Research Article

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Oral treprostinil use in children: a multicenter, observational experience

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Abstract

Pulmonary arterial hypertension is a progressive, incurable disease that occurs in adults and children alike. Therapeutic options for children are limited and infrequently described, including newer agents such as treprostinil, an oral prostanoid. Herein, we describe the pooled pediatric experience in 28 patients from four pediatric pulmonary hypertension programs over two years. This descriptive, observational study describes the various methods of initiation of oral treprostinil in both prostanoid-naïve patients and those transitioning from parenteral or inhaled prostanoids. The youngest patient was four years old and the smallest weighed 16 kg. We describe adverse reactions and their management. Most patients in this study (27/28) were able to successfully initiate therapy. However, gastrointestinal adverse reactions were common; half of the patients started on this therapy had discontinued it within the two-year study period.

Keywords

pediatric pulmonary hypertension, pulmonary hypertension, pulmonary arterial hypertension

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Pulmonary arterial hypertension (PAH) is a rare, progressive disease of the pulmonary vasculature affecting individuals at all ages.[1] Intravenous epoprostenol was the first medication approved specifically for the treatment of PAH in the 1990s and prostanoids remain a mainstay of PAH management.[2,3] Indeed, many clinicians believe that this drug class remains a crucial targeted therapy in the treatment of PAH and, accordingly, prostanoid are featured in guidelines for treating advanced PAH.[4–6] However, given the complexity, risks, and side effect profile associated with parenteral delivery, continuous prostanoids may be underutilized in the treatment of even severe PAH.[7] There is also a moderately high rate of treatment failure with parenteral prostanoid therapy.[8] Inhaled prostanoids have their own challenges and adverse reactions and the dose delivered to the lung is variable.

To avoid the complications associated with indwelling central venous catheters, the discomfort associated with subcutaneous administration, and to allow for higher doses than achievable through the inhalational route, an orally available prostanoid has been developed. Oral treprostinil (Orenitram®) was approved in the USA by the Food and Drug Administration in late 2013 as it was shown to be effective as initial monotherapy treatment in adult PAH, but not as add-on therapy.[9,10] No similar trials have been performed in children. Available experience on the use of oral treprostinil

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in children is entirely anecdotal. There are no peer-reviewed publications describing the use of this agent in children.

The purpose of this study is to describe the real-world use of oral treprostinil off label in a pediatric PAH population across four centers. We aim to describe the use of this medication, its safety, and tolerability profile. Using a retrospective methodology, we describe the initiation process in prostanoid-naïve patients and the transition process for those switching from a parenteral or inhaled prostanoid to oral treprostinil. While the study is not designed to assess efficacy, we describe clinical, hemodynamic, and imaging changes observed while receiving oral treprostinil.

Methods

This report is a multicenter, retrospective, observational case series describing the use of oral treprostinil in a pediatric population at four centers in the USA: Children's Healthcare of Atlanta; Children's Hospital Colorado; University of Utah Health Care; and Texas Children's Hospital.

Institutional review board (IRB) approval for this retrospective chart review study was obtained at each individual institution and data use agreements were established, where applicable. Individuals were eligible for inclusion if they were: (1) diagnosed with PAH by standard catheter definition (mean pulmonary artery pressure [mPAP] $\geq$ 25 mmHg, pulmonary vascular resistance index [PVRI] $>$ 3 WU*m^2, pulmonary artery wedge pressure [PAWP] $\leq$ 15 mmHg) or had conclusive evidence of PAH when cardiac catheterization could not be performed; (2) treated with oral treprostinil between 1 December 2013 and 1 June 2017 and received at least one dose; and (3) aged $<$21 years at the time of the first dose. Participants were assigned a unique identifier and de-identified patient information related to the PAH diagnosis, clinical status, and diagnostic testing was placed at each center into a REDCap database housed at Children's Healthcare of Atlanta. REDCap is a secure, web-based application designed to support data capture for research studies. Efforts were made to fully describe the circumstances of initiation of oral treprostinil, the dosing regimen, any adverse reactions, and their management.

Descriptive statistics were used. Numbers are listed as median (interquartile range [IQR]) unless otherwise stated.

Results

Population

Baseline demographic and diagnostic information shows a largely school-aged population of broad ethnic diversity (Table 1). A total of 28 participants are included from four centers, of whom six were prostanoid-naïve and 22 transitioned from another prostanoid to oral treprostinil. The youngest patient was four years old; the median age of the entire cohort was 13.8 years. As in other PAH series, there was a female preponderance. All participants were diagnosed with World Health Organization (WHO) Group 1 pulmonary hypertension (PH), including one transition patient with cystic fibrosis diagnosed as idiopathic PAH because her PH was felt to be out of proportion to the degree of lung disease. This patient's response to oral treprostinil (therapeutic benefit and adverse reactions) was similar to the broader WHO Group 1 population.

