DOI: 10.1002/pul2.12328

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRI Pulmonary Vascular Research Institute | WILEY

Younger age at initiation of subcutaneous treprostinil is associated with better response in pediatric Group 1 pulmonary arterial hypertension

Justin J. Kochanski[1] | **Jeffrey A. Feinstein**[1] | **Michelle Ogawa**[1] | **Victor Ritter**[2] | **Rachel K. Hopper**[1] | **Gregory T. Adamson**[1]

[1]Department of Pediatrics (Cardiology), Stanford University School of Medicine, Palo Alto, California, USA

[2]Stanford University School of Medicine, Quantitative Sciences Unit, Palo Alto, California, USA

Correspondence
Justin J. Kochanski, MD, 750 Welch Rd, Suite 315, Palo Alto, CA 94304, USA.
Email: jkochan@stanford.edu

Funding information
None

Abstract

Children with severe Group 1 pulmonary arterial hypertension (PAH) have an unpredictable response to subcutaneous treprostinil (TRE) therapy, which may be influenced by age, disease severity, or other unknown variables at time of initiation. In this retrospective single-center cohort study, we hypothesized that younger age at TRE initiation, early hemodynamic response (a decrease in pulmonary vascular resistance by ≥30% at follow-up catheterization), and less severe baseline hemodynamics (Rp:Rs < 1.1) would each be associated with better clinical outcomes. In 40 pediatric patients with Group I PAH aged 17 days−18 years treated with subcutaneous TRE, younger age (cut-off of 6-years of age, AUC 0.824) at TRE initiation was associated with superior 5-year freedom from adverse events (94% vs. 39%, $p = 0.002$), better WHO functional class (I or II: 88% vs. 39% $p = 0.003$), and better echocardiographic indices of right ventricular function at most recent follow-up. Neither early hemodynamic response nor less severe baseline hemodynamics were associated with better outcomes. Patients who did not have a significant early hemodynamic response to TRE by first follow-up catheterization were unlikely to show subsequent improvement in PVRi (1/8, 13%). These findings may help clinicians counsel families and guide clinical decision making regarding the timing of advanced therapies.

KEYWORDS
outcomes, prostacyclin, pulmonary hypertension, pulmonary vascular disease

INTRODUCTION

Patients with severe Group 1 pulmonary arterial hypertension (PAH) are commonly treated with prostacyclin analogues, a medication class that induces pulmonary vasodilation, reduces platelet aggregation, and inhibits endothelial growth.[1–5] Treprostinil (TRE) specifically has been shown to improve hemodynamics, clinical status, and survival in some pediatric patients with severe PAH.[6–8]

Although TRE generally improves outcomes, disease progression is seen in most patients.[6,7,9,10] Predicting which patients will respond to TRE, and to what degree, remains challenging, and there are few studies to guide risk stratification. Age is not a well-defined prognostic factor in this patient population, as both younger and older age have been shown to be associated with worse outcomes.[11,12] A limited number of studies have demonstrated that early hemodynamic improvement after starting prostacyclin therapy is associated with long-term freedom from adverse events (AE), and others have shown that a higher indexed pulmonary vascular resistance (PVRi) at the time of starting therapy to be a risk-factor for death.[11,13–16]

Better understanding of prognostic factors could impact clinical decisions, from timing of cardiac catheterization to implementation of advanced therapies such as a reverse Potts shunt or lung transplantation. We conducted a single center retrospective study of outcomes for pediatric patients with severe Group 1 PAH treated with TRE. We hypothesized that younger age at start of therapy, early hemodynamic response to therapy, and lower pulmonary to systemic vascular resistance ratio (Rp:Rs) would each be associated with superior outcomes.

METHODS

This was a single-institution, retrospective cohort study of pediatric patients with Group 1 PAH initiated on TRE between January 2010 and December 2020. The study was approved by our Institutional Review Board with a waiver of consent. Patients 21 years of age or less when initiated on TRE were identified using an institutional database. Group I PAH patients were identified and included on initial review if they had a mean pulmonary arterial pressure > 20 mmHg, PVRi > 3 Wood units*m^2, and a mean pulmonary capillary wedge pressure < 15 mmHg.[17] Patients with unrepaired congenital heart disease other than small atrial or restrictive ventricular septal defects were excluded.

Demographic, clinical, and imaging data were extracted from institutional electronic medical records. The baseline hemodynamic data were defined as those obtained during the catheterization preceding initiation of TRE. Hemodynamic calculations were standardized and verified by a single cardiologist (G. T. A.) specifically for this analysis. When cardiac index and pulmonary blood flow calculations were performed using both thermodilution and Fick, thermodilution was used to calculate PVRi and for analysis. For Fick, oxygen consumption (VO_2) was determined using a standardized table utilizing patient age, sex, and heart rate.[18] Data were collected for each clinical encounter through July 2022 or until an AE as defined by lung or heart-lung transplant, balloon-atrial septostomy, reverse Potts shunt, or death. Echocardiogram data were re-measured manually from the baseline and most recent studies by two reviewers (G. T. A. and J. J. K.), which included right ventricular (RV) systolic function, intraventricular septal position, RV fractional area change (RVFAC), tricuspid annular plane systolic excursion (TAPSE and BSA indexed), and estimated RV pressure using the tricuspid regurgitation doppler velocity.

To select for patients who had a robust response, early hemodynamic response was defined as a PVRi

TABLE 1 Baseline demographics.

