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RESEARCH ARTICLE

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Failure to tolerate continuous subcutaneous treprostinil in pediatric pulmonary hypertension patients

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Abstract

Continuous subcutaneous (SubQ) treprostinil is an effective therapy for pediatric patients diagnosed with pulmonary hypertension (PH). To date, the clinical characteristics and factors associated with failure to tolerate this therapy have not been described. The purpose was to describe patient-reported factors contributing to SubQ treprostinil intolerance in pediatric patients with PH. A retrospective descriptive study was performed at 11 participating sites in the United States and Canada for patients younger than 21 years of age diagnosed with PH who failed treatment to tolerate SubQ treprostinil between January 1, 2009, and December 31, 2019. All data were summarized using

descriptive statistics. Forty-one patients met the inclusion criteria. The average age at SQ treprostinil initiation, and length of treatment, was 8.6 years and 22.6 months, respectively. The average maximum dose, concentration, and rate were 95.8 ng/kg/min, 6.06 mg/mL, and 0.040 mL/h, respectively. The reasons for failure to tolerate SubQ treprostinil included intractable site pain (73.2%), frequent site changes (56.1%), severe site reactions (53.7%), infections (26.8%), and noncompliance/depression/anxiety (17.1%). Thirty-nine (95.1%) patients transitioned to a prostacyclin therapy with 23 patients transitioning to intravenous prostacyclin, 5 to inhaled prostacyclin, 5 to oral prostacyclin, and 7 to a prostacyclin receptor agonist. A subset of pediatric PH patients failed to tolerate SubQ treprostinil infusions despite advances in SubQ site maintenance and pain management strategies. Intractable site pain, frequent SubQ site changes, and severe localized skin reactions were the most common reasons for failure.

KEYWORDS
advanced practice nursing, prostacyclin, pulmonary hypertension, treprostinil

INTRODUCTION

Pulmonary hypertension (PH) is a rare, chronic, and life-threatening disease characterized by elevated pulmonary vascular resistance (PVR) and pulmonary arterial pressure (PAp) that can result in right ventricular failure and death.[1] Pediatric patients with severe PH require treatment with parenteral prostacyclins (epoprostenol and treprostinil), which have been associated with improvement in symptoms, exercise capacity, pulmonary hemodynamics, and survival.[2–4] However, administration of intravenous (IV) epoprostenol and treprostinil requires a central venous catheter (CVC) which can be associated with complications including administration error, bloodstream infection, thrombosis, and malposition. Pediatric patients receiving IV prostacyclins have been reported to experience complications in 1.73 per 1000 CVC days.[5]

Given these risks, subcutaneous (SubQ) treprostinil is the preferred method of prostacyclin administration in pediatrics as it has a superior safety profile and is not associated with the side effects and complications that can occur with IV prostacyclins.[6] Treprostinil is a synthetic prostacyclin analog with an elimination half-life of 4 h.[6] It is rapidly and completely absorbed with 100% bioavailability.[6] The most significant side effect of SubQ treprostinil is the site discomfort associated with new site placement, yet some patients also experience site erythema, tenderness, swelling, induration, bleeding, discharge, and infection.[7] There are other patients that do not experience any discomfort at all. The reason that some patients experience pain and others do is not well-understood. SubQ treprostinil is generally thought to be a well-tolerated therapy with localized site pain lasting for 3–4 days surrounding the placement of a new SubQ site.[8] A variety of pharmacologic and nonpharmacologic techniques are utilized to minimize the pain and discomfort associated with SubQ treprostinil. The Pediatric Pulmonary Hypertension Network (PPHNet) Advanced Practice Provider and Nursing Initiative have created guidelines for site maintenance and pain control strategies with the use of SubQ treprostinil in pediatric patients.[9] This study seeks to describe the factors that may play a role in determining which pediatric patients do not tolerate SubQ treprostinil.