Baseline clinical characteristics before oral treprostinil initiation (Table 2) show a relatively healthy cohort for

Table 1. Demographics.

Characteristic	Prostanoid-naïve n = 6 (21.4%)	Transition n = 22 (78.6%)	Overall n = 28
Age at diagnosis (years)	10.5 (10.0–14.0)	5.1 (2.0–9.0)	6.5 (3.6–10.5)
Age at first dose (years)	14.7 (8.6–18.3)	11.8 (10.4–16.3)	13.8 (10.8–16.2)
Gender			
Male	0 (0.0)	8 (36.4)	8 (28.6)
Female	6 (100.0)	14 (63.6)	20 (71.4)
Weight (kg)	52.0 (31.4–69.0)	40.6 (28.0–62.8)	44.9 (28.6–63.6)
Race			
Asian	1 (16.7)	2 (9.1)	3 (10.7)
Black/African American	2 (33.3)	1 (4.5)	3 (10.7)
Caucasian	3 (50.0)	17 (77.3)	20 (71.4)
Other	0 (0.0)	2 (9.1)	2 (7.1)
Ethnicity			
Hispanic	1 (16.7)	5 (22.7)	6 (21.4)
Non-Hispanic	5 (83.3)	17 (77.3)	22 (78.6)

Values are given as median (IQR) or n (%).

Table 2. Baseline clinical data before initiation of oral treprostinil.

Characteristic	Prostanoid-naïve n = 6 (21.4%)	Transition n = 22 (78.6%)	Overall n = 28
WHO Functional Class			
I	1 (16.7)	3 (13.6)	4 (14.3)
II	2 (33.3)	12 (54.5)	14 (50.0)
III	3 (50.0)	6 (27.3)	9 (32.1)
IV	0 (0.0)	0 (0.0)	0 (0.0)
Not done	0 (0.0)	1 (4.5)	1 (3.6)
Concomitant PH medications			
PDEI only	1 (16.7)	2 (9.1)	3 (10.7)
ERA only	0 (0)	1 (4.5)	1 (3.6)
Dual therapy with PDEI and ERA	5 (83.3)	19 (86.4)	24 (85.7)
6MWD (m)	514 (441–532)	532 (441–576)	517 (441–573)
n (%)	6 (100)	19 (86.4)	25 (89.3%)
Time between test and initiation (months)	1.3 (1.0–2.3)	2.0 (1.0–4.0)	1.3 (1.0–3.4)
BNP (pg/mL)	20.0 (17.0–62.1)	31.5 (13.5–82.0)	29.3 (15.0–80.0)
n (%)	6 (100.0)	20 (90.9)	26 (92.9)
Time between test and initiation (months)	1.3 (1.0–2.0)	2.5 (0.0–4.0)	2.0 (0.5–3.4)
NT-pro-BNP (pg/mL)	159 (125–193)	156 (99–1160)	156 (125–183)
n (%)	2 (33.3)	3 (13.6)	5 (17.9)
Time between test and initiation (months)	1.8 (1.3–2.3)	1.3 (0.0–3.4)	1.3 (1.3–2.3)
Echocardiographic measures			
TR gradient (mmHg)	61 (50–62)	62 (52–79)	62 (50–79)
n (%)	5 (83.3)	17 (77.3)	22 (78.6)
Time between test and initiation (months)	1.3 (0.5–2.3)	3.0 (1.0–4.0)	2.2 (1.0–4.0)
TAPSE (cm)	2.1 (1.8–2.3)	2.0 (1.4–2.2)	2.0 (1.8–2.2)
n (%)	4 (66.7)	7 (31.8)	11 (39.3)
Time between test and initiation (months)	1.3 (0.9–1.8)	2.0 (1.3–3.4)	1.3 (1.2–3.0)
Invasive hemodynamic measures			
mRAP (mmHg)	9.0 (7.0–10.0)	7.0 (6.0–9.0)	7.0 (6.0–9.5)
n (%)	5 (83.3)	19 (86.4)	24 (85.7)
Time between test and initiation (months)	13.7 (2.0–24.6)	12.0 (6.0–21.8)	12.5 (4.7–23.2)
mPAP (mmHg)	43 (40–44)	50 (37–62)	49 (39–60)
n (%)	5 (83.3)	19 (86.4)	24 (85.7)
Time between test and initiation (months)	13.7 (2.0–24.6)	12.0 (6.0–21.8)	12.5 (4.7–23.2)
Mean PAWP (mmHg)	11 (7–11)	10 (8–12)	11 (8–12)
n (%)	5 (83.3)	19 (86.4)	24 (85.7)
Time between test and initiation (months)	13.7 (2.0–24.6)	12.0 (6.0–21.8)	12.5 (4.7–23.2)
Cardiac index (L/min/m^2)	3.6 (3.6–4.9)	3.3 (2.8–4.4)	3.5 (3.0–4.5)
n (%)	5 (83.3)	17 (77.3)	22 (78.6)
Time between test and initiation (months)	13.7 (2.0–24.6)	12.0 (6.0–17.3)	12.0 (3.3–24.6)
PVRI (Wood units*m^2)	8.9 (5.9–9.4)	12.1 (6.5–15.3)	9.7 (5.9–14.9)
n (%)	5 (83.3)	18 (81.8)	23 (82.1)
Time between test and initiation (months)	13.7 (2.0–24.6)	12.0 (6.0–21.8)	12.0 (3.3–24.6)

