Use of Treprostinil in Pediatric Pulmonary Hypertension: Case Reports and Review of the Literature

Arthur Gavotto, MD,*† Fanny Thomas, MD,* Oscar Werner, MD,* Johan Moreau, MD,*†
and Pascal Amedro, MD, PhD*†

Background:

Add-on therapy with prostacyclin in pediatric refractory pulmonary hypertension (PH) poses a challenge, especially when considering continuous intravenous administration in younger children. A search for alternate routes of drug delivery has led to the clinical investigation of stable and long-acting prostacyclin analogues, such as subcutaneous treprostinil. We reported 2 pediatric cases of PH treated with subcutaneous treprostinil and reviewed the literature on treprostinil use in children.

Method:

The literature review used 3 electronic databases and a combination of terms (treprostinil, pediatric, PH, prostanoid, etc). We also searched for pediatric clinical trials on treprostinil registered on international clinical trial registries.

Results:

The reported cases highlighted the multifactorial nature of PH in pediatrics: a female child with a giant omphalocele, and intracardiac and extracardiac shunts; and a male premature child with a congenital diaphragmatic hernia and long-term PH. The literature review identified 19 studies reporting treprostinil use in 421 children with various types of PH (groups 1 and 3). Subcutaneous treprostinil was the most administered formulation, at a mean dose of 40 ng/kg/ min. Overall, 12 clinical trials on treprostinil for children with PH were registered on the clinical trial registries. Most authors concluded that subcutaneous treprostinil was effective, well tolerated, and represented an alternative to intravenous epoprostenol.

Conclusions:

Subcutaneous treprostinil may be a useful adjunct in the therapeutic algorithm for children with severe PH, refractory to oral drugs, and after a complete check-up for all PH etiologies. Key Words: pulmonary arterial hypertension, treprostinil, pediatrics, children, neonate, prostacyclin

INTRODUCTION

Pulmonary hypertension (PH) is a severe hemodynamic condition defined by an elevated mean pulmonary arterial pressure (PAP) above 20 mm Hg, as assessed by cardiac catheterization.¹ The association with a pulmonary vascular resistance ≥ 3 Wood units defines precapillary PH. In pediatrics,

PH is associated with a dramatically high level of morbidity and mortality.^{2,3} Since its first version from 1973, the WHO classification of PH has seen multiple revisions, reflecting advances in disease understanding, and has been progressively expanded to 5 groups: group 1, pulmonary arterial hypertension (PAH); group 2, PH due to left heart disease; group 3, PH due to lung disease and/or hypoxia; group 4, chronic thromboembolic PH; and group 5, PH with unclear multifactorial mechanisms.⁴ The distribution of pediatric PH etiologies differs from the adult population, with mostly group 1 forms (idiopathic, associated with congenital heart diseases, or inherited), and group 3 forms (associated with bronchopulmonary dysplasia or congenital diaphragmatic hernia). The most common genetic cause of inherited PAH is a mutation in Bone Morphogenetic Protein Receptor type II (BMPR2). Indeed, pediatric PH is rarely associated with other conditions such as connective tissue, thromboembolic diseases, or left heart diseases.⁵

Current practices regarding pharmacotherapy for PH in children are commonly in line with adult guidelines, despite, the lack of drug trials in pediatric PH.^{6,7} First and foremost, the main cause underlying PH requires to be actively treated, when possible (eg, left heart disease, respiratory disease, left-to-right shunt, etc). Then, pulmonary vasodilators (eg, endothelin, receptor antagonist, phosphodiesterase-5 inhibitor, and, prostacyclin) are indicated for PH involving pulmonary artery, disease and elevated pulmonary vascular resistance (eg, the group 1 WHO classifications).^{4,7,8,}

Nevertheless, it is not uncommon for pediatric PH to involve several pathophysiological mechanisms acting together in the elevation of PAP. Therefore, treating such young patients remains challenging, especially in the neonatal period.⁹ In severe refractory pediatric PH, add-on therapy with prostacyclin analogues is occasionally required. Intravenous epoprostenol stands as the main therapy used in this situation, but central venous line exposes to infectious, mechanical, and thromboembolic complications.¹⁰ In this context, subcutaneous treprostinil has shown growing interest and is being increasingly used in pediatrics.^{2,3,11–23} Indeed, a recent review on pediatric PH recommended the use of treprostinil in severe and/or rapidly progressive forms but also concluded that future research remained necessary for treprostinil use in children.²⁴ Treprostinil sodium is a chemically stable prostacyclin analogue that shares some of the pharmacologic actions of epoprostenol, as both activate the prostacyclin receptor, but treprostinil has some unique properties to remaining stable at room temperature, with a longer half-life (2–3 hours).^{13,14,25}

From the *Pediatric Cardiology and Pulmonology Department, M3C Regional Referral CHD Center, University Hospital, Montpellier, France; and

†PhyMedExp, CNRS, INSERM, University of Montpellier, Montpellier, France.

The authors report no conflicts of interest.

Study concept and design: P. Amedro and A. Gavotto. Drafting of the manuscript: all. Critical revision of the manuscript for important intellectual content: all. Administrative, technical, or material support: P. Amedro. Study supervision: P. Amedro.

Reprints: Arthur Gavotto, MD, Pediatric Cardiology and Pulmonology Department, Montpellier University Hospital, 371 Avenue du Doyen Giraud, 34295 Montpellier, France (e-mail: a-gavotto@chu-montpellier.fr).

Currently, treprostinil has not received drug approval in the pediatric population. This study aims to highlight the interest of treprostinil in children from 2 cases of severe and complex PH, as well as from a review of the literature regarding the current use of treprostinil in pediatrics.

METHODS

Informed consent has been obtained from the patients' guardians for publication of the case reports and accompanying images.

