min walking distance (6MWD) $\leq 250\,m$ were excluded.

Only patients who underwent parenteral to oral treprostinil transition following a previously reported transition protocol[5] were included (see transition protocol below). Patients were classified by the principal investigator (PI) at the time last assessment as:

– Successful transition (sTransition): Continued FC I-II AND unchanged hemodynamics >24 weeks from transition;
– Unsuccessful transition (uTransition): FC deterioration to III/IV *and* hemodynamic deterioration *or* unable to tolerate sufficient oral trerpostinil to maintain disease stability;
– Parenteral comparator (cParenteral): Individuals eligible to enroll (see inclusion/exclusion criteria) but did not transition due to early trial closure or personal choice to remain on parenteral treprostinil. The purpose of this group was to "control" for disease progression (vs. transition failure).

Upon assessment of transition failure, it has been our standard of care to transition patients back to parenteral treprostinil before initiation of a second oral, if the patient was only on one oral agent.

Transition protocol

Baseline pre-transition hemodynamics and RV function were assessed with RHC, echocardiography, 6MWD, and measurement of brain natriuretic peptide (BNP) and were collected at the time of enrollment. Participants who transitioned were hospitalized for supervised transition from parenteral to oral treprostinil for <5 days. Titration and transition of parenteral and oral treprostinil were performed based on study protocol.[5] The patients were transitioned gradually in a stepwise fashion reducing parenteral treprostinil while simultaneously increasing oral treprostinil. Goal dose of oral treprostinil was based on previous experience that 1 mg oral treprostinil TID is equivalent to 6 ng/kg/min parenteral treprostinil.[5] Relatively small dose adjustments were made after discharge based on tolerance and side effect mitigation.

Assessments

In addition to baseline RHC measurements, transition individuals were evaluated with clinic visits monthly for three months then every three months for 12 months. Transition patients were also followed with a RHC on at least two separate occasions defined as follow-up visits 1 and 2 (Fig. 1). These latter RHC evaluations were clinically indicated occurring at varying times. For the transition groups

(sTransition and uTransition), follow-up 1 occurred at 6 ± 1 months for all except one patient. This patient failed transition during the first six-month period and had follow-up 1 outside this window. For the cParenteral group, evaluations were either based on routine care or due to clinical indications. BNP and echocardiography are shown at baseline only due to variability in the measurement at follow-up. Follow-up 2 evaluation was typically undertaken in the transition groups to assess disease stability. Several uTransition patients (n = 6) had a follow-up 3 to establish disease stability after transition back to parenteral treprostinil.

Pulmonary vascular resistance (PVR) was calculated based on measurements derived during RHC and defined as ([mean pulmonary artery pressures (mPAP) – wedged PAP (PCWP)]/cardiac output [CO]). Pulmonary artery capacitance was defined as stroke volume/systolic PAP-diastolic PAP. Echocardiography was performed by technicians specifically trained in right heart analysis. Images were obtained using commercially available equipment (GE, Philips) with a 3.5-MHz transducer in standard views with the patient in the left decubitus position. Standard M-mode and two-dimensional images were obtained during a breath-hold according to American Society of Echocardiography Guidelines.[8] RV end-diastolic area (RVEDA), RV end-systolic area (RVESA), RV fractional area change, % ($RVFAC = (RVEDA - RVESA)/RVEDA \times 100$), and tricuspid annular plane systolic excursion (TAPSE) were obtained as echocardiographic measures of RV function.