		***n* = 40**
Age (years)		7.3 (3.0–11.0)
Weight (kg)		25.2 (4.3–88.0)
Female		27 (67%)
Race		
White		19 (48%)
Asian		8 (20%)
Pacific Islander		1 (3%)
Other		9 (23%)
Unknown		3 (8%)
Diagnosis		
IPAH		31 (78%)
Heritable		9 (22%)
	TBX4	3
	ENG	2
	BMPR2	1
	AVCRL	1
	SOX17	1
	Unknown	1
Therapy		
Single therapy		4 (10%)
Dual therapy		17 (42%)
Triple therapy		19 (48%)
Baseline		
PVRi (WU)		16.5 (3.2–43.0)
Rp:Rs		0.9 (0.1–35.8)
RVFAC (%)		22.3 (7.5–40.0)
Diagnosis to TRE start (days)		70 (9–802)
TRE dose (ng/kg/min)		68.4 (20.0–150.0)

reduction ≥ 30% from baseline at first follow-up catheterization. PAH severity was defined as severe if the pulmonary-to-systemic vascular resistance ratio (Rp:Rs) was ≥1.1.

Statistics

Descriptive statistics were presented as frequency counts and percentages for categorical data, and continuous data as median (range). Wilcoxon Rank Sum and two-sided Fischer's Tests were used to study associations between study variables and outcomes. Log-rank testing was used to determine differences in 5-year freedom from AEs between groups. Sensitivity analysis was conducted to determine optimal age-cutoff using a receiving operator curve. All statistical tests were performed using SPSS version 28.0.0.0 (190).

RESULTS

A total of 170 patients started on TRE during the study timeline were identified. Of those, 41 met inclusion criteria (Supplemental Figure 1). One patient was treated with TRE for less than 1 month due to adverse medication effect and was excluded from analysis, yielding a final study cohort of 40 patients. Most patients were female ($n = 27$, 68%), and the median age and weight at the time of TRE initiation was 7.3 (3.0–11.1) years and 25.2 (4.3–88.0) kg. The median dose of TRE was 68.4 (IQR 51.5–91.9, Range 20.0—150.0) ng/kg/min (Table 1).

At baseline catheterization, in 36 (90%) patients thermodilution was used to measure flows, and in 4 (10%) the Fick method was used. The median baseline PVRi was 16.5 (3.2–43.0) WU, Rp:Rs was 0.9 (0.1–35.8), and by echocardiogram the RVFAC was 22.3 (7.5–40.0)%. Of these 40 patients, 23 (58%) underwent genetic testing. Nine of these patients were found to have a genetic diagnosis associated with PAH and were classified as heritable disease ($n = 9$ 22%). The remaining cases were classified as idiopathic (IPAH) ($n = 31$, 78%), although roughly half of these patients did not undergo genetic testing ($n = 17/31$, 54%). All of the patients who did not undergo genetic testing were diagnosed before 2014, and it is more recently standard of care to offer genetic testing to all patients.

The median time from PAH diagnosis to TRE start was 70 days (9–802). By 4 months after initiation of TRE, 4 (10%) were on single TRE therapy, 17 (42%) on dual-therapy, and 19 (48%) on triple therapy. The median follow-up time was 4.7 years (IQR 1.5–6.6) from TRE initiation to the most recent clinical encounter or AE. Most patients underwent at least one catheterization after initiation of TRE ($n = 32$, 80%) with median time from baseline to follow-up catheterization of 12.8 months (11.1–15.6), and all patients had follow-up echocardiograms and clinical encounters.

Approximately half of the patients ($n = 21$, 52%) experienced AEs over the study period. Twelve (30%)

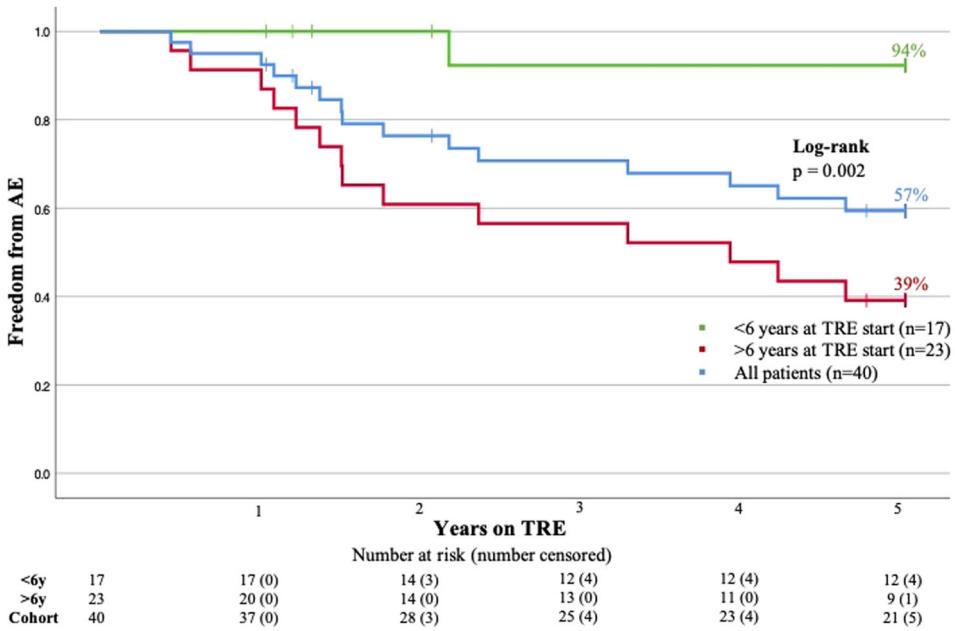

FIGURE 1 Kaplan—Meier curve for freedom from adverse events in patients started on TRE before 6 years (green), after 6 years (red), and all patients (blue).