Values are given as median (IQR) or n (%).

PDEI, type 5 phosphodiesterase inhibitor; ERA, endothelin receptor antagonist; 6MWD, 6-min walk distance; BNP, B-type natriuretic peptide; NT-pro BNP, N-terminal pro-B-type natriuretic peptide; TR, tricuspid regurgitation; TAPSE, tricuspid annular plane systolic excursion; mRAP, mean right atrial pressure; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial web pressure; PVRI, pulmonary vascular resistance index.

a PAH population. Overall, 64% were in functional class (FC) I or II and there were no FC IV patients. Patients transitioned from other prostanoids tended to have better functional classification compared to the prostanoid-naïve group. Six-minute walk test (6MWT) distances were high with a median distance of >500 m. B-type natriuretic peptide (BNP) and N-terminal-pro-BNP levels were low consistent with preserved cardiac output and normal filling pressures at cardiac catheterization. Despite these reassuring data, PAPs were significantly elevated with median tricuspid regurgitation gradient of 62 mmHg (IQR = 50–79 mmHg), mPAP 49 mmHg (IQR = 39–60 mmHg), and PVRI 9.7 WU*m^2 (IQR = 5.9–14.9 WU*m^2).

At the time of oral treprostinil initiation, all patients were either on mono (16%) or dual (84%) PH-targeted therapy. The following non-prostanoid medication classes were in use: 26/28 (93%) type 5 phosphodiesterase inhibitor (PDEI; sildenafil or tadalafil); 24/28 (86%) endothelin receptor antagonist (ERA; ambrisentan, bosentan, or macitentan); 11/28 (39%) aspirin; 9/28 (32%) oxygen; 8/28 (29%) diuretics; 4/28 (14%) digoxin; 2/28 (7%) warfarin; and 1/28 (4%) dabigatran.

Transition patients receiving baseline prostanoid therapy

Details regarding baseline prostanoid therapy at the time of transition for the 22 patients transitioning from other medications in this class are shown in Table 3. Twenty-one of 22 patients transitioned from another treprostinil formulation (one from intravenous [IV], five from subcutaneous [SQ], and 15 from inhaled). One patient transitioned from inhaled iloprost. Median dose for the six patients receiving IV or SQ treprostinil was 63 ng/kg/min (IQR = 40–118 ng/kg/min). Inhaled treprostinil was prescribed at a median of 9 breaths per dose (IQR = 6–10 breaths per dose), either three or four times per day. No patient was transitioned from epoprostenol or selexipag.

Reason for transition to oral treprostinil was predominantly patient preference with SQ site pain listed as a reason for 3/5 (60%) who transitioned from that mode of delivery. Approximately one-quarter of patients transitioned from inhaled treprostinil due to disease progression with refusal of IV or SQ therapy.

Transition was performed at home for >80% of participants, whereas the remaining were split between the hospital wards and intensive care unit. Median hospital length of stay for the transition was seven days (IQR = 5–8 days) while the home transition duration was highly variable with a median of 46 days (IQR = 6–64 days). At the end of the transition period, patients were taking a median of 2.0 mg per dose (IQR = 1.4–3.0 mg per dose) with 14/22 (63.6%) taking three doses per day and 8/22 (36.4%) taking two doses per day.