Statistical analysis

All analyses were conducted in program R (version 3.3.2[9]). For continuous variables, summary statistics are given as mean ± 1 standard deviation (SD) or mean (range), unless otherwise noted. Comparisons among the three groups were conducted with Kruskal–Wallis rank-sum tests with P values adjusted for false discovery rate (FRD) using the method of Benjamini and Hochberg.[10] Where there were statistically significant differences among the three groups ($\alpha = 0.05$), Wilcoxon rank-sum tests were used to test for differences between each pair of groups (these post-hoc tests were not adjusted for multiple comparisons). A Cox regression analysis was done to analyze the relationship of baseline hemodynamic and RV function variable to clinical failure. Receiver operating characteristic (ROC) curves were used to compare the variables with the highest hazard ratios from the Cox analysis for their utility to predict successful transition. Only individual in the sTransition and uTransition groups were included. These analyses used the R package "pROC" (version 1.10.0[11]). The optimal cut-off was determined using the Youden index.[11] A Mann–Whitney U-test was used to test whether the AUC for a ROC curve was different from 0.5.[12] Statistical testing was done while grouping patient cohorts according to their last assessment.

Results

Demographics, clinical characteristics, and treprostinil dosing

There were 43 individuals screened and 37 individuals enrolled in the study (Fig. 1). Six individuals were excluded due to drug non-compliance, protocol deviation, and/or crossing the pre-defined RAP threshold. Of the 37 enrolled, 24 (65%) were transitioned to oral treprostinil. As Table 1 demonstrates, a majority of the participants were women. Individuals were largely diagnosed with idiopathic PAH when compared to other etiologies and most patients utilized subcutaneous administration versus intravenous formulation of treprostinil. PAH was diagnosed >900 days previously on average in the transition groups compared to the PC group. Before transition, the average baseline parenteral treprostinil dosing was similar across the groups. Additional background oral therapy largely consisted of individuals treated with PDE5 inhibitor monotherapy or a combination therapy involving PDE5 inhibitors + ERA antagonists.

Of the 24 transition patients, 11 (46%) were considered transition failures. Of the $_U$Transition patients, all had deterioration in FC and 10/11 had deterioration in hemodynamics. One patient was unable to tolerate oral dosing requiring discontinuation and transition back to parenteral treprostinil. After transition to oral treprostinil, the total initial mean daily dose for $_S$Transition and $_U$Transition individuals was 32 mg and 35 mg, respectively, as shown in Table 2. There were only modest adjustments in dosing from initial transition to the current dose. The average time to transition failure for the $_U$Transition group was 557 days (range = 87–1253 days). Of the 11 $_U$Transition group individuals, nine returned to parenteral treprostinil and the average "rescue" dose was approximately 73 ng/kg/min. Two of the $_U$Transition group participants refused parenteral re-transition despite PAH provider

Table 2. Treprostinil dosing characteristics of the transition cohort.

	$_S$Transition	$_U$Transition
Oral TRE dose at transition (total daily dose mg)	32 (17–48)	35 (12–48)
Oral TRE dose most current (total daily dose (mg)	30 (10–48)	33 (9–63)
Time to failure (days)		557 (87–1253)
Parenteral treprostinil rescue dose (ng/kg/min)		73 (48–120)

Values in the summary column are presented as dose/days (range).
$_S$Transition, successful transition; $_U$Transition, unsuccessful transition.

Table 1. Demographics and clinical characteristics of the study cohort.

	$_S$Transition	$_U$Transition	$_C$Parenteral
n	13	11	13
Age (years)	55 (28–72)	49 (23–66)	51 (34–70)
Gender			
Female	9 (69)	9 (82)	11 (85)
Male	4 (31)	2 (18)	2 (15)
PAH etiology			
CHD	1 (8)		1 (8)
CTD	6 (50)	2 (18)	
Drugs/Toxins		3 (27)	1 (8)
iPAH	5 (42)	6 (55)	9 (75)
Portal hypertension			1 (8)
Background PAH therapy			
ERA	2 (15)		
PDE 5	8 (62)	5 (45)	8 (67)
ERA + PDE5	3 (23)	6 (55)	4 (33)
Parenteral delivery method			
SC	13 (100)	9 (82)	12 (100)
IV		2 (18)	
Treprostinil dose at enrollment (ng/kg/min)	50 (27–70)	59 (38–84)	46 (30–62)
Time since PAH diagnosis (days)	2886 (2143–3717)	2124 (1231–3524)	1214 (739–1666)