For the literature review, we searched 3 electronic databases on July 2019 (PubMed, EMBASE, and Web of Science) by using a combination of the terms “treprostinil” and “pediatric.” We also used the terms “pulmonary hypertension,” “pulmonary arterial hypertension,” “children,” “pulmonary vasodilator,” “prostacyclin,” “prostanoid,” “Remodulin,” “Tyvaso,” and “Orenitram,” in combination. We did not set any restriction to study setting, era, or locale. Only pediatric patients (21 years old) were eligible. We excluded articles that were not written in English. Pharmacodynamic and pharmacokinetic studies with no clinical data, as well as mixed adult and pediatric cohorts with less than 5% pediatric subjects, were excluded. In title and abstract screening, 2 reviewers (P.A. and A.G.) independently reviewed articles identified by the search. Studies identified in title or abstract screening were included for full-text review. We also searched for all clinical trials on treprostinil in pediatrics registered on any international clinical trial registry, as defined by the World Health Organization^{26,27} and recommended by the International Committee of Medical Journal Editors.²⁸ Patients were categorized upon the last classification of PH.⁸

CASE REPORTS

First Case

A female child born at 37 weeks' gestation with a prenatal diagnosis of giant omphalocele presented with a severe persistent PH of the newborn. Despite surgical repair of the omphalocele and invasive ventilation including high-frequency oscillatory ventilation with inhaled nitric oxide, PH remained isosystemic. Cardiopulmonary evaluation diagnosed several

mechanisms suspected to maintain elevated pulmonary pressure levels. First, the omphalocele was associated with a left lung hypoplasia and its surgical repair aggravated the restrictive lung disease (Fig. 1A). Then, the patient also presented with bronchomalacia (Fig. 1B). Finally, the pulmonary blood was increased as a result of significant intracardiac and extracardiac left-to-right shunts, eg, a patent ductus arteriosus and ostium secundum atrial septal defect. Several pulmonary arteriovenous fistulae were also found (Fig. 1C). No genetic BMPR2 mutation was found.

Upon parents' request and following a multidisciplinary ethical discussion, we decided to actively treat this patient. Phosphodiesterase-5 inhibitor was started at day 26 (sildenafil, 2 mg/kg q.i.d., oral). At day 67, tracheotomy was performed. At day 160, the patient underwent cardiac catheterization (under nitric oxide, sildenafil and $\text{FiO}_2 = 80\%$), which confirmed isosystemic PH (mean PAP = 45 mm Hg), postcapillary PH (left atrium pressure = 19 mm Hg), and significant left-to-right shunts (atrial septal defect and patent ductus arteriosus). Because of the patient's unstable hemodynamic condition during the procedure, the evaluation of the pulmonary arteriovenous fistula was limited and the percutaneous closure of patent ductus arteriosus was not possible. Surgical closure of patent ductus arteriosus was performed at day 166. At day 221, PH measured by echocardiography remained isosystemic and treprostinil was started (maximum tolerated dose of 8 ng/kg/min, subcutaneous) with an immediate effect on the right ventricle systolic pressure, decreasing from isosystemic to hemisystemic levels. Infusion-site pain was managed with analgesic transdermal lidocaine patches. The respiratory condition also improved and patient could be ventilated with continuous positive airway pressure through tracheotomy and oxygen. At day 558, a new cardiac catheterization (under sildenafil, treprostinil, and $\text{FiO}_2 = 25\%$) was performed under better hemodynamic conditions and found a precapillary PAH with increased pulmonary blood flow (mean PAP = 35 mm Hg; left atrial pressure = 4 mm Hg; Qp/Qs ratio = 2), related to the existence of a large atrial septal defect. This cardiac catheterization always found numerous pulmonary arteriovenous fistulae. None of these shunts were accessible to percutaneous closure. At day 710, the patient underwent surgical fenestrated atrial septal defect closure under cardiopulmonary bypass (child's weight: 11 kg). After cardiac surgery, the right pulmonary systolic pressure decreased to 1/3 of the systemic pressures, ventilation with continuous positive airway pressure could be decreased from 15 to 8 hours a day, and oxygen was suspended. At day 793, treprostinil was diminished to 6 ng/kg/min and sildenafil to 1 mg/kg t.i.d. under close echocardiography monitoring. At day 853, treprostinil was suspended. At the age of 3, tracheostomy decannulation was successfully performed. Currently, the systolic PAP from echocardiography is normal (Case 1 graphic F2 timeline is reported in Fig. 2).

Second Case

A male child born prematurely at 29 weeks' gestational age with a left diaphragmatic hernia presented with a severe PH requiring cardiopulmonary resuscitation including intubation, synthetic lung surfactant, epinephrine, high-frequency oscillatory ventilation, and inhaled nitric oxide. Surgical repair of the diaphragmatic hernia was performed on day 3 and phosphodiesterase-5 inhibitor was started at day 4 (sildenafil, 1 mg/kg t.i.d., oral). As a result of the severe lung hypoplasia associated with bronchopulmonary dysplasia, tracheotomy was performed at day 102, and the patient needed noninvasive ventilation and oxygen for an overall period of 3 years. Regular echocardiography evaluations reported that PH progressively decreased from isosystemic to hemisystemic levels within the first 6 months of life. At day 297, the child presented with an acute liver failure severe associated with isosystemic PH, after an episode of bronchiolitis. Treprostinil was started (maximum tolerated dose of 9 ng/kg/min, subcutaneous), and right ventricular systolic pressures and liver function

both normalized within 5 days. Infusion-site pain was managed with analgesic transdermal lidocaine patches. Treprostinil was stopped after 2 months of treatment. At the age of 4, the patient presented with a severe acute respiratory distress syndrome after a viral bronchitis, resulting in recurrence of isosystemic PH. Treprostinil (9 ng/kg/min, subcutaneous) and sildenafil (2 mg/kg q.i.d., oral) were started with an immediate effect. Three months after this episode, treprostinil was suspended and cardiac catheterization was performed, under sildenafil and oxygen, reporting hemisystemic nonreversible PAH (mean PAP = 28 mm Hg, pulmonary vascular resistance = 5 Wood units/m²). An endothelin receptor antagonist (bosentan, 32 mg b.i.d., oral) was added to noninvasive ventilation, oxygen, and sildenafil, with a good tolerance. No genetic BMPR2 mutation was found (Case 2 graphic timeline is reported in Fig. 3).