TABLE 2 Comparison of baseline (a) and follow-up (b) data between age groups of patients started on TRE.

Baseline (a)	<6 years ($n = 17$)	>6 years ($n = 23$)	p	Follow-up (b)	<6 years ($n = 17$)	>6 years ($n = 23$)	p
Male	6 (35%)	7 (30%)	0.504	**TRE start to follow-up cath** (days)	345 (24–1243)	365 (49–534)	0.419
Race			0.891	**Outcomes**			
White	9 (53%)	10 (43%)		Death	3 (18%)	9 (39%)	0.179
Asian	3 (18%)	5 (21%)		AE	4 (24%)	17 (74%)	**0.003**
Pacific Islander	0	1 (4%)					
Other	4 (24%)	5 (22%)					
Unknown	1 (6%)	2 (9%)		**WHO-FC**			**0.003**
Diagnosis			0.456	I/II	15 (88%)	9 (39%)	
IPAH	12 (71%)	19 (83%)		III/IV	2 (12%)	14 (61%)	
Heritable	5 (29%)	4 (17%)					
Rx			0.219	**Rx**			
Mono Therapy	1 (6%)	3 (13%)		No Therapy	4 (24%)	0	**0.026**
Dual Therapy	10 (59%)	7 (30%)		Triple Therapy	10 (59%)	20 (87%)	0.066
Triple Therapy	6 (35%)	13 (57%)					
NT-proBNP	7095 (20–23,735)	218 (30–3715)	**0.007**	**NT-proBNP**	198 (30–10,869)	183 (30–7397)	0.622
Diagnosis to TRE start (days)	27 (1–1264)	297 (1–4187)	**0.039**				
Hemodynamics				**Hemodynamics**	*(n = 14/17)*	*(n = 18/23)*	
PVRi	15 (3.2–34.5)	18 (6.3–43.0)	0.075	PVRi	7.0 (1.7–19.0)	12.8 (2.8–39.0)	**0.005**
mPAP	61 (40–109)	63 (30–102)	0.342	mPAP	49 (16–95)	61 (24–100)	0.099
CI	4.0 (2.4–5.1)	2.8 (1.39–13.7)	**0.009**	CI	4.7 (2.6–5.6)	3.8 (2.2–6.5)	0.193
SVRi	17.7 (8.3–57.3)	19.6 (1.2–40.6)	0.588	SVRi	12.9 (7.3–22.7)	14.0 (0.7–23.0)	0.779
Rp/Rs	0.8 (0.1–2.3)	0.9 (0.4–35.8)	0.516	Rp/Rs	0.5 (0.1–1.3)	0.9 (0.2–2.7)	**0.034**
Echo				**Echo**			
Septal Position			0.282	**Septal Position**			**0.003**
Normal	1 (6%)	0		Normal	7 (41%)	1 (4%)	
Flattened	6 (35%)	5 (21%)		Flattened	5 (29%)	4 (17%)	
Bowing	10 (59%)	18 (78%)		Bowing	5 (29%)	18 (78%)	
TRPG (mmHG)	79 (43–120) [$n = 12/17$]	87 (49–125) [$n = 20/21$]	0.534	**TRPG** (mmHG)	67 (22–146)	96 (49–130)	0.163
RV Function			0.337	**RV Function**			**<0.001**
Normal-mildly depressed	9 (53%)	8 (35%)		Normal-mildly depressed	15 (88%)	5 (21%)	
Moderate-severely depressed	8 (47%)	15 (65%)		Moderate-severely depressed	2 (12%)	18 (78%)	
TAPSE-Z	−2.7 (−7.0 to 3.6) [$n = 16/17$]	−5.7 (−7.6 to 2.8) [$n = 20/23$]	**0.049**	**TAPSE-Z**	−0.2 (−6.3 to 2.35)	−4.5 (−9.0 to 3.5)	**0.002**
RVFAC (%)	25.7 (7.7–39.8) [$n = 16/17$]	21.5 (7.5–36.7) [$n = 20/23$]	0.305	**RVFAC** (%)	38.9 (9.7–49.7)	18.7 (4.5–50.3)	**<0.001**

Note: Categorical data presented as frequency (percentage) and continuous data as median (range). Bold values represent $p < 0.05$.