Values are presented as n (%) or n (range) where applicable.
$_S$Transition, successful transition; $_U$Transition, unsuccessful transition; $_C$Parenteral, parenteral comparator; BSA, body surface area; iPAH, idiopathic PAH; CTD, connective tissue disease-associated PAH; CHD, congenital heart disease-associated PAH; ERA, endothelin antagonist; PDE5, phosphodiesterase 5 inhibitor; SC, subcutaneous; IV, intravenous.

recommendations and were treated with the addition of oral therapy. There were no deaths in either transition arm. There were three deaths in the $_C$Parenteral arm during the follow-up period due to RV failure.

Hemodynamic and RV function measurements

At diagnosis, there were no significant differences in mPAP, PVR, CI, or RAP between groups ($P > 0.05$) although all patients generally had very elevated mPAP, depressed CI, and elevated RAP (see Table 3). mPAP and PVR at enrollment discriminated $_S$Transition from $_U$Transition and $_C$Parenteral groups at baseline/pre-transition (Table 3). At baseline/pre-transition, mPAP and PVR were significantly lower in the $_S$Transition group than the $_U$Transition and $_C$Parenteral groups. All other hemodynamics and metrics of RV function including BNP, RVFAC, and TAPSE were similar.

The median time from enrollment/pre-transition to post-transition assessment were similar, about 24 weeks, between the $_U$Transition and $_S$Transition groups (Table 3). After transition and follow-up visit 1, the elevated PVR remained significantly higher among the $_U$Transition group ($P < 0.05$; Table 3). Generally, follow-up 1 was done to assess continued stability in the transition groups and was 1008 days (range = 552–1445 days) and 696 days (range = 100–1245 days) in the $_S$Transition and $_U$Transition groups, respectively, from baseline. Among the transition patients, follow-up 2 was generally done to assess stability after changes in therapy among the $_U$Transition group at 842 days (range = 476–1106 days) since enrollment. The $_C$Parenteral group had follow-up assessments as clinically indicated. As Fig. 2 demonstrates, the increase in PVR in the $_U$Transition group persisted on follow-up 2 ($P = 0.05$), relative to the other groups despite re-initiation of parenteral treprostinil and/or addition of oral therapy.

Pre-transition prediction of transition success and failure

Cox regression analysis demonstrated a significant chance of transition failure in the $_U$Transition relative to the $_S$Transition group in measures of RV afterload (PVR, mPAP, and capacitance) (Table 4) and RAP whereas other measures of RV function, pre-transition parenteral, and post-transition oral treprostinil showed no relationship. ROC curves were used to predict the probability of transition success from baseline (before transition) hemodynamics or RV function with the lowest P value from the Cox analysis. As Fig. 3 shows, PVR was the best baseline predictor with AUC 0.9 (range = 0.78–1.0; $P < 0.001$) and a specificity of 0.77 and sensitivity of 0.91.

Discussion

To our knowledge, this study is the first protocolized parenteral transition trial with long-term follow-up in the combination treatment era. The findings demonstrate, in contrast to the initial 24-week trial,[5] a higher rate of transition failure. Transition failure is accurately predicted by PVR at enrollment which increases on follow-up beyond a similar group of patients remaining on parenteral therapy. Transition appeared successful in nearly all patients with enrollment PVR ≤ 4.16 WU to a mean follow-up period of 1008 days (range = 552–1445 days; nearly three years). Additionally, "rescue" therapy was unable to bring PVR back to baseline levels in a subset of patients in the $_U$Transition group.