FIGURE 1. Association of left lung hypoplasia (A), bronchomalacia (B), and pulmonary arteriovenous fistulae (C). AVF, arteriovenous fistulae; RPA, right pulmonary artery.

LITERATURE REVIEW

The use of treprostinil in pediatrics was first reported in 2007, among 13 children with PH associated with CHD (atrial septal defect, ventricular septal defect, patent ductus arteriosus, and transposition of the great arteries), bronchopulmonary dysplasia, or idiopathic form.¹⁶

A total of 54 studies were found; after applying the inclusion and exclusion criteria, only 19 studies were selected for this literature review. 19 studies from the literature reported the use of treprostinil in pediatrics, of which only 3 were prospective studies (including a study on acute vasodilator testing).^{23, 29, 30} The remaining 16 retrospective studies reported data from small cohorts (1–85 patients), including 1 controlled³¹ (children with congenital diaphragmatic hernia receiving treprostinil vs. children with congenital diaphragmatic hernia without treprostinil) and 5 multicenter studies.^{11, 21, 32–34} Most authors suggested that treprostinil was an alternative to treat pediatric PH (Table 1).^{29, 35} However, no data from pediatric randomized controlled trials were reported in the literature, and currently treprostinil has only been approved in adult PAH treatment by European and US drug agencies (Table 2).

From this literature review, treprostinil was used in a total of 421 children aged from 1 day to 21 years, including subcutaneous (n = 285), inhaled (n = 51), intravenous (n = 25), and oral (n = 60) administration. The type of PH was undetermined (because studies pooled patients with Epoprostenol and Treprostinil and the type of PH were unspecified for Treprostinil patients) for 51 patients (12%).^{36, 37} Of the 421 children, 328 (78%) presented with a severe form of group 1 PAH, divided into the following subgroups: idiopathic (n = 110, 26%), CHD-related (n = 83, 19.7%), heritable (n = 16, 3.8%), HIV-related (n = 1, 0.2%),

PAH of the newborn (n = 2, 0.5%), other PAH of group 1 (n = 3, 0.7%), and unspecified (n = 113, 26.8%).^{32,34} A total of 42 (10%) children presented with a severe PH related to lung diseases (group 3), such as chronic lung disease (n = 7, 1.7%), congenital diaphragmatic hernia (n = 34, 8.1%), and pulmonary hypoplasia (n = 1, 0.2%). No cases of treprostinil were reported in pediatric patients with PH from the group 1 (pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis), group 2 (left heart diseases), group 4 (thromboembolic diseases), and group 5 (unclear or multifactorial).

FIGURE 2. Case 1 graphic timeline. CPAP, continuous positive airways pressure; HFO, high-frequency oscillatory ventilation; SC, subcutaneous. *On tracheostomy.

FIGURE 3. Case 2 graphic timeline. CPAP, continuous positive airways pressure; HFO, high-frequency oscillatory ventilation; SC, subcutaneous. *On tracheostomy.

In this review, many studies claimed that treprostinil was effective in terms of improvement in the WHO functional class,^{11,21,35,36,38} the 6-minute walk test (increase range from 109% to 175%),^{11,21,36,38} the oxygen uptake (mean increase of 107%),²¹ or the echocardiography parameters,^{29,31,36,39,40} as well as in terms of decrease in BNP levels (decrease range from 1.6 to 14.7 times),^{11,21,31,36,38,40} pulmonary vascular resistance (decrease range from 13% to 25%), or mean PAP (decrease range from 11% to 21%).^{11,23,33,40,41} All those studies claimed that treprostinil was well tolerated, excluding when orally administered, where treatment failure has been related to either disease progression or poor tolerance of side effects.^{30,34} Furthermore, subcutaneous treprostinil stood as an alternative to intravenous prostacyclin treatment, avoiding complications of permanent central line placement.¹¹ Indeed, most authors claimed that epoprostenol, despite being the first treatment approved for PAH, required administration through a central venous line and therefore carried risks of thrombosis and sepsis, particularly in children.^{42–44} These authors also reported a better tolerance of treprostinil and less site pain than reported data from the adult population.^{14,15,45} Indeed, side effects were scarcely reported in children, even with very high doses (up to 350 ng/kg/min).^{16,31,35} Most site pain episodes could be effectively managed in almost all children with simple analgesics, or by site replacement.^{11,29,38,39} Desole et al⁴⁶ proposed an alternative at central venous line with an implantable pump with intravenous treprostinil.

Studies on inhaled treprostinil were not designed to show any superiority over intravenous or subcutaneous administration; nevertheless, their results also reported good efficacy and tolerability.^{21,23,36} Of note, the authors suggested that inhaled treprostinil might potentially worsen respiratory symptoms in patients with reactive airway disease, including

cough (24%), sore throat (14%), and bronchospasm (7%). The authors also specified that pre-treatment with bronchodilators and steroids was successful in preventing bronchospasm in some patients with history of asthma. They also suggested that patients with very severe reactive airway disease may not be candidates for inhaled treprostinil therapy or may need additional therapy for their asthma.^{21,23}

In this review, many studies reported transition from epoprostenol to treprostinil.^{16,33,37} The transition protocols from Ivy et al used 2 methods (slow or rapid), with a preference for the rapid transition protocol.¹⁶ The rapid transition method involved discontinuing epoprostenol and initiating treprostinil at the original epoprostenol dose. Dose escalation of treprostinil continued every 20–60 minutes by 5–10 ng/kg/min while monitoring symptoms and side effects. The goal was to achieve a dose of treprostinil 1.25 to 1.75 times that of epoprostenol by the completion of the transition. The effect of treprostinil on PH outcomes was evaluated by echocardiography measures, the functional class (World Health Organization classification), the oxygen saturation, and functional tests (6-minute walk test, maximum oxygen uptake, and brain natriuretic peptide). Only 6 studies reported PH data from cardiac catheterization.^{11,33,39,41,45}