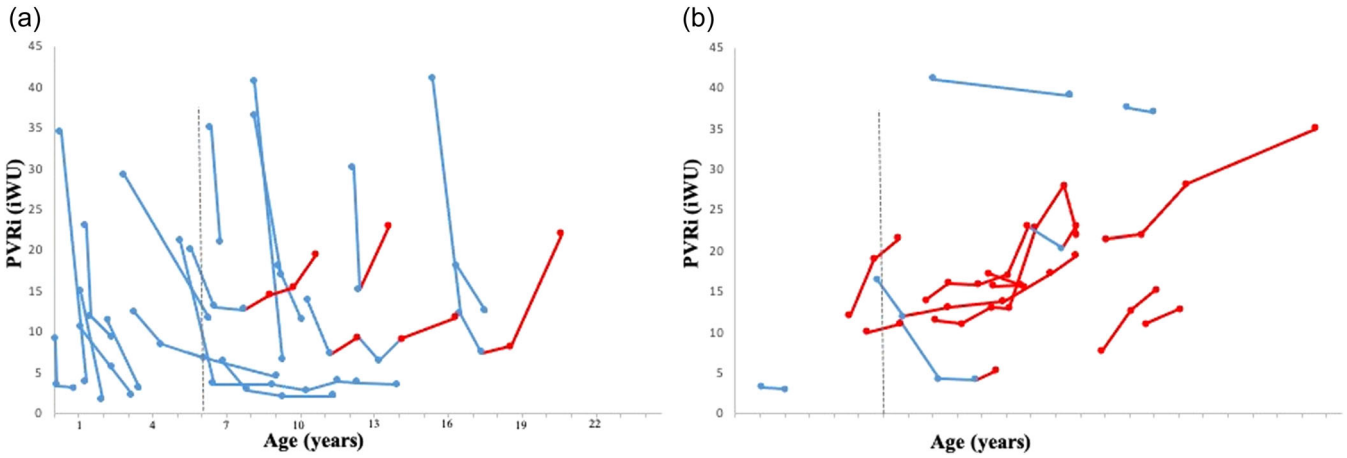

FIGURE 2 (a) Trends in PVRi in patients categorized as responders (30% or greater reduction in PVRi), with blue series showing interval improvement or stable PVRi while red shows worsening PVRi. (b) PVRi trends in patients who did not meet criteria for response (red) with the same color coding of series.

patients died, 12 (30%) underwent lung or heart-lung transplantation, two (5%) underwent Potts shunt, and one (3%) underwent balloon-atrial septostomy. The 5-year freedom from AE in the cohort was 57% (Figure 1) with a 5-year survival rate of 83%.

Using ROC analysis, it was determined that 6-years of age was the cutoff with highest combined sensitivity and specificity for 5-year freedom from AEs (Figure S2). When dichotomized using this cutoff ($n = 17$ under 6 years, $n = 23$ over 6 years), the younger cohort had superior 5-year freedom from AE (94% vs. 39%, $p = 0.002$, Figure 1). The younger cohort also had shorter median duration from PAH diagnosis to TRE start (27 vs. 297 days, $p = 0.039$), higher baseline median cardiac index (4.0 vs. 2.8 $p = 0.009$), higher baseline median brain natriuretic peptide (7095 vs. 218, $p = 0.007$), and higher baseline median TAPSE (z −2.7 vs. −5.7, $p = 0.049$) (Table 2). The two cohorts otherwise had similar baseline hemodynamics and echo markers, including similar baseline PVRi (15.0 vs. 18.0, $p = 0.075$) and Rp:Rs (0.8 vs. 0.9, $p = 0.516$). At first follow-up catheterization, the younger cohort had a lower median PVRi (7.0 [1.7–19.0] vs. 12.8 [2.8–39.0] WU, $p = 0.005$) and Rp:Rs (0.5 [0.1–1.3] vs. 0.9 [0.2–2.7], $p = 0.034$). At time of most recent follow up, more patients in the younger cohort had been weaned off PH therapy entirely ($n = 4/17$, 24% vs. $n = 0/23$, 0%, $p = 0.026$). The younger group also had superior WHO functional class (I or II) (15/17, 88% vs. 9/23, 39%, $p = 0.003$) and superior echo markers of RV function (Table 2).

Of the 32 patients who had a follow up catheterization during this study period, 19 (59%) had a reduction in PVRi ≥ 30% after starting TRE and were classified as the "responder group." Longitudinal PVRi data for each patient is shown in Figure 2. The responder group had a shorter median duration from PAH diagnosis to TRE start and higher baseline SVR, but no other differences before starting therapy (Table 3). At follow up, the responder group had no difference in 5-year freedom from AEs ($n = 14/19$, 74% vs. $n = 8/13$, 62%, log rank $p = 0.512$), or proportion of patients on triple therapy at most recent follow up ($n = 14/19$, 74% vs. $n = 9/13$, 69%, $p = 0.545$). At most recent follow-up there were no differences in NYHA I/II functional class (13/19, 68% vs. 6/13, 46%, $p = 0.281$). On most-recent echo, the responder group had higher RV-FAC (37.5 [IQR 19.3–42.8] vs. 22.1 [14.3–30.7], $p = 0.045$) and lower estimation of RV pressure (70.8 [46.1–89.7] vs. 102 [80.6–117.1] $p = 0.023$) (Table 3).

When dichotomized by Rp:Rs, 14/40 (35%) patients were defined as severe (Rp:Rs ≥ 1.1). There were no significant differences in demographics between these groups, and by design the baseline hemodynamics were significantly worse in the severe group (Table 4). At follow-up catheterization and on most recent echocardiogram, the severe group continued to have significant elevation in RV pressure (Table 4). There were no differences in 5-year freedom from AE's (17/26, 65% and 8/14, 57%, log rank $p = 0.473$) between the two groups.

DISCUSSION

In this contemporary cohort of 40 pediatric Group 1 PAH patients started on TRE therapy, The 5-year freedom from AE was 57% with a 5-year survival rate of 83%, similar to that reported in a previous studies of pediatric patients treated with prostacyclin analogues (68–87%).[7,10]

TABLE 3 Comparison of baseline (a) and follow-up (b) data between patients started on TRE classified as responders (>30% reduction in PVRi) and non-responders.