All but one patient was able to successfully transition (defined as remaining on oral treprostinil for at least seven days after reaching goal dose), though 7/22 (31.8%) reported problems during the transition process (see below).

Table 3. Characteristics of patients transitioned from inhaled or parental prostanoids.

Characteristic	n = 22 (78.6%)
Initial prostanoid	
Treprostinil	21 (95.5)
Intravenous	1 (4.8)
Subcutaneous	5 (23.8)
Parenteral treprostinil dose (ng/kg/min)	63 (40–118)
Inhaled	15 (71.4)
Breaths/dose	9 (6–10)
Doses per day	
Four times per day	12 (80.0)
Three times per day	3 (20.0)
Inhaled iloprost	1 (4.5)
Doses per day of 2.5 mcg inhalations	2–3
Time on medication before transition (years)	3.1 (2.1–4.5)
Reason for transition	
Patient preference	17 (77.3)
Disease progression	4 (18.2)
Adverse reaction to other medication	3 (13.6)
Site pain (% of those receiving subcutaneous medication)	3 (60)
Central line complications	0 (0.0)
Transition venue	
Hospital ward	2 (9.1)
Hospital intensive care unit	2 (9.1)
Home	18 (81.8)
Transition duration (home and hospital) (days)	46 (6–64)
Hospital length of stay for those transitioned in hospital (days)	7 (5–8)
Dose at end of transition (mg per dose)	2.0 (1.4–3.0)
Final dosing interval	
Twice per day	8 (36.4)
Three times per day	14 (63.6)
Completed ≥7 days at goal dose	21 (95.5)

Values are given as n (%) or median (IQR).

The single patient who was unable to complete transition had been receiving high dose subcutaneous treprostinil infusion. The transition was attempted in the hospital setting where his subcutaneous dose was decreased by 25% each day from baseline of 118 ng/kg/min with a concomitant increase in oral dose of 5 mg per dose per day. On day 3 (i.e. 25% of initial parenteral dose and 15 mg per dose three times per day of oral dose), he had significant gastrointestinal complaints of nausea, vomiting, and anorexia. The following day, off parenteral treprostinil entirely, he had worsening echocardiographic findings and he was unable to complete a 6MWT due to dyspnea and cyanosis. He was, therefore, switched back to SQ treprostinil during

that hospitalization, with improvement in his echocardiogram and clinical symptoms, and he was able to complete a 6MWT.

The highest baseline parenteral treprostinil dose was in a teenage boy receiving 153 ng/kg/min. Due to intolerable subcutaneous site pain, he was transitioned at home over 61 days with gradual cross-titration of oral and subcutaneous doses to an eventual oral dose of 25 mg three times per day. As with other patients transitioning from parenteral treprostinil, choice of goal oral treprostinil dose was informed by the comparable dose calculation provided by the manufacturer: oral treprostinil total daily dose (mg) = 0.0072 × parenteral treprostinil dose (ng/kg/min) × weight (kg).[9] He was able to make this transition despite substantial gastrointestinal symptoms but had no worsening of his PH status. After being initially stabilized on this dose, he eventually had the dose lowered due to significant gastrointestinal adverse reactions and, finally, due to patient insistence, the medication was discontinued; he refused all prostanoids. His symptoms and quality of life improved per his report. However, in follow-up, his echocardiogram worsened and he developed worsening hypoxemia during 6MWT due to right to left atrial shunting. He is currently receiving an ERA and PDEI.

Problems reported during the transition process included practical/administrative concerns, class-related adverse reactions, and hemodynamic compromise (as detailed above). For one patient transitioning at home, concerns were raised regarding unclear destination dose at the time of initiation of the process. This led to some confusion with insurance pre-authorization and concern regarding delivery of adequate numbers of pills to the patient though there were no resulting interruptions in treatment. Prostanoid-related adverse reactions were common and were largely gastrointestinal in nature. This led to slower uptitration than initially planned in some patients (e.g. by 0.125 mg per dose twice per week in one patient) and other supportive measures (antacids, reminder to take with at least 250 kcal meal or snack, increasing fat or fiber content in meals, anti-diarrheal medication, antiemetics) with improvement in tolerability. Other expected adverse reactions included flushing and headaches. One patient had decreased blood pressure requiring reduction in the dose.