Subcutaneous treprostinil was the most administered formulation for 11 out of 19 studies, at a mean dose of 40 ng/ kg/min. Three studies reported the use of inhaled treprostinil in 51 children with various types of PH; however, the treatment had to be suspended for 4 children as a result of serious adverse events (bronchospasm or aggravation of PH).²¹

Treprostinil was used either as a second-line therapy, added to a phosphodiesterase-5 inhibitor (sildenafil) or an endothelin receptor antagonist (bosentan), or as a third-line therapy, added to a bitherapy with sildenafil and bosentan. Overall, 12 clinical trials on treprostinil for children with PH were registered on the clinical trial registries from the World Health Organization network. A total of 8 clinical trials were declared as terminated, among which 4 trials failed to recruit children (NCT01588405; NCT03055221; NCT00494533; NCT01934582, NCT00325403) and 4 trials were completed without published results (NCT02276872; NCT00705133; NCT01799473; NCT00004497). Currently, 4 drug trials are still recruiting children:

1. The FREEDOM-EXT open-label extension trial of UT-15C SR (treprostinil diethanolamine) in subjects with PAH (NCT01027949);
2. Remodulin as add-on therapy for the treatment of PH of the newborn (NCT02261883);
3. Perioperative treprostinil in pediatric patients undergoing the Fontan operation (NCT02498444);
4. Study of Remodulin in pediatric PH with single ventricular physiology after Fontan surgery (NCT02865733).

DISCUSSION

Our reported cases are in line with the literature review and suggest that subcutaneous treprostinil may improve pulmonary hemodynamic and respiratory functions in children with severe PH. These 2 cases highlighted the multifactorial nature of PH etiologies in pediatric and the importance of a complete cardiac evaluation in PH related to lung diseases. Therefore, subcutaneous treprostinil should be used in experienced pediatric PH centers, for complex and life-threatening PH, as a second-line treatment, in children with PH refractory to oral drugs. Overall, most studies reported that subcutaneous treprostinil provided hemodynamic and clinical benefit in the majority of children.

TABLE 1. Use of Treprostinil in Pediatrics: Review of the Literature

Author	Year	Study Design	Population	Adminis- tration	Treprostinil		Outcomes	Other PH Treatments	Adverse Effects	Main Results
					Dose Range (ng/kg/ min)	Follow- up				
Ivy et al ⁴	2007	Retrospective, single-center	N = 13 Age: 11 yr (3.6- 17.5) 7 IPAH, 5 CHD, 1 CLD	IV	Mean 86 ± 40	12 months 2 deaths	WHO, 6MWT, catheterization	2 CCB, 2 ERA, 12 PDE5	Better adverse effect profile with treprostinil than epoprostenol	Transitioning stable pediatric patients with PAH from epoprostenol to treprostinil is safe and well tolerated
Levy et al ¹⁸	2011	Retrospective, single-center	N = 8 Age: 4 yr (1.5-10) 2 IPAH, 1 HPAH, 5 CHD	SC	Median 40 (37-60)	Median 15 mo (6-18) 2 deaths	BNP, WHO, catheterization, 6MWT	7 ERA & PDE5	Site pain could be effectively managed in all children.	Treprostinil might be a potentially valuable rescue therapy in children with refractory PAH
Krishnan et al ¹	2012	Retrospective, 2 centers (United States)	N = 29 children Age: 11.3 yr (3.2- 19) 19 IPAH, 8 CHD, 1 CDH, 1 HIV	INH	3 to 9 breaths 4 times/d (6 mg/breath)	3-18 mo 2 deaths	WHO, 6MWT, BNP, CPET	4 CCB, 26 PDE5, 22 ERA, 18 ERA & PDE5	Bronchospasm (n = 3), or increased PAH (n = 1). Cough (9), sore throat (6), headache and nausea (4)	Inhaled treprostinil was associated with improvement in exercise capacity and WHO functional class when added to background targeted and had an acceptable safety profile.
Takatsuki et al ²⁵	2013	Prospective, single-center. AVT	N = 13 children Age: 10 yr (4-17) 7 IPAH, 4 CHD, 1 CLD, 1 other group 1	INH	6 to 9 breaths 1.53 µg/kg (0.7-2.9)	—	Catheterization	13 PDE5, 9 ERA, 3 CCB, 2 iloprost, 1 epoprostenol	Cough (1) and hypotension (2)	Inhaled treprostinil may be useful for AVT with tolerability and safety profiles.
Siehr et al ¹³	2013	Retrospective, 2 centers	N = 77 children (40 TRE) Age: 7.7 ± 5.2 yr 21 IPAH, 17 CHD, 2 other group 1	SC	Median 36.5 (16-75) ± 1 yr 61.5 (11- 95) at 2 yr	Mean 4.3 ± 3.4 yr 70% 5-yr transplant- free survival	Catheterization	Unspecified	Unspecified	Efficacy of treprostinil equivalent to epoprostenol, with similar long- term outcomes.
McIntyre et al ¹⁷	2013	Retrospective single-center	N = 36 children (9 TRE) Age: 44 d (1-359) 2 IPAH, 6 CHD, 9 CDH, 9 CLD, 6 PPHN, 4 bronchiolitis	IV	Mean 36.4 ± 25.6	29 d 21 deaths	Safety and tolerability	11 ECMO, 30 NO, 15 PDE5, 16 milrinone	2 bleeding events, 6 pain (lower than that reported in adults patients), 7 hypotension, 4 flushing	
Fordman et al ¹⁹	2014	Retrospective, single-center	N = 5 premature infants Age: 53 d (28- 128) 5 CLD	SC	20 to 50	3-30 wk	Echocardiography, ventilation parameters	5 PDE5, 2 ERA, 4 NO, 4 epopr- ostenol	None of the children presented severe site erythema, bleeding, bruising, or infection	
Olson et al ⁴⁰	2015	Case report, single-center	N = 2 infants Age: 46 and 48 d 2 CDH	SC	48 and 52	7-8 mo	BNP, echocardiography, catheterization	PGE1, NO, milrinone	Minimal problems with the catheter	
Carpentier et al ²⁹	2017	Prospective, single-center	N = 14 infants Age: 12 d (5-157) 14 CDH	SC	16 ± 17	141 d [5- 598] 2 deaths	Echocardiography, SpO2	10 NO, 9 PDE5, 6 PGE1	Local inflammation did not usually require a change in the SC infusion site	
Handler et al ⁴¹	2017	Retrospective, single-center	N = 17 children CHD (single ventricle) 6 shunts, age: 8.4 m (1-13) 6 Glenn, age: 2.6 yr (0.7-8) 6 Fontan, age: 12.8 yr (3.8-15.4)	SC	Unspecified	Unspecified	Catheterization, SpO2	4 NO, 11 PDE5	Unspecified	
Park et al ⁴⁴	2017	Case report, single-center	N = 2 infants Age: 1 and 2 d 2 PPHN	IV	15 and 20	3-6 mo	Clinical, SpO2	PGE1, NO, milrinone	Unspecified	Patients showed dramatic clinical improvement, and no systemic side effects were observed
Ablonczy et al ¹⁵	2018	Retrospective, single-center	N = 8 children Age: 12.4 yr (2.6- 14.7) 7 IPAH, 1 pulmonary hypoplasia	SC	60-100	6 mo 2 deaths	WHO	PDE5, ERA, ambriesentan (n = unspecified)	Pain managed by Paracetamol only	Long-term subcutaneous treprostinil could be a safe and well-tolerated therapy in children with severe PAH even at high doses.
Hart et al ¹²	2018	Retrospective, multicenter	N = 280 children (85 TRE) Age: 10.9 ± 6 yr IPAH and HP AH	SC	Unspecified	1 yr 1 death	Cost	27 PDE5, 37 ERA 3 CCB	Unspecified	Treprostinil initiation was associated with less resource utilization and lower cost compared to epoprostenol initiation.
Lawrence et al ¹¹	2018	Retrospective, controlled, single-center	N = 17 infants Age: 37 d (6-180) 17 CDH	SC	20	54.5 d (44.3- 110) 6 deaths	BNP, echocardiography	13 ECMO, 17 NO, 9 PDE5, 15 PGE1	Well tolerated.	Improved severity of PH