Baseline (a)	Responder ($n = 19$)	Nonresponder ($n = 13$)	p	Follow-up (b)	Responder ($n = 19$)	Nonresponder ($n = 13$)	p
Male	6 (32%)	5 (38%)	0.487	**TRE start to follow-up cath** (days)	347 (24–1243)	359 (49–534)	0.383
Race			0.112	**Outcomes**			
White	8 (42%)	8 (62%)		Death	6 (32%)	4 (31%)	0.636
Asian	3 (16%)	2 (15%)		AE	7 (37%)	9 (69%)	0.149
Pacific Islander	0	0					
Other	5 (26%)	3 (23%)					
Unknown	3 (16%)	0		**WHO-FC**			0.281
Diagnosis				I/II	13 (68%)	6 (46%)	
IPAH	15 (79%)	12 (92%)	0.271	III/IV	6 (32%)	7 (54%)	
Heritable	4 (21%)	1 (8%)	0.308				
Rx			0.328	**Rx**			
Mono Therapy	2 (11%)	2 (15%)		No Therapy	3 (16%)	1 (8%)	0.458
Dual Therapy	11 (58%)	4 (31%)		Triple Therapy	14 (74%)	9 (69%)	0.545
Triple Therapy	6 (32%)	7 (54%)					
NT-proBNP	2780 (33–21,969)	574 (30–3321)	0.135	**NT-proBNP**	182 (86–10,869)	217 (30–7397)	0.539
Diagnosis to TRE start (days)	28 (3–161)	878 (26–1548)	**0.003**				
Hemodynamics				**Hemodynamics**			
PVRi	20.0 (6.3–41)	13.9 (3.2–41.0)	0.223	PVRi	8.4 (1.7–21.0)	12.8 (3.0–39.0)	**0.008**
mPAP	63 (30–102)	62 (41–109)	0.910	mPAP	50 (16–90)	63 (22–10)	**0.011**
CI	4.5 (1.4–13.7)	3.3 (2.3–4.5)	0.596	CI	4.7 (2.6–6.5)	3.9 (2.2–5.7)	0.108
SVRi	24.1 (9.1–57.3)	17.7 (8.1–24.2)	**0.018**	SVRi	12.4 (6.6–22.7)	15.6 (0.7–23.0)	0.850
Rp/Rs	0.97 (0.42–1.95)	0.97 (0.13–2.09)	0.850	Rp/Rs	0.62 (0.03–2.65)	0.91 (0.19–1.61)	0.077
Echo				**Echo**			
Septal Position			0.431	**Septal Position**			0.532
Normal	0	1 (8%)		Normal	6 (31%)	2 (15%)	

TABLE 3 (Continued)

Baseline (a)	Responder ($n = 19$)	Nonresponder ($n = 13$)	p	Follow-up (b)	Responder ($n = 19$)	Nonresponder ($n = 13$)	p
Flattened	5 (26%)	4 (31%)		Flattened	6 (31%)	4 (31%)	
Bowing	14 (74%)	8 (61%)		Bowing	7 (38%)	7 (54%)	
TRPG (mmHG)	86.5 (60.0–109.9) [$n = 16/19$]	77.5 (49.0–125.0) [$n = 12/13$]	0.767	**TRPG** (mmHG)	70.8 (46.1–89.7)	102 (80.6–117.1)	**0.023**
RV Function			0.149	**RV Function**			0.149
Normal-mildly depressed	6 (32%)	8 (62%)		Normal-mildly depressed	12 (63%)	4 (30%)	
Moderate-severely depressed	13 (68%)	5 (38%)		Moderate-severely depressed	7 (37%)	9 (70%)	
TAPSE-Z	−4.3 (−7.6 to −0.2) [$n = 16/19$]	−3.8 (−7.1 to 3.6)	0.650	**TAPSE-Z**	−1.8 (−4.0 to 0.4)	−3.3 (−6.6 to −0.6)	0.287
RVFAC (%)	19.5 (7.7–39.1) [$n = 16/19$]	22.9 (7.5–39.8)	0.144	**RVFAC**	37.5 (19.3–42.8)	22.1 (14.3–30.7)	**0.045**

Note: Categorical data presented as frequency (percentage) and continuous data as median (range). Bold values represent $p < 0.05$.

Patients started on TRE before 6 years of age had superior outcomes and, contrary to our expectations, neither early hemodynamic response to TRE nor the presence of the most severe disease were associated with AEs.

Patients started on TRE before 6 years of age had superior outcomes, many with normalization of PVRi and RV performance. Normal echo markers of RV function have been shown to be associated with ongoing lower risk of mortality.[19–21] Though prior studies have shown TRE to have greatest effect on PVRi in the first 1–2 years of therapy, our data suggest that this effect could be longer lasting in younger patients.[7,10] Historically, our center has advocated early initiation of TRE in pediatric patients with Group 1 PAH. A recent study by Douwes et al. found earlier initiation of treatment with prostacyclin analogues to be associated with better outcomes in children with PAH, corroborating our findings and strengthening the rationale for early TRE initiation, particularly in younger patients.[22]

One possible reason for this finding is the anti-inflammatory and antiproliferative properties of TRE could modify disease progression.[8] Additionally, dosing early in life during periods of microvascular lung maturation might offer more opportunity for remodeling. In this study, the younger group did have significantly shorter duration from initial diagnosis to initiation of TRE, and it's possible that earlier initiation promotes vascular remodeling before a tipping point of irreversible progression, resulting in better and sustained outcomes. This is supported as well by the fact that the younger group had significantly higher baseline cardiac output in the face of similar PVRi, and perhaps were treated in a compensated window before clinical decline. An alternate explanation could be that the pathophysiology of Group 1 PAH presenting early in life may be fundamentally different from Group 1 PAH that presents later in later childhood. Perhaps early PAH is driven by developmental immaturity of the pulmonary vasculature that is ameliorated with lung growth during early childhood.