Initiation in prostanoid-naïve patients

Details regarding the initiation process for patients naïve to prostanoids are outlined in Table 4. Of these six patients in whom oral treprostinil was initiated de novo, suboptimal response to other therapies and/or disease progression were reasons for initiation in all cases. All patients in this group initiated therapy at home. Median duration of uptitration was 83 days (IQR = 72–132 days) achieving median dose of 2.5 mg (IQR = 2.5–3.5 mg) per dose three times (4/6, 66.7%) or twice a day (2/6, 33.3%).

Table 4. Characteristics of prostanoid-naïve patients.

Characteristic	n = 6 (21.4)
Reason for initiation	
Suboptimal response to existing therapy	5 (83.3)
Disease progression	3 (50.0)
Initiation venue	
Hospital ward	0 (0.0)
Hospital intensive care unit	0 (0.0)
Home	6 (100.0)
Duration of up-titration (days)	83 (72–132)
Dose at end of initiation (mg per dose)	2.5 (2.5–3.5)
Final dosing interval	
Twice per day	2 (33.3)
Three times per day	4 (66.7)
Completed ≥7 days at goal dose	6 (100.0)

Values are given as n (%) or median (IQR).

All six patients in this group were able to successfully complete seven days on goal doses though half reported problems during initiation. One patient was admitted to the hospital for overnight observation due to chest pain and hypoxemia, though the chest pain was ultimately thought to be gastro-esophageal reflux-related. As with the transition group, gastrointestinal adverse reactions predominated with abdominal pain, nausea, and diarrhea reported after up-titrations. These generally responded to supportive measures, as described in the above section on transition patients, or resolved with time at the new dose.

Safety and tolerability

Adverse reaction features are described in Table 5, with organ system affected and number of adverse reactions per patient outlined in Table 6. Adverse events were common in our patients with 75% reporting adverse reactions at some point during therapy and individual patients reporting a median of two complaints (maximum of nine for one patient). A total of 81 adverse reactions were reported by 21 patients. Gastrointestinal symptoms predominated (nausea, vomiting, and diarrhea in particular), accounting for > 50% of the complaints, followed by headache in 15%. No death or permanent disability was deemed to be related to medication exposure; however, one patient died during the study period. She had transitioned three months prior from inhaled treprostinil 12 breaths four times a day to oral treprostinil 2 mg in the morning, 1 mg mid-day, and 1 mg in the evening. She reported feeling better on the oral treprostinil though she remained in FC III. She was seen in the outpatient clinic for routine follow-up on the day of her death and was thought by the treating team to be improving with a subjective increase in exercise tolerance and a decrease in B-type natriuretic peptide. She died suddenly

Table 5. Adverse reaction features.

Characteristic	Prostanoid-naïve n = 6 (21.4%)	Transition n = 22 (78.6%)	Overall n = 28
Patients with adverse reaction	5 (83.3)	16 (72.7)	21 (75.0)
Adverse events (n)	22	59	81
Adverse reaction severity			
Mild	6 (27.3)	16 (27.1)	22 (27.1)
Moderate	12 (54.6)	27 (45.8)	39 (48.1)
Severe	3 (13.6)	16 (27.1)	19 (23.5)
Not defined	1 (4.5)	0 (0.0)	1 (1.3)
Timing of symptom			
Immediately	1 (4.5)	4 (6.8)	5 (6.2)
Days	4 (18.2)	24 (40.8)	28 (34.6)
Weeks	5 (22.8)	20 (33.8)	25 (30.7)
Months	9 (40.9)	11 (18.6)	20 (24.6)
Years	2 (9.1)	0 (0.0)	2 (2.6)
Not defined	1 (4.5)	0 (0.0)	1 (1.3)
Symptom setting			
Dose increase	11 (50.0)	6 (10.2)	17 (21.0)
Initiation/transition only	2 (9.1)	6 (10.2)	8 (10.0)
Initiation/transition/ maintenance	0 (0.0)	23 (39.0)	23 (28.4)
Maintenance only	4 (18.2)	16 (27.1)	20 (24.6)
Other	5 (22.7)	8 (13.5)	13 (16.0)
Symptom duration			
Transient	16 (72.7)	34 (57.6)	50 (61.7)
Persistent	6 (27.3)	23 (39.0)	29 (35.8)
Other	0 (0.0)	2 (3.4)	2 (2.6)
Symptom resolution			
Partial	3 (13.6)	20 (33.9)	23 (28.5)
Complete	13 (59.2)	21 (35.6)	34 (41.9)
Not defined	6 (27.2)	18 (30.5)	24 (29.6)
Management			
No change	11 (50)	24 (40.8)	35 (43.3)
Dose lowered	3 (13.6)	13 (22.0)	16 (19.8)
Uptitration rate slowed	7 (31.9)	15 (25.4)	22 (27.1)
Discontinued treprostinil (patients)	1 (16.7)	4 (9.1)	5 (17.9)

Values are given as n (%).
The percent noted relates to the number of adverse reactions, not the number of patients affected except for "Patients with adverse reactions" and "Discontinued treprostinil," which report the number of patients.
Adverse reactions that occurred during initial study period through 1 June 2017; includes initiation, transition, and maintenance.