METHODS

After receiving Institutional Review Board (IRB) approval from the lead site, 11 (10 located in the United States and 1 center in Canada) of 13 centers that are active in the (PPHNet) Advanced Practice Provider Initiative elected to participate in a retrospective review of patients cared for in their hospitals from January 1, 2009, to December 31, 2019. Pediatric patients less than 21 years of age with PH that failed to tolerate continuous SubQ treprostinil were included. Treatment failure was defined as initial patient tolerance of SubQ treprostinil infusion (for at least 24 h), with the ultimate inability to tolerate the infusion due to side effects. Adult patients greater than 21 years of age, patients that tolerated

treatment with SubQ treprostinil, and patients that discontinued SubQ treprostinil due to disease progression and/or clinical worsening were excluded.

Each center obtained IRB approval or IRB exempt status, and a Data Use Agreement (DUA) as required. A REDCap database was created and used as the study EDC (electronic data capture) system. The clinical lead(s) from each of the sites identified the patients that met inclusion criteria and collected the patient data. All data were entered into the REDCap database with secure password protection. Boston Children's Hospital served as the lead site for data management, with UCSF collaborators as co-leads. Data were cleaned and summarized as an aggregate using descriptive statistics.

The data collected included patient demographics, World Health Organization (WHO) Diagnostic Classification, and Panama Diagnostic Classification. The WHO Diagnostic Classification is comprised of PH categories sharing similar hemodynamic characteristics, pathology and/or management.[10] The Panama Diagnostic Classification is a comprehensive classification of PH specific to pediatric patients with pulmonary vascular disease.[11] The patient's weight, height, WHO functional class, and Panama functional class data were collected both at the time of SubQ treprostinil initiation and at discontinuation. Specifics of SubQ treprostinil infusion, including maximum dose reached (ng/kg/min), maximum rate reached (mL/h), maximum concentration reached (mg/mL), type of SubQ catheter used, and pain management strategies employed were collected. Concomitant pulmonary vasodilator therapy during treatment with SubQ treprostinil, as well as outcomes including the need for invasive intervention or transition to alternative prostacyclin, were included. Participating centers were asked to identify the reason(s) attributable to SQ treprostinil failure and if failure/discontinuation of SQ treprostinil resulted in clinical deterioration.

TABLE 1 Treprostinil initiation versus discontinuation ($n = 41$).

$n = 41$		Mean [Median] (Range)
Age at SubQ Treprostinil initiation[a]		8.6 [7] (0.1–18)
Average length of treatment (months)		22.6 [19.1] (0.1–84)
	Initiation Mean [Median] (Range)	**Discontinuation Mean [Median] (Range)**
Weight (kg)	30.6 [21.9] (2.9, 68.4)	35.0 [26] (6.1, 85.2)
Height (cm)	124.6 [121.5] (49, 180)	134.7 [130] (56.5, 180.5)
	***n* (%)**	***n* (%)**
Panama functional class		
I	0	1 (2.4)
II	13 (31.7)	18 (43.9)
IIIa	12 (29.3)	11 (26.8)
IIIb	3 (7.3)	3 (7.3)
IV	5 (12.2)	1 (2.4)
Missing	8 (19.5)	7 (17.1)
WHO functional class		
I	0	1 (2.4)
II	18 (43.9)	24 (58.5)
III	16 (39.0)	11 (26.8)
IV	6 (14.6)	2 (4.9)
Missing	1 (2.4)	3 (7.3)

[a]Missing age data for five patients.

RESULTS

Across the 11 participating centers, 41 patients met the inclusion criteria. Twenty-three (56.1%) patients were female. The average age at initiation of SubQ treprostinil therapy was 8.6 years (0.1–18 years), and the average length of treatment was 22.6 months (0.1–84 months). Twenty-five patients (61%) were Panama functional class II and IIIa at initiation, with 29 patients (70.7%) falling into these same categories at the time of SubQ treprostinil discontinuation. WHO functional class was in keeping with the Panama Functional Class, with 34 patients (59.9%) in WHO functional class II and III at initiation, which increased to 35 patients (85.3%) at discontinuation (Table 1).