TABLE 1. (Continued) Use of Treprostinil in Pediatrics: Review of the Literature

Author	Year	Study Design	Population	Administration	Treprostinil		Outcomes	Other PH Treatments	Adverse Effects	Main Results
					Dose Range (ng/kg/min)	Follow-up				
Levy et al ¹¹	2018	Retrospective, multicenter (Europe and America)	N = 56 children Age: 96.8 ± 68 wk 23 IPAH, 13 HPAH, 20 CHD	SC	55 [15–350]	6 mo 10 deaths	BNP, WHO, catheterization, 6MWT	ERA or PDE5 or both (n = unspecified)	Site pain resistant to simple analgesics occurred in 12 patients, but could be managed in 9/12 children	Subcutaneous treprostinil infusion was an effective therapy without serious side effects in children with PAH.
Hopper et al ¹⁶	2018	Retrospective, single center	N = 49 children 42 TRE Age: 2.6 yr (0.02–29) 17 IPAH, 1 HPAH, 9 CHD, 21 CLD & CDH, 1 chronic thromboembolic PH	33 SC/IV 9 INH	—	12 mo 7 deaths	Echocardiography (Sears), BNP, WHO, 6MWT	21 PDE5, 6 ERA, 6 ambroxanthin, 3 tadalafil	Unspecified	Consistent improvement in RV function that correlates with clinical improvement.
Desole et al ⁴⁶	2019	Care report, single center	N = 1 Age: 14 yr HPAH	IV Implantable pump	170	7 yr	Clinical status	PDE5 & ERA	No side effects	Implantable pumps might be a valuable alternative to external pumps for treprostinil infusion in pediatric PAH.
Kanaan et al ¹⁴	2019	Retrospective, multicenter (United States)	N = 28 children Age: 13.8 yr (10.8–16.2) WHO group 1 but type unspecified	Oral	2.0 (1.4–3.0) mg 2 to 3 times per day	2 yr, 1 death	Clinical status	3 PDE5, 1 ERA, 24 PDE5 & ERA	Gastrointestinal symptoms, headache	Oral treprostinil is an option for the treatment of some pediatric PAH patients. Treatment failure is commonly due to either disease progression or poor tolerance of side effects.
Ivy et al ²⁰	2019	Prospective, multicenter (United States)	N = 32 children Age: 12 yr (7–17) 24 IPAH, 1 HPAH, 7 CHD	Oral	4.5 (1.25–10.0) mg 3 times per day	24 wk	6MWT, WHO, cMRI, CPET, quality of life	Current PAH therapy are unspecified	Headache (81%), diarrhea (69%), nausea (66%), vomiting (66%), and flushing (56%)	Pediatric patients maintained transition to oral treprostinil with preservation of exercise capacity and WHO FC. Prostanoid-related adverse events were most common and similar to those reported in adults.

Values are mean ± SD or median (minimum, maximum). ACE, angiotensin-converting enzyme inhibitor (ACE inhibitor); AVT, acute pulmonary vasodilator testing; BNP, brain natriuretic peptide; CCB, calcium channel blockers; CDH, congenital diaphragmatic hernia; CHD, congenital heart disease; CLD, chronic lung disease; cMRI, cardiac magnetic resonance imaging; CPET, cardiopulmonary exercise test; d, days old; EMCO, extracorporeal membrane oxygenation; ERA, endothelin receptor antagonist; HPAH, heritable pulmonary arterial hypertension; INH, inhaled; IPAH, idiopathic pulmonary arterial hypertension; m, months old; NO, nitric oxide; PDE5, Phosphodiesterase-5; PGE1, prostaglandin E1; PPHN, persistent pulmonary hypertension of the newborn; PVR, pulmonary vascular resistance; 6MWT, 6-minute walk test; SC, subcutaneous; SpO2, oxygen saturation; TRE, treprostinil; VO2, oxygen uptake; w, weeks; WHO, World Health Organization functional class of pulmonary hypertension; y, years old.