All patients in this trial adhered to the initial trial transition protocol.[5] During the initial trial, one patient (3%) and three more (11%) required parenteral "rescue" during the 24-week and extension periods (median = 214 days follow-up), respectively. What is unique to this trial cohort is that the patients participated in follow-up over twice as long as the 24-week and extension periods combined. The average enrollment PVR of our transition groups (approximately 5.0 WU) was very similar to the baseline mean PVR (5.2 WU) in the initial trial. Time since diagnosis, RV function, and parenteral and oral treprostinil dosing at enrollment were also similar between the trials. Although the pharmacokinetic AUC was similar to parenteral to oral in that study,[5] small perturbations may be poorly tolerated in a marginally adapted RVPA system. Therefore, we theorize that the higher failure rate in our trial was due to other pharmacokinetic factors (such as greater peaks and troughs), between oral and parenteral treprostinil, in the context of high RV afterload.

Our trial is also unique including a parenteral comparator ($_C$Parenteral) group. This group, being similar to the $_U$Transition group at diagnosis and enrollment, illustrates the destabilizing effect of transition off parenteral prostaglandin and also controls for natural progression of disease. Further, once PVR increased in the $_U$Transition group after transition, it generally did not return to that of the $_C$Parenteral group, possibly indicating an irreversible condition despite "rescue" therapy in the $_U$Transition group. Lastly, the $_C$Parenteral group had similar hemodynamics to the $_S$Transition (and $_U$Transition) group at diagnosis indicating that the $_S$Transition group had a "robust" response to therapy rather than milder disease (Table 3).

Previous attempts at transitioning from parenteral to oral therapy in patients with PAH have met limited success.[13] Both prospective[14–16] and retrospective[17–20] studies evaluating the transition from inter-class parenteral to oral medications have found similarly that baseline hemodynamics generally predict probability of success. The study with the longest follow-up by Escolar et al.[20] demonstrated a similar 50% success rate after a mean >30-month (>900 days) follow-up from parenteral treprostinil to oral PDE5i/ERA. In this trial, both mPAP and PVR were predictive of transition success similar to our trial. Given that the successful transitions in the above study had a similar initial response to parenteral therapy as our $_S$Transition group, transition

Table 3. Hemodynamics and RV function by time point and transition cohort.

	sTransition	uTransition	cParenteral	P value
Diagnosis of PAH				
n	5	5	13	
mPAP (mmHg)	51 ± 14	53 ± 9.4	57 ± 11	0.9158
PCWP (mmHg)	10 ± 4.1	13 ± 2.7	12 ± 4.7	0.7917
RAP (mmHg)	7 ± 3.7	12 ± 3.1	16 ± 6.1	0.0977
PVR (WU)	12 ± 4.4	11 ± 4	14 ± 4.2	0.6985
CI (L/min/m^2)	2.4 ± 0.8	2 ± 0.6	2.1 ± 0.5	0.6985
Baseline/Pre-transition				
n	13	11	13	
mPAP (mmHg)	31 ± 7.8	47 ± 11	43 ± 10	**0.0123**
PCWP (mmHg)	11 ± 2.9	8.5 ± 3.9	6.8 ± 2.9	0.1169
RAP (mmHg)	5.2 ± 2.8	7.3 ± 3.3	5.5 ± 3	0.3720
PVR (WU)	3.4 ± 1.4	6.7 ± 2	6.4 ± 3.3	**0.0167**
CI (L/min/m^2)	3.3 ± 0.6	3.2 ± 0.8	3.6 ± 1.6	0.9268
BNP (pg/mL)	59 ± 68	36 ± 27	69 ± 48	0.5351
TAPSE (mm)	22 ± 3.7	22 ± 2.4	21 ± 3.9	0.8625
RVFAC (%)	33 ± 9.5	30 ± 5.7	27 ± 11	0.6004
Post-transition				
n	13	9		
Time to assessment (days)	178 (70–1073)	157 (195–504)	–	0.0977
mPAP (mmHg)	30 ± 12	46 ± 14	–	0.0977
PCWP (mmHg)	9.1 ± 2.9	6 ± 29	–	0.9344
RAP (mmHg)	6.3 ± 3.2	5 ± 2.5	–	0.6985
PVR (WU)	3.5 ± 1.5	6.9 ± 1.8	–	**0.0282**
CI (L/min/m^2)	3.4 ± 1.2	2.9 ± 0.7	–	0.6840
Follow-up 1				
n	10	11	9	
Time to assessment (days)	1008 (552–1445)	696 (100–1245)	246 (116–394)	
mPAP (mmHg)	28 ± 10	57 ± 9.3	37 ± 9.1	**0.0058**
PCWP (mmHg)	6.5 ± 4.5	8.3 ± 2.3	5.6 ± 0.9	0.5805
RAP (mmHg)	4.1 ± 2.8	9.5 ± 5.6	4.1 ± 2.6	0.1407
PVR (WU)	3.7 ± 1.7	10 ± 4	5.5 ± 1.6	**0.0058**
CI (L/min/m^2)	3.4 ± 0.6	2.7 ± 0.7	3.5 ± 0.8	0.1056
Follow-up 2				
n	1	6	8	
Time to assessment (days)	1259	842 (476–1106)	574 (314–1036)	
mPAP (mmHg)	20	51 ± 15	41 ± 7.9	0.4082
PCWP (mmHg)	–	6 ± 3.2	8 ± 4.6	0.6840
RAP (mmHg)	7	7 ± 5.5	5.8 ± 3.9	0.9580
PVR (WU)	1.8	8.1 ± 3	7.2 ± 5	0.4518
CI (L/min/m^2)	2.8	2.8 ± 0.4	3.5 ± 0.7	0.5351