Table 6. Adverse reaction by system.

Adverse reactions	Prostanoid-naïve n = 6 (21.4%)	Transition n = 22 (78.6%)	Overall n = 28
Total adverse events	22	59	81
Gastrointestinal	13	32	45
Abdominal pain	2	2	4
Decreased appetite	0	4	4
Diarrhea	4	8	12
Nausea	3	9	12
Vomiting	2	9	11
Reflux	2	0	2
Neurologic	3	12	15
Headache	3	9	12
Facial numbness	0	1	1
Altered mood	0	2	2
Cardiovascular	3	7	10
Chest pain	1	1	2
Flushing	1	2	3
Hypotension	0	1	1
Tachycardia with exercise	0	1	1
Dizziness	1	1	2
Pre-syncope	0	1	1
Respiratory	2	5	7
Shortness of breath	1	1	2
Decreased exercise tolerance	0	2	2
Decreased oxygen saturation	1	2	3
Musculoskeletal	1	3	4
Jaw pain	0	1	1
Leg pain	0	1	1
Back pain	1	1	2
Adverse reaction per patient (n (%))			
0	1 (16.6)	6 (27.2)	7 (25)
1	0 (0)	3 (13.6)	3 (10.7)
2	0 (0)	4 (18.2)	4 (14.3)
3–5	4 (66.8)	6 (27.2)	10 (35.7)
6–9	1 (16.6)	3 (13.6)	4 (14.3)

Number of adverse reactions by organ system that occurred during initial study period through 1 June 2017; includes initiation, transition, and maintenance.

on the drive home from clinic. The treating center did not believe the death was medication-related.

Severity of adverse events was rated by providers as mild in 27.1%, moderate in 48.1%, and severe in 23.5%. Adverse reactions occurred at any time during treatment from immediately on initiation to maintenance phase. Most symptoms occurred with initiation/transition or with dose increases but one in four occurred during maintenance therapy only. Symptoms were described as transient in 61.7% and persistent in 35.8%. Adverse reactions slowed the up-titration process or led to a dose decrease in approximately half of the patients. A combination of dosing adjustments and supportive care led to partial or complete resolution of most complaints. Five patients (17.8%) discontinued oral treprostinil during the initial study period (through 1 June 2017) due to adverse reaction or treatment failure.

Late follow-up

Due to the observation among the study collaborators that many patients included in this report had been transitioning off oral treprostinil during the analysis and writing phase of this study (i.e. after the initial data collection period), the decision was made to extend data collection for an additional year. IRB amendments were made where required. By 1 June 2018, only 14/28 patients originally started on oral treprostinil were still taking it. Reasons for discontinuation are listed in Table 7 with several patients reporting more than one reason for discontinuation. The majority of patients cited adverse reactions as the reason for discontinuation, while four patients had either clinical worsening or inadequate clinical response. One patient was deemed to no longer need it due to improvement in her PAH with more aggressive treatment of her underlying scleroderma. Challenges with medication compliance were also a factor for two patients. There were no additional deaths during late follow-up.

Of the 14 patients who discontinued oral treprostinil, one was transitioned to IV treprostinil, two to SQ treprostinil, and five to selexipag. Median total daily dose for the 14 patients still taking oral treprostinil was 9 mg (IQR = 5–12 mg).

Table 7. Reasons for discontinuing oral treprostinil.

Reasons for discontinuing oral treprostinil	Patients (n = 14)
Gastrointestinal	
General gastrointestinal side effects	4
Nausea/vomiting	2
Gastroesophageal reflux	2
Cardiovascular	
Flushing	2
Dizziness	2
Respiratory	
Dyspnea	3
Decreased exercise tolerance	2
Hypoxemia	1
Other	
Death	1
Clinical improvement	1
Clinical worsening/inadequate response	4
Non-compliance	2

Some patients listed several reasons, so number of reasons exceeds number of patients who discontinued treprostinil.
Table includes discontinuations during the initial data collection period through 1 June 2017 (n = 5) and long-term follow up through 1 June 2018 (n = 9).