Contrary to our hypothesis and other studies, early hemodynamic response to TRE was not associated with a difference in AEs, functional class, or echocardiographic markers of RV function at 5-years or most recent follow-up.[11,13,14] Additionally, patients who did not respond to therapy at the initial follow-up catheterization were unlikely to respond at later catheterizations. Knowing this trajectory could be helpful in limiting the number of invasive catheterizations in non-responders. It also may be reasonable to consider a Potts shunt earlier in the disease course rather than waiting any more than 1–2 years for a hemodynamic response, particularly for

TABLE 4 Comparison of baseline (a) and follow-up outcome (b) data between patients started on TRE classified as severe hemodynamics (Rp/Rs ≥ 1.1) versus nonsevere.

Baseline (a)	Nonsevere ($n = 26$)	Severe ($n = 14$)	p	Follow-up (b)	Nonsevere ($n = 26$)	Severe ($n = 14$)	p
Male	11 (42%)	2 (14%)	0.071	**TRE start to follow-up cath** (days)	360 (24–534)	312 (35–1,243)	0.272
Race			0.112	**Outcomes**			
White	8 (31%)	11 (79%)		Death	6 (23%)	6 (43%)	0.173
Asian	3 (12%)	5 (36%)		AE	11 (42%)	10 (71%)	0.105
Pacific Islander	0	1 (7%)					
Other	2 (8%)	7 (50%)					
Unknown	1 (4%)	2 (14%)		**WHO-FC**			0.176
Diagnosis				I/II	6 (23%)	6 (43%)	
IPAH	22 (85%)	9 (64%)	0.224	III/IV	18 (77%)	8 (57%)	
Heritable	4 (15%)	5 (36%)	0.234				
Rx			0.710	**Rx**			
Mono Therapy	2 (8%)	2 (14%)		No Therapy	4 (15%)	0	0.164
Dual Therapy	13 (50%)	4 (29%)		Triple Therapy	18 (69%)	12 (86%)	0.226
Triple Therapy	12 (46%)	8 (57%)					
NT-proBNP	308 (20–21,969)	590 (45–23,735)	0.225	**NT-proBNP**	154 (30–4,270)	1,045 (31–10,869)	**0.018**
Diagnosis to TRE start (days)	105 (10–493)	29 (8–1823)	0.664				
Hemodynamics				**Hemodynamics**	*(n = 20/26)*	*(n = 12/14)*	
PVRi	13.7 (3.2–40.7)	29.6 (11.5–43.0)	**<0.001**	PVRi	7.8 (1.7–22.0)	14.1 (11.0–39.0)	**0.007**
mPAP	56.5 (30–87)	76 (49–109)	**<0.001**	mPAP	46 (16–95)	67 (56–100)	**<0.001**
CI	3.3 (1.5–4.9)	3.7 (1.4–13.7)	0.685	CI	4.3 (2.6–6.5)	4.2 (2.2–5.7)	0.578
SVRi	19.7 (9.2–50.0)	17.6 (1.2–57.2)	0.492	SVRi	15.0 (0.66–22.7)	10.4 (1.3–23.0)	0.326
Rp/Rs	0.69 (0.13–1.00)	1.56 (1.2–35.8)	**<0.001**	Rp/Rs	0.6 (0.3–1.2)	1.2 (0.7–2.7)	**<0.001**
Echo				**Echo**			
Septal Position			0.591	**Septal Position**			0.051
Normal	1 (4%)	0		Normal	8 (31%)	1 (7%)	
Flattened	8 (31%)	3 (7%)		Flattened	10 (38%)	3 (21%)	

TABLE 4 (Continued)

Baseline (a)	Nonsevere ($n = 26$)	Severe ($n = 14$)	p	Follow-up (b)	Nonsevere ($n = 26$)	Severe ($n = 14$)	p
Bowing	17 (65%)	11 (93%)		Bowing	8 (31%)	10 (71%)	
TRPG (mmHG)	77.5 (43.0–110.0) [$n = 20/26$]	94.0 (49.0–125.0)	0.767	**TRPG** (mmHG)	78.0 (49.9–98.5)	100 (82.9–124)	**0.018**
RV Function			0.092	**RV Function**			0.096
Normal-mildly depressed	14 (54%)	3 (7%)		Normal-mildly depressed	16 (62%)	4 (29%)	
Moderate-severely depressed	12 (46%)	11 (93%)		Moderate-severely depressed	10 (38%)	10 (71%)	
TAPSE-Z	−4.4 (−7.0 to 3.6) [$n = 24/26$]	−3.4 (−7.6 to 2.8) [$n = 12/14$]	0.650	**TAPSE-Z**	−2.7 (−4.7 to 0.46)	−3.1 (−6.8 to 0.0)	0.585
RVFAC (%)	22.7 (7.7–39.1) [$n = 24/26$]	20.4 (7.5–39.8) [$n = 12/14$]	0.144	**RVFAC**	34.7 (20.1–41.2)	16.8 (13.8–29.9)	**0.007**

Note: Categorical data presented as frequency (percentage) and continuous data as median (range). Bold values represent $p < 0.05$.

patients with severe baseline hemodynamics.[23] Contrary to our findings, Tella and colleagues recently reported a > 25% drop in mean pulmonary artery pressure at follow-up catheterization in 31 pediatric patients started on TRE and/or epoprostenol was associated with freedom from AEs with a greater than 80% accuracy.[13] The reason for the difference in our study may reflect differences in patient cohorts. Although we report a similar median time from baseline to follow-up catheterization (12.8 vs. 11.1 months), there is still a wide range in the timing of follow-up catheterization in both studies which can influence results.