Nevertheless, most data from the literature come from a limited number of noncontrolled studies, with small cohorts of heterogeneous patients. Treatments associated with treprostinil were heterogeneous as well, in terms of dosage and type of drugs. The results provided by these studies may also be limited by the lack of consistent outcomes, such as hemodynamic measures from cardiac catheterization, functional tests, and biomarkers. Indeed, the decision of add-on therapy with treprostinil was mostly made upon clinical and echocardiography assessments. The current pediatric and adult PH guidelines recommend performing cardiac catheterization at diagnosis, but also when drug therapy needs to be upgraded, especially before starting prostanoids.^{7,8} In our reported cases, as in many cases from the literature, patients' hemodynamic and respiratory instability made impossible the performance of cardiac catheterization before treprostinil initiation. Cardiac catheterization in children with PH is associated with significant adverse events and should be performed in experienced centers to reduce related morbidity or mortality and to improve the quality of comprehensive studies.^{47–49} Nevertheless, exceptions may involve critically ill patients requiring immediate initiation of advanced therapies.⁶ Moreover, functional tests recommended in adult PH guidelines, such as the 6-minute walk test and cardiopulmonary exercise tests (maximum oxygen uptake and ventilatory efficiency), are not adapted to the youngest pediatric population.⁸ When assessed, B-type natriuretic peptide plasma levels decreased from 1.6 to 14.7 times after introduction of treprostinil.^{11, 21, 31, 36, 40} Interestingly, the recent study from Ahmad et al⁵⁰ used the oxygenation index reduction to measure prostacyclin efficacy in PH of the newborn.

TABLE 2. Current Drug Approval for the Use of Treprostinil

Drug Agency	Intravenous/Subcutaneous (Remodulin)		Inhaled (Tyvaso)		Oral (Orenitram)	
	Children	Adults	Children	Adults	Children	
EMA	Idiopathic and heritable PAH & WHO III	None (current PIP)	Withdrawal in 2010	None	Pending approval	None (current PIP)
FDA	Group 1 PAH & WHO II, III, and IV	None	Group 1 PAH & WHO II, III, and IV	None	Group 1 PAH & WHO II, III, and IV	None

EMA, European Medicines Agency; FDA, Food and Drug Administration (drug approval in the United States, Asia, Australia, New Zealand, and South America); PIP, pediatric investigation plan; WHO, World Health Organization functional class of pulmonary hypertension.

In this review, the mean dose of treprostinil (eg, 40 ng/kg/min) seemed to be in line with the current adult guidelines, stating that the optimal dose may vary between individual patients, ranging between 20 and 80 ng/kg/min.⁵¹ However, this dose is higher than the mean dose of 9.3 ng/kg/min used in the original randomized trial,⁵² probably because PH is more aggressive in pediatrics (10-month median survival in untreated children) or also because they may tolerate higher doses.

In this review, many children with PH related to respiratory diseases (group 3), such as congenital diaphragmatic hernia, were treated by treprostinil. Yet, no study could really demonstrate the efficacy of treprostinil in this situation because controlled data are missing, and the current advances in respiratory neonatal intensive care may bias the overall outcomes. This debate has been recently highlighted by the exchanges between Madenci et al and Hopper et al^{53,54} Indeed, the use of advanced therapy (prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors) in PH associated with lung diseases is not recommended in the current pediatric and adult PH guidelines.^{7,8} Nevertheless, these drugs have been used in neonatal intensive units for congenital diaphragmatic hernia.⁵⁵ In the current era, further research aims to identify the pathophysiological relevance of using a prostanoid in congenital diaphragmatic hernia.^{56,57}

In this pediatric review, many authors reported that treprostinil seemed to be as effective as epoprostenol.^{16,29,39,41,45} Despite a low level of evidence for this statement, we may consider previous results from adult studies. Indeed, in open-labeled or retrospective long-term analysis of subcutaneous treprostinil in adults, observed survival seems to be similar or even slightly better than those seen with intravenous epoprostenol in patients with similar baseline characteristics.^{15,58} In children with severe PAH (group 1) and indication for prostanoid therapy, subcutaneous treprostinil may stand as an alternative to intravenous epoprostenol, with an acceptable tolerance in pediatric patients^{11,24,29,31,35,38–40} compared to studies from the adult population reporting that site pain was the most common adverse effect (85% of cases), resulting in discontinuation of treprostinil in 8% of cases.⁵² In our experience, as well as in the literature review, subcutaneous treprostinil represents a feasible alternative mode for PH drug delivery, avoiding central venous line complications in a vulnerable population. Indeed, intravenous epoprostenol in children with PH brings additional risks of sepsis, delivery system malfunctions, maintenance issues, delayed home discharge, and interruption of the perfusion.⁵⁹

The current data from the literature is too limited to draw any conclusion on the use of inhaled and oral treprostinil in pediatrics PH. Nevertheless, studies on inhaled treprostinil seemed to report good efficacy and tolerability, despite some concern on potential reactive airway disease. As for oral treprostinil, poor tolerance and disease progression lead to some caution.

The existence of 12 drug trials on treprostinil for children registered on clinical trials registries represents a positive sign for pediatric PH research advancement. Nevertheless, as in most PH specific therapies used in pediatrics, the level of evidence for treprostinil use in children remains poor. Unfortunately, many of these clinical trials were terminated without any published results. Other formulations than subcutaneous treprostinil were scarcely studied, with 2 clinical trials on oral treprostinil including a small number of children, with negative results. Only one study showed a low efficacy of inhaled treprostinil²¹ and no study found a better efficacy of intravenous treprostinil compared to epoprostenol.⁶⁰ Therefore, original study designs using relevant outcomes in pediatric PH drug trials need to be drawn, to optimize the management of PH in children.

Study Limitation

This review was designed as a summary; therefore, no conclusions can be drawn.