Clinical measures

Comparison of clinical data between pre-initiation, earliest evaluation after achieving goal dose, and most recent follow-up are shown for the combined groups in Table 8. While this study was not designed to assess efficacy and is not adequately powered to do so, follow-up data are shown here for completeness.

Discussion

Despite many treatment options available, PAH continues to be a challenging disease with a high mortality rate. There is no cure and PAH often progresses despite maximal medical therapy. Treatment options are expensive, many are associated with significant side effects, and, in the case of prostanoids, often have cumbersome and uncomfortable delivery modalities. Randomized control trial data on pediatric PH treatment are scarce and, to date, no medication other than bosentan has been approved in the USA for the long-term outpatient treatment of PAH in children.

Oral treprostinil is the first oral prostanoid approved for treatment of adults with PAH in the USA. Its efficacy has been investigated in adults as monotherapy[10] and add-on therapy.[11,12] The efficacy signals in the monotherapy trial were modest (26-m improvement in 6MWD versus placebo in FREEDOM-M, $P < 0.05$) and the add-on therapy trials failed to show improvement versus placebo. A long-term open label investigation of oral treprostinil efficacy from a single center participating in FREEDOM failed to show improvement in important clinical measures (6MWT distance, FC, or hemodynamics).[13] It should be noted that optimal dosage even in adults remains obscure. The mean dose achieved in the FREEDOM-M trial (and referenced in the package insert) after 12 weeks of gradual dose increase was 3.4 mg twice daily,[9,10] whereas a 2018 case series and literature review describes total daily dosage as high as 75 mg among transition patients.[14] The package insert states that "maximum dose is determined by tolerability," and thus little guidance is provided in determining appropriate dosing in adults. In our multicenter experience, a wide range of doses were also employed. Many children on high dose oral treprostinil were weaned or discontinued due to significant side effects.

Despite concerns related to efficacy, unclear dosing guidelines, and the absence of data in children, pediatric PAH physicians are prescribing oral treprostinil. The opportunity to provide patients with potential benefits of prostanoid exposure without the risks, inconvenience, and discomfort of parenteral or inhaled therapy makes it an appealing choice. However, this study emphasizes the challenges of patient selection, tolerance of higher doses, significant GI symptoms in many patients, and discontinuation in half of the patients.

We present a large, diverse cohort of children receiving oral treprostinil. Oral treprostinil was successfully administered in children as small as 16 kg and four years of age. There were no life-threatening reactions in this cohort, though one patient with advanced PAH could not complete transition from high dose subcutaneous treprostinil due to symptomatic right heart failure. One patient had

Table 8. Clinical characteristics of all patients: pre-treatment, end of initial study, and latest follow-up.

Characteristic	Pre-treatment	End of initial study	Latest follow-up
Functional Class			
I	4 (14.3)	5 (17.9)	2 (7.2)
II	14 (50)	8 (28.5)	10 (35.7)
III	9 (32.1)	9 (32.1)	7 (25)
IV	0 (0)	1 (3.6)	0 (0)
Not Done	1 (3.6)	5 (17.9)	9 (32.1)
6MWD (m)	517 (441–573)	514 (428–547)	582 (555–600)
n (%)	25 (89.3)	21 (75)	13 (46.4)
Time between test and initiation (months)	1.3 (1.0–3.4)	2 (1.5–3.0)	12 (5–14.9
BNP (pg/mL)	29.3 (15.0–80)	21 (11–56)	19 (16–45.3)
n (%)	26 (92.9)	19 (67.8)	15 (53.5)
Time between test and initiation (months)	2.0 (0.5–3.4)	2 (1.5–6.0)	6 (4–14.9)
NT-pro BNP (pg/mL)	156 (125–183)	274 (270–278)	133 (108–243)
n (%)	5 (17.9)	4 (14.2)	6 (21.4)
Time between test and initiation (months)	1.3 (1.3–2.3)	5.2 (3.4–69.9)	16.1 (12.6–19.1)
Echocardiographic measures			
TR gradient (mmHg)	62 (50–79)	74 (49–93)	73.5 (51–92)
n (%)	22 (78.5)	19 (67.8)	14 (50)
Time between test and initiation (months)	2.2 (1.0–4.0)	2 (1.5–3.0)	9.3 (5–14.9)
TAPSE (cm)	2.0 (1.8–2.2)	2.0 (1.6–2.4)	1.9 (1.6–2.16)
n (%)	11 (39.3)	12 (42.8)	11 (39.2)
Time between test and initiation (months)	1.3 (1.2–3.0)	2.3 (1–6.9)	12.6 (8.6–19.1)
Invasive hemodynamic measures			
mRAP (mmHg)	7.0 (6.0–9.5)	8 (7–8)	7 (4–10)
n (%)	24 (85.7)	6 (21.4)	2 (7.1)
Time between test and initiation (months)	12.5 (4.7–23.2)	6.4 (1.7–20)	17.6 (12.1–23.1)
mPAP (mmHg)	49 (39–60)	36.5 (35–75)	69.5 (65–75)
n (%)	24 (85.7)	6 (21.4)	2 (7.1)
Time between test and initiation (months)	12.5 (4.7–23.2)	6.4 (1.7–20)	17.6 (12.1–23.1)
Mean PAWP (mmHg)	11 (8–12)	10 (7–11)	9 (5–13)
n (%)	24 (85.7)	5 (17.8)	2 (7.1)
Time between test and initiation (months)	12.5 (4.7–23.2)	1.8 (1.7–11)	17.6 (12.1–23.1)
Cardiac index (L/min/m^2)	3.5 (3.0–4.5)	3.7 (3.0–4.4)	3 (2.7–3.3)
n (%)	22 (78.6)	6 (21.4)	2 (7.1)
Time between test and initiation (months)	12.0 (3.3–24.6)	6.4 (1.7–20)	17.6 (12.1–23.1)
PVRI (Wood units*m^2)	9.7 (5.9–14.9)	10.2 (4.8–17.3)	21.6 (14.9–28.2)
n (%)	23 (82.1)	6 (21.4)	2 (7.1)
Time between test and initiation (months)	12.0 (3.3–24.6)	6.4 (1.7–20.0)	17.6 (12.1–23.1)