Data are expressed as mean ± standard deviation or n (range). The number (n) at each assessment time includes the individuals with valid measurements defined by last assessment to groups, sTransition (successful transition), uTransition (unsuccessful transition), and cParenteral (parenteral comparator). Time to assessment (days) represents the time relative to baseline/pre-transition. P<0.05 is indicated in bold text.

mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; PVR, pulmonary vascular resistance; CI, cardiac index; BNP, brain natriuretic peptide; RVFAC, right ventricular fractional area change; TAPSE, tricuspid annular systolic excursion.
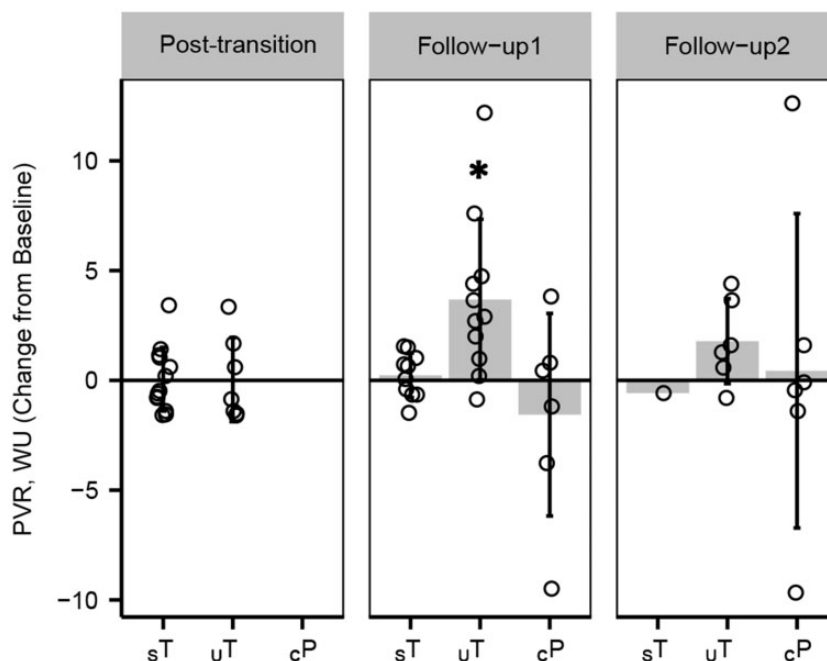
Fig. 2. Change from pre-transition PVR after transition, follow-up 1, and follow-up 2 by transition cohort. The high PVR in the unsuccessful transition ($_u$T) group at enrollment was also accompanied by increasing PVR at follow-up 1. This change in PVR was not reversed by follow-up 2 by "rescue" therapy. *Denotes that mean PVR by follow-up 1 was significantly higher in the $_u$T vs. successful transition ($_s$T) ($P = 0.0001$) and the $_u$T vs. parenteral comparator ($_c$P) groups ($P = 0.003$).