In this study, although we hypothesized that patients with severe disease (Rp:Rs ≥1.1) would have a higher likelihood of AEs, we found no difference in 5-year freedom from AEs between groups. A number of previous studies have investigated the prognostic value of baseline hemodynamics in the survival of pediatric patients with PAH. While some of these studies have demonstrated baseline PVRi to be predictive of survival, others have demonstrated no correlation.[11,14–16] This could in-part be related to the age effect demonstrated in our study—at 5 years, the younger patients with severe baseline hemodynamics were largely doing well clinically with few AEs (1/5, 20%). This is a stark contrast to the older cohort, as the majority of patients with nonsevere baseline hemodynamics experienced AEs (10/13, 56%).

There are a number of limitations to our study and findings. A number of patients in this study were on other PAH-directed therapies either before or after initiation TRE, which may confound any findings ascribed as specific to TRE. It is possible, for example, that younger age at treatment with any targeted PAH therapy would have a better outcome than treatment at older age. Results may have differed had we chosen different cutoffs for hemodynamic response to TRE (PVRi decrease of 30% or more) and for severe baseline disease (Rp:Rs 1.1 or higher). Due to small sample size, we did not utilize a linear mixed model to delineate the relative effects of age, diagnosis, cardiac index, and other variables on outcomes in this population. Our findings are subject to time-to-effect bias, as 13% of patients in this study did not have follow-up through 5-years. The variable timing of follow-up catheterizations may impact the assignment of responders and non-responders. Since many patients before 2014 did not undergo genetics testing, we cannot determine the impact of genetic diagnoses on outcomes. We followed a similar dosing strategy for all patients during the study period, initiating TRE at a low dose (1–2 ng/kg/min) with uptitration to 8–10 ng/kg/min over 2–3 days before discharge. TRE was then uptitrated to an initial goal dose of 50 ng/kg/min over a 4–6 week period, with further adjustments made

as per patients symptoms. Due to small sample size and a similar dosing strategy utilized for all patients, we are not able to perform an analysis of optimal TRE dosing.

In conclusion, in this contemporary cohort of children with Group 1 PAH managed with subcutaneous TRE, 5-year freedom from AEs and survival rates were similar to previous reports. Children initiated on TRE before 6 years of age had significantly fewer AEs and superior RV performance over time. Neither the absence of early hemodynamic response to TRE nor significantly elevated Rp:Rs (>1.1) were associated with worse outcomes. These observational data suggest that TRE should be considered as a primary therapy in young patients with severe Group I PAH.

AUTHOR CONTRIBUTIONS

Justin J. Kochanski, Jeffrey A. Feinstein, Michelle Ogawa, and Gregory T. Adamson designed the study. Justin J. Kochanski, Michelle Ogawa, and Gregory T. Adamson collected and verified data. Victor Ritter and Justin J. Kochanski performed statistical analysis. Justin J. Kochanski and Gregory T. Adamson wrote the initial manuscript draft. All authors (Justin J. Kochanski, Jeffrey A. Feinstein, Michelle Ogawa, VR, and Gregory T. Adamson) provided critical manuscript revisions.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

Stanford IRB approval with a waiver of consent (protocol number 49231).

ORCID

Justin J. Kochanski http://orcid.org/0000-0002-5952-3493
Rachel K. Hopper http://orcid.org/0000-0002-7483-2825