Values are given as n (%) or median (IQR).

Note time between test and initiation is months before start for the "Pre" state and after start for the post and latest states.

BNP, B-type natriuretic peptide; NT-pro BNP, N-terminal pro-B-type natriuretic peptide; TR, tricuspid regurgitation; TAPSE, tricuspid annular plane systolic excursion; mRAP, mean right atrial pressure; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVRI, pulmonary vascular resistance index.

hypotension requiring a dose adjustment. One patient died while receiving oral treprostinil during the study period though this death was not felt to be medication-related.

Although safety concerns did not predominate, tolerability of this agent remains a concern. Patients were instructed to take medication with food (at least 250 kcal snack) per the package insert. Despite this, most patients had significant adverse reactions. Generally, the prostanoid class has a more significant adverse effect profile than non-prostanoid PAH therapies and oral treprostinil is no exception, with gastrointestinal reactions and headache predominating in this oral formulation.

We are unable to comment on efficacy due to limited numbers of patients and limited follow-up information. Available follow-up data show a mixture of some parameters showing improvement while others showing worsening. The observational nature of this multicenter review limited the completeness of follow-up data available for comparison, particularly for cardiac catheterization which was performed in only one of the prostanoid-naïve patients and one of the transition patients.

A significant proportion of patients had to reduce their dose and over one-quarter discontinued oral treprostinil during the initial data collection period due to adverse reactions or lack of efficacy. With the addition of another year of follow-up, half of the 28 patients in this study stopped the medication and either transitioned to another prostanoid, prostacyclin receptor agonist (selexipag), or discontinued this class altogether. Again, this was primarily due to a combination of inadequate clinical response and adverse reactions.

In conclusion, oral treprostinil is an option for the treatment of some pediatric PAH patients and should be considered for children who do not tolerate their inhaled or parenteral prostanoid therapy or who are experiencing disease progression despite medical therapy. Although continuous forms of prostacyclin therapy are recommended, some patients refuse IV or SQ therapy. Initiation can be done at home for the prostanoid naïve. Transition from other prostanoids can usually be accomplished quickly in the hospital or at home over long duration. Adverse reactions, particularly gastrointestinal, are common though many patients can manage these with careful dose adjustments and supportive measures. Treatment failure is common due to either disease progression or poor tolerance of side effects. More research is needed in pediatric PH pharmacotherapy, in general, and oral treprostinil use in children, in particular.

Conflict of interest

The University of Colorado receives fees for Dr Ivy to be a consultant for United Therapeutics (UT). Dr Ivy has participated in clinical trials for UT. Baylor College of Medicine receives fees for Dr. Varghese's work on behalf of UT. UT is the manufacturer of the compound treprostinil described in this independent research. UT did not influence this publication, was not aware of the work being done, has not seen the data or the manuscript, and had no role in the production of this manuscript.

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