Table 4. Cox regression analysis using baseline hemodynamic, RV function, and treprostinil dosing variables to predict transition failure.

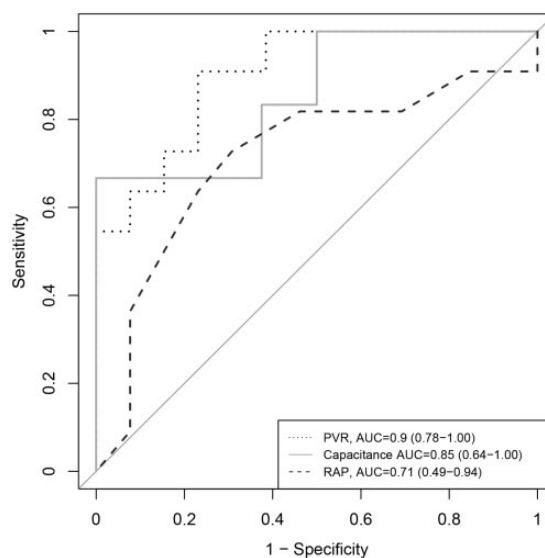|	Hazard ratio [95% confidence interval]	P value
mPAP (mmHg)	1.048 [1.008–1.09]	0.0184*
PVR (WU)	1.452 [1.131–1.864]	0.00343*
CI (L/min/m^2)	0.7741 [0.3194–1.876]	0.571
RAP (mmHg)	1.294 [1.004–1.667]	0.0463*
PA Ca (mL/mmHg)	0.1292 [0.0265–0.6299]	0.0133*
TAPSE (cm)	1.021 [0.8028–1.298]	0.868
FAC (%)	0.9513 [0.8563–1.057]	0.352
6 MWD (m)	0.9887 [0.9689–1.009]	0.271
Parenteral treprostinil dose, ng/kg/min	1.031 [0.9858–1.078]	0.183
Treprostinil dose at transition	1.017 [0.9591–1.079]	0.572

Hazard ratios represent the unsuccessful transition relative to successful transition group. The P values are not adjusted for multiple comparisons.
*$P < 0.05$.
mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; CI, cardiac index; RAP, right atrial pressure; PA Ca, pulmonary arterial capacitance; TAPSE, tricuspid annular plain systolic excursion; FAC, fractional area change; 6MWD, 6-min walk distance.

Fig. 3. ROC curves on RV afterload and performance at pre-transition enrollment. PVR demonstrated superior (AUC 0.9 [range = 0.78–1.0], $P = 0.0001$) accuracy in prediction of transition success than do capacitance and RAP. The optimal PVR cut-off was 4.16 WU, 2.2 mL/mmHg for capacitance, and 6.5 mmHg for RAP.

success may be better defined by initial response than the transition regimen.

Our trial has several limitations. It is retrospective in design and therefore many measures such as 6MWD, BNP, and echocardiography data are incomplete. Another limitation is the small number of participants enrolled in this trial. However, the exclusionary nature of the enrollees was necessary to maintain control of many factors including

dosing and follow-up testing. Next, due to study design, it was challenging to quantify medication-related adverse events. Therefore, it was difficult to exclude the possibility that some of the transition failures may also be in part due to side effects limiting optimal dosing. Lastly, given recent data demonstrating significant effects of triple upfront therapy[2] in FC IV patients and superior efficacy of upfront ERA/PDE5i therapy,[1] it is possible that if all our patients were on this combination that additional failures could have been avoided.