CONCLUSIONS

Subcutaneous treprostinil may be a useful adjunct in the therapeutic algorithm for infants and children with severe PH, providing an alternative to intravenous epoprostenol, with a low level of side effects. Nevertheless, subcutaneous treprostinil should be used in experienced pediatric PH centers, as a second-line treatment, in children with PH refractory to oral drugs, and after a complete check-up for all PH etiologies. The level of evidence for treprostinil in PH associated with lung diseases remains poor, as it is for prostanoid in general. In the modern era, original and noninvasive study designs for pediatric PH drug trials need to be drawn to optimize the management of PH in children.

FUTURE RESEARCH DIRECTIONS

Pediatric research should promote randomized controlled trials on treprostinil, as well as all advanced PH therapies, and determine the most appropriate outcomes in this population, especially in critically ill neonates and infants.

REFERENCES

1. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53.
2. Rosenzweig EB, Widlitz AC, Barst RJ. Pulmonary arterial hypertension in children. *Pediatr Pulmonol*. 2004;38:2–22.
3. Widlitz A, Barst RJ. Pulmonary arterial hypertension in children. *Eur Respir J*. 2003;21:155–176.
4. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 suppl):D34–D41.
5. Ivy DD, Abman SH, Barst RJ, et al. Pediatric pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 suppl):D117–D126.
6. Abman SH, Hansmann G, Archer SL, et al. American Heart Association Council on Cardiopulmonary CCP, Resuscitation, Council on Clinical C, Council on Cardiovascular Disease in the Y, Council on Cardiovascular R, Intervention, Council on Cardiovascular S, Anesthesia, the American Thoracic S. Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society. *Circulation*. 2015;132:2037–2099.
7. Hansmann G, Apitz C, Abdul-Khalik H, et al. Executive summary. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. *Heart*. 2016; 102(suppl 2):ii86–ii100.
8. 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 Heart J*. 2016;37:67–119.
9. Greenough A, Khatriwal B. Pulmonary hypertension in the newborn. *Paediatr Respir Rev*. 2005;6:111–116.
10. McGee DC, Gould MK. Preventing complications of central venous catheterization. *N Engl J Med*. 2003;348:1123–1133.
11. Levy M, Del Cerro MJ, Nadaud S, et al. Safety, efficacy and Management of subcutaneous treprostinil infusions in the treatment of severe pediatric pulmonary hypertension. *Int J Cardiol*. 2018;264:153–157.
12. Yu YP, Huang XM. Progress in pharmacotherapy of pulmonary arterial hypertension in children [in Chinese]. *Zhongguo Dang Dai Er Ke Za Zhi*. 2012;14:236–240.
13. McLaughlin VV, Gaine SP, Barst RJ, et al. Efficacy and safety of treprostinil: an epoprostenol analog for primary pulmonary hypertension. *J Cardiovasc Pharmacol*. 2003;41:293–299.