REFERENCES

1. Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, Hanna BD, Rosenzweig EB, Raj JU, Cornfield D, Stenmark KR, Steinhorn R, Thébaud B, Fineman JR, Kuehne T, Feinstein JA, Friedberg MK, Earing M, Barst RJ, Keller RL, Kinsella JP, Mullen M, Deterding R, Kulik T, Mallory G, Humpl T, Wessel DL. Pediatric pulmonary hypertension. Circulation. 2015;132(21):2037–99.
2. Ivy D, Frank BS. Update on pediatric pulmonary arterial hypertension. Curr Opin Cardiol. 2021;36(1):67–79.
3. Rosenzweig EB, Abman SH, Adatia I, Beghetti M, Bonnet D, Haworth S, Ivy DD, Berger RMF. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. Eur Respir J. 2019;53(1):1801916.
4. Hansmann G, Koestenberger M, Alastalo TP, Apitz C, Austin ED, Bonnet D, Budts W, D'Alto M, Gatzoulis MA, Hasan BS, Kozlik-Feldmann R, Kumar RK, Lammers AE, Latus H, Michel-Behnke I, Miera O, Morrell NW, Pieles G, Quandt D, Sallmon H, Schranz D, Tran-Lundmark K, Tulloh RMR, Warnecke G, Wåhlander H, Weber SC, Zartner P. 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. J Heart Lung Transplant. 2019;38(9):879–901.
5. Lindegaard Pedersen M, Krüger M, Grimm D, Infanger M, Wehland M. The prostacyclin analogue treprostinil in the treatment of pulmonary arterial hypertension. Basic Clin Pharmacol Toxicol. 2020;126(1):32–42.
6. Simonneau G, Barst RJ, Galie N, Naeije R, Rich S, Bourge RC, Keogh A, Oudiz R, Frost A, Blackburn SD, Crow JW, Rubin LJ. 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(6):800–4.
7. Siehr SL, Dunbar Ivy D, Miller-Reed K, Ogawa M, Rosenthal DN, Feinstein JA. Children with pulmonary arterial hypertension and prostanoid therapy: long-term hemodynamics. J Heart Lung Transplant. 2013;32(5):546–52.
8. Hiremath J, Thanikachalam S, Parikh K, Shanmugasundaram S, Bangera S, Shapiro L, Pott GB, Vnencak-Jones CL, Arneson C, Wade M, White RJ. Exercise improvement and plasma biomarker changes with intravenous treprostinil therapy for pulmonary arterial hypertension: a placebo-controlled trial. J Heart Lung Transplant. 2010;29(2):137–49.
9. Levy M, Del Cerro MJ, Nadaud S, Vadlamudi K, Colgazier E, Fineman J, Bonnet D, Adatia I. Safety, efficacy and management of subcutaneous treprostinil infusions in the treatment of severe pediatric pulmonary hypertension. Int J Cardiol. 2018;264:153–7.
10. Barst RJ, Galie N, Naeije R, Simonneau G, Jeffs R, Arneson C, Rubin LJ. Long-term outcome in pulmonary arterial hypertension patients treated with subcutaneous treprostinil. Eur Respir J. 2006;Dec 1 28(6):1195–203.
11. Benza RL, Gomberg-Maitland M, Naeije R, Arneson CP, Lang IM. Prognostic factors associated with increased survival in patients with pulmonary arterial hypertension treated with subcutaneous treprostinil in randomized, placebo-controlled trials. J Heart Lung Transplant. 2011;30(9):982–9.
12. Ploegstra MJ, Ivy DD, Beghetti M, Bonnet D, Alehan D, Ablonczy L, Mattos S, Bowers D, Humpl T, Berger RMF, TOPP Investigators. Long-term outcome of children with newly diagnosed pulmonary arterial hypertension: results from the global TOPP registry. Eur Heart J - Qual Care Clin Outcomes. 2023:qcad020. Epub 2023 Mar 27.
13. Tella JB, Kulik TJ, McSweeney JE, Sleeper LA, Lu M, Mullen MP. Prostanoids in pediatric pulmonary hypertension: clinical response, time-to-effect, and dose–response. Pulm Circ. 2020;10(4):1–10.
14. Sitbon O, Humbert M, Nunes H, Parent F, Garcia G, Hervé P, Rainisio M, Simonneau Gé. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension. J Am Coll Cardiol. 2002;40(4):780–8.

15. Ablonczy L, Ferenci T, Somoskövi O, Osváth R, Reusz GS, Kis E. Prognostic value of early risk stratification in pediatric pulmonary arterial hypertension. Transplant Proc. 2021;53(5):1439–42.
16. Zijlstra WMH, Douwes JM, Rosenzweig EB, Schokker S, Krishnan U, Roofthooft MTR, Miller-Reed K, Hillege HL, Ivy DD, Berger RMF. Survival differences in pediatric pulmonary arterial hypertension. J Am Coll Cardiol. 2014;63(20):2159–69.
17. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1):1801913.
18. LaFarge CG, Miettinen OS. The estimation of oxygen consumption. Cardiovasc Res. 1970;4(1):23–30.
19. Hopper RK, Wang Y, DeMatteo V, Santo A, Kawut SM, Elci OU, Hanna BD, Mercer-Rosa L. Right ventricular function mirrors clinical improvement with use of prostacyclin analogues in pediatric pulmonary hypertension. Pulm Circ. 2018;8(2):1–8.
20. Bano M, Kanaan UB, Ehrlich AC, McCracken C, Morrow G, Oster ME, Sachdeva R. Improvement in tricuspid annular plane systolic excursion with pulmonary hypertension therapy in pediatric patients. Echocardiography. 2015;32(8):1228–32.
21. Kassem E, Humpl T, Friedberg MK. Prognostic significance of 2-dimensional, m-mode, and Doppler echo indices of right ventricular function in children with pulmonary arterial hypertension. Am Heart J. 2013;165(6):1024–31.
22. Douwes JM, Zijlstra WMH, Rosenzweig EB, Ploegstra MJ, Krishnan US, Haarman MG, Roofthooft MTR, Postmus D, Hillege HL, Ivy DD, Berger RMF. Parenteral prostanoids in pediatric pulmonary arterial hypertension: start early, dose high, combine. Ann Am Thorac Soc. 2022;19(2):227–37.
23. Baruteau AE, Serraf A, Lévy M, Petit J, Bonnet D, Jais X, Vouhé P, Simonneau G, Belli E, Humbert M. Potts shunt in children with idiopathic pulmonary arterial hypertension: long-term results. Ann Thorac Surg. 2012;94(3):817–24.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Kochanski JJ, Feinstein JA, Ogawa M, Ritter V, Hopper RK, Adamson GT. Younger age at initiation of subcutaneous treprostinil is associated with better response in pediatric Group 1 pulmonary arterial hypertension. Pulm Circ. 2024;14:e12328. https://doi.org/10.1002/pul2.12328