In conclusion, our data suggest that in a subset of PAH patients on combination background therapy, intra-class transition from parenteral to oral treprostinil is successful in the long term in 54% of participants. Pre-transition PVR can accurately predict failure which occurs gradually >24 weeks later. This deterioration in hemodynamics appears greater than that if they had stayed on parenteral treprostinil and may not be reversed by "rescue" therapy. Therefore, these authors recommend extreme caution when transitioning patients with greatly elevated PVR. Future directions in transition research may reveal measurable differences in imaging or biomarkers that will obviate the need for catheterization to predict success.

Conflict of interest

Funding

References

1. Galie N, Barbera JA, Frost AE, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med* 2015; 373: 834–844.
2. Sitbon O, Jais X, Savale L, et al. Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study. *Eur Respir J* 2014; 43: 1691–1697.
3. Simonneau G, Barst RJ, Galie N, 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.
4. Jing ZC, Parikh K, Pulido T, et al. Efficacy and safety of oral treprostinil monotherapy for the treatment of pulmonary arterial hypertension: a randomized, controlled trial. *Circulation* 2013; 127: 624–633.
5. Chakinala MM, Feldman JP, Rischard F, et al. Transition from parenteral to oral treprostinil in pulmonary arterial hypertension. *J Heart Lung Transplant* 2017; 36: 193–201.
6. Vonk-Noordegraaf A, Haddad F, Chin KM, et al. Right heart adaptation to pulmonary arterial hypertension: physiology and pathobiology. *J Am Coll Cardiol* 2013; 62: D22–33.
7. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Respir J* 2015; 46: 903–975.
8. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010; 23: 685–713; quiz 86–88.
9. Computing RFfS. *A language and environment for statistical computing.* Vienna, Austria: R Core Team, 2016.
10. Benjamini Y and Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J Roy Stat Soc B* 1995; 57: 289–300.
11. Robin X, Turck N, Hainard A, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics* 2011; 12: 77.
12. Mason SJ and Graham NE. Areas beneath the relative operating characteristics (ROC) and relative operating levels (ROL) curves: Statistical significance and interpretation. *Q J Roy Meteorol Soc* 2002; 128: 2145–2166.
13. Sofer A, Ryan MJ, Tedford RJ, et al. A systematic review of transition studies of pulmonary arterial hypertension specific medications. *Pulm Circ* 2017; 7: 326–338.
14. Steiner MK, Preston IR, Klinger JR, et al. Conversion to bosentan from prostacyclin infusion therapy in pulmonary arterial hypertension: a pilot study. *Chest* 2006; 130: 1471–1480.
15. Suleman N and Frost AE. Transition from epoprostenol and treprostinil to the oral endothelin receptor antagonist bosentan in patients with pulmonary hypertension. *Chest* 2004; 126: 808–815.
16. Johnson RF, Loyd JE, Mullican AL, et al. Long-term follow-up after conversion from intravenous epoprostenol to oral therapy with bosentan or sildenafil in 13 patients with pulmonary arterial hypertension. *J Heart Lung Transplant* 2007; 26: 363–369.
17. Keogh AM, Jabbour A, Weintraub R, et al. Safety and efficacy of transition from subcutaneous treprostinil to oral sildenafil in patients with pulmonary arterial hypertension. *J Heart Lung Transplant* 2007; 26: 1079–1083.
18. Diaz-Guzman E, Heresi GA, Dweik RA, et al. Long-term experience after transition from parenteral prostanoids to oral agents in patients with pulmonary hypertension. *Respir Med* 2008; 102: 681–689.
19. Safdar Z. Outcome of pulmonary hypertension subjects transitioned from intravenous prostacyclin to oral bosentan. *Respir Med* 2009; 103: 1688–1692.
20. Escolar E, Pineda AM, Correal B, et al. Transition from prostacyclin analogue infusion to oral therapy in patients with pulmonary arterial hypertension: a 5-year follow-up. *Pulm Circ* 2013; 3: 880–888.