14. Barst RJ, Galie N, Naeije R, et al. Long-term outcome in pulmonary arterial hypertension patients treated with subcutaneous treprostinil. *Eur Respir J*. 2006;28:1195–1203.
15. Lang I, Gomez-Sanchez M, Kneussl M, et al. Efficacy of long-term subcutaneous treprostinil sodium therapy in pulmonary hypertension. *Chest*. 2006;129:1636–1643.
16. Ivy DD, Claussen L, Doran A. Transition of stable pediatric patients with pulmonary arterial hypertension from intravenous epoprostenol to intravenous treprostinil. *Am J Cardiol*. 2007;99:696–698.
17. Walsh M, Hanna BD. A pediatric case study of treprostinil overdose. *J Heart Lung Transplant*. 2009;28:297–298.
18. Ivy DD. Prostacyclin in the intensive care setting. *Pediatr Crit Care Med*. 2010;11(2 suppl):S41–S45.
19. Benza RL, Gomberg-Maitland M, Naeije R, et al. 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;30:982–989.
20. Smadja DM, Mauge L, Gaussem P, et al. Treprostinil increases the number and angiogenic potential of endothelial progenitor cells in children with pulmonary hypertension. *Angiogenesis*. 2011;14:17–27.
21. Krishnan U, Takatsuki S, Ivy DD, et al. Effectiveness and safety of inhaled treprostinil for the treatment of pulmonary arterial hypertension in children. *Am J Cardiol*. 2012;110:1704–1709.
22. 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.
23. Takatsuki S, Parker DK, Doran AK, et al. Acute pulmonary vasodilator testing with inhaled treprostinil in children with pulmonary arterial hypertension. *Pediatr Cardiol*. 2013;34:1006–1012.
24. Hansmann G, Koestenberger M, Alastalo TP, et al. 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;38:879–901.
25. Skoro-Sajer N, Lang I. Treprostinil for the treatment of pulmonary hypertension. *Expert Opin Pharmacother*. 2008;9:1415–1420.
26. Gulmezoglu AM, Pang T, Horton R, et al. WHO facilitates international collaboration in setting standards for clinical trial registration. *Lancet*. 2005;365:1829–1831.
27. Stegmann H. The International Clinical Trials Registry platform—ICTRP [in Spanish]. *Arch Latinoam Nutr*. 2007;57:311–312.
28. De Angelis CD, Drazen JM, Frizelle FA, et al. Is this clinical trial fully registered?—A statement from the International Committee of Medical Journal Editors. *N Engl J Med*. 2005;352:2436–2438.
29. Carpenter E, Mur S, Aubry E, et al. Safety and tolerability of subcutaneous treprostinil in newborns with congenital diaphragmatic hernia and life-threatening pulmonary hypertension. *J Pediatr Surg*. 2017;52:1480–1483.
30. Ivy DD, Feinstein JA, Yung D, et al. Oral treprostinil in transition or as add-on therapy in pediatric pulmonary arterial hypertension. *Pulm Circ*. 2019;9:2045894019856471.
31. Lawrence KM, Hedrick HL, Monk HM, et al. Treprostinil improves persistent pulmonary hypertension associated with congenital diaphragmatic hernia. *J Pediatr*. 2018;200:44–49.
32. Hart SA, Arora G, Feingold B. Resource utilization at the time of prostacyclin initiation in children in pulmonary arterial hypertension: a multicenter analysis. *Pulm Circ*. 2018;8:2045893217753357.
33. Siehr SL, Ivy DD, Miller-Reed K, et al. Children with pulmonary arterial hypertension and prostanoid therapy: long-term hemodynamics. *J Heart Lung Transplant*. 2013;32:546–552.
34. Kanaan U, Varghese N, Coleman R, et al. EXPRESS: oral treprostinil use in children—a multi-center, observational experience. *Pulm Circ*. 2019;9:2045894019862138.
35. Ablonczy L, Tordas D, Kis E, et al. Use of subcutaneous treprostinil in pediatric pulmonary arterial hypertension—Bridge-to-transplant or long-term treatment? *Pediatr Transpl*. 2018;22.
36. Hopper RK, Wang Y, DeMatteo V, et al. Right ventricular function mirrors clinical improvement with use of prostacyclin analogues in pediatric pulmonary hypertension. *Pulm Circ*. 2018;8:2045894018759247.
37. McIntyre CM, Hanna BD, Rintoul N, et al. Safety of epoprostenol and treprostinil in children less than 12 months of age. *Pulm Circ*. 2013;3: 862–869.
38. Levy M, Celermajer DS, Bourges-Petit E, et al. Add-on therapy with subcutaneous treprostinil for refractory pediatric pulmonary hypertension. *J Pediatr*. 2011;158:584–588.
39. Ferdman DJ, Rosenzweig EB, Zuckerman WA, et al. Subcutaneous treprostinil for pulmonary hypertension in chronic lung disease of infancy. *Pediatrics*. 2014;134:e274–278.
40. Olson E, Lusk LA, Fineman JR, et al. Short-Term Treprostinil use in infants with congenital diaphragmatic hernia following repair. *J Pediatr*. 2015;167:762–764.
41. Handler SS, Ogawa MT, Hopper RK, et al. Subcutaneous treprostinil in pediatric patients with failing single-ventricle physiology. *J Heart Lung Transplant*. 2017;37:306–307.
42. Sitbon O, Vonk Noordegraaf A. Epoprostenol and pulmonary arterial hypertension: 20 years of clinical experience. *Eur Respir Rev*. 2017;26.
43. Badesch DB, McLaughlin VV, Delcroix M, et al. Prostanoid therapy for pulmonary arterial hypertension. *J Am Coll Cardiol*. 2004;43(12 supplS):S6S–61S.
44. Ivy DD, Calderbank M, Wagner BD, et al. Closed-hub systems with protected connections and the reduction of risk of catheter-related bloodstream infection in pediatric patients receiving intravenous prostanoid therapy for pulmonary hypertension. *Infect Control Hosp Epidemiol*. 2009;30:823–829.
45. Rubenfire M, McLaughlin VV, Allen RP, et al. Transition from IV epoprostenol to subcutaneous treprostinil in pulmonary arterial hypertension: a controlled trial. *Chest*. 2007;132:757–763.
46. Desole S, Richter MJ, Heine A, et al. Intravenous treprostinil via an implantable pump in pediatric pulmonary arterial hypertension. *Pulm Circ*. 2019;9:2045894018788846.
47. O'Byrne ML, Glatz AC, Hanna BD, et al. Predictors of catastrophic Adverse outcomes in children with pulmonary hypertension undergoing cardiac catheterization: A multi-institutional analysis from the pediatric health information systems database. *J Am Coll Cardiol*. 2015;66:1261–1269.
48. Zuckerman WA, Turner ME, Kerstein J, et al. Safety of cardiac catheterization at a center specializing in the care of patients with pulmonary arterial hypertension. *Pulm Circ*. 2013;3:831–839.
49. Apitz C, Hansmann G, Schranz D. Hemodynamic assessment and acute pulmonary vasoreactivity testing in the evaluation of children with pulmonary vascular disease. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. *Heart*. 2016;102(suppl 2):ii23–29.

50. Ahmad KA, Banales J, Henderson CL, et al. Intravenous epoprostenol improves oxygenation index in patients with persistent pulmonary hypertension of the newborn refractory to nitric oxide. *J Perinatol*. 2018;38:1212–1219.
51. 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.
52. 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.
53. Madenci AL, Baer HJ, Vitali SH, et al. Time versus treatment: interpreting longitudinal data analysis of treprostinil. *J Pediatr*. 2019;206:304–305.
54. Hopper RK, Rogers R, Lawrence KM, et al. Reply. *J Pediatr*. 2019;206: 305–306.
55. Snoek KG, Reiss IK, Greenough A, et al. Standardized postnatal management of Infants with congenital diaphragmatic hernia in Europe: The CDH EURO consortium consensus—2015 update. *Neonatology*. 2016; 110:66–74.
56. Ford WD, James MJ, Walsh JA. Congenital diaphragmatic hernia: association between pulmonary vascular resistance and plasma thromboxane concentrations. *Arch Dis Child*. 1984;59:143–146.
57. Bos AP, Tibboel D, Hazebroek FW, et al. Congenital diaphragmatic hernia: impact of prostanooids in the perioperative period. *Arch Dis Child*. 1990;65:994–995.
58. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonaryhypertension: the impact of epoprostenol therapy. *Circulation*. 2002;106: 1477–1482.
59. Sammut D, Elliot CA, Kiely DG, et al. Central venous catheter-related blood stream infections in patients receiving intravenous iloprost for pulmonary hypertension. *Eur J Clin Microbiol Infect Dis*. 2013;32:883–889.
60. Paramothayan NS, Lasserson TJ, Wells AU, et al. Prostacyclin for pulmonary hypertension in adults. *Cochrane Database Syst Rev*. 2005;2: CD002994.
61. Park BY, Chung SH. Treprostinil for persistent pulmonary hypertension of the newborn, with early onset sepsis in preterm infant: 2 case reports. *Medicine (Baltimore)*. 2017;96:e7303.