Thirty-nine patients (95.1%) met the criteria for WHO Group I Diagnostic Classification (pulmonary arterial hypertension), and six (13.6%) patients met the criteria for WHO Group III Classification (PH secondary to lung disease). Of note, patients can meet diagnostic requirements for multiple groups. No patients were WHO Group II, IV, or V Diagnostic Classification. The majority of patients were in Panama Classification 5 (26 patients, 63.4%), which isolated pediatric pulmonary hypertensive vascular disease (PHVD). Two patients (4.9%) were Panama Classification 1, or prenatal or developmental PHVD, and 11 (26.8%) patients were categorized as having pediatric cardiovascular disease or Panama Classification 3. Three (7.3%) of the patients were Panama Classification 4/bronchopulmonary dysplasia, three patients were Panama Classification 6/multifactorial PHVD, and two patients were Panama Category 7/pediatric lung disease. No patients were classified in Panama Categories 2, 8, 9, or 10.

The maximum SubQ treprostinil dose achieved was 95.8 ng/kg/min on average, with a median of 79 ng/kg/min and a wide range in dosing from 6 to 458 ng/kg/min. The average maximum infusion rate was 0.040 mL/h, and the average maximum concentration of treprostinil infusion was 6.06 mg/mL. Patients often trialed multiple SQ catheters, with the Cleo (33, 80.5%) and Silhouette (21, 51.2%) most commonly used. Most patients received a combination of pharmacologic and nonpharmacologic therapies targeted at SQ site maintenance and pain management. Thirty-seven patients (90.2%) were treated with pharmacologic therapies, including topical pain relievers, narcotic and nonnarcotic oral pain relievers, and antihistamines. Thirty patients (73.2%) employed nonpharmacologic strategies, including compression, heat, elevation, ice, and vibration (Table 2).

The most common reason for discontinuation of SubQ treprostinil was intractable site pain (30, 73.2%). The need for frequent SQ site changes (23, 56.1%) and severe localized site reactions (22, 53.7%) were also common contributors to the discontinuation of therapy. Infections such as cellulitis or abscess (11, 26.8%) were less common. Noncompliance (2, 4.9%), depression (2, 4.9%), and anxiety (3, 7.3%) were less frequently reported. No patients discontinued therapy due to prostacyclin side effects such as headaches, nausea, vomiting, diarrhea, flushing, jaw pain, or musculoskeletal pain. Most patients were on combination PH therapy, with 39 patients receiving phosphodiesterase type 5 inhibitors (95.1%), 35 patients receiving endothelin receptor antagonists (85.4%), and 3 receiving calcium channel blockers (7.3%). Thirty-nine (95%) patients were transitioned to another prostacyclin analog or prostacyclin receptor agonist after failing to tolerate SubQ treprostinil. Over half of patients (23, 56.1%) transitioned to an IV prostacyclin. Ten patients (24.4%) experienced clinical deterioration after discontinuation of SubQ treprostinil, with two patients (4.9%) undergoing a Potts procedure and three patients (7.3%) undergoing lung transplantation (see Table 3).

TABLE 2 SQ treprostinil ($n = 41$).

$n = 41$	Mean [Median] (Range)
Maximum SubQ Treprostinil dose reached (ng/kg/min):	95.8 [79] (6, 458)
Maximum SubQ Treprostinil rate reached (mL/h):	0.040 [0.026] (0.008, 0.42)
Maximum SubQ Treprostinil concentration reached (mg/mL):	6.06 [5] (0.8, 10)
	n (%)
SubQ catheters used:	
Cleo	33 (80.5)
Neria	1 (2.4)
Silhouette	21 (51.2)
MiniMed Quick-set	3 (7.3)
Unknown, not in documentation	1 (2.4)
Pain strategies used:	
Pharmacologic therapies	37 (90.2)
Topical pain relievers	34 (82.9)
Nonnarcotic oral pain relievers	39 (95.1)
Antihistamines	37 (90.2)
Narcotic	18 (43.9)
Other	8 (19.5)
(5) H2 Blocker/inhibitor	
(1) PLO gel, topical hydrocortisone	
(1) Ranitidine	
(1) Steroids	
Nonpharmacologic therapies	30 (73.2)
Compression	19 (46.3)
Elevation	5 (12.2)
Heat	23 (56.1)
Ice	34 (82.9)
Vibration	2 (4.9)
Other: Dry site	1 (2.4)

DISCUSSION

SubQ treprostinil is an effective therapy for treating PH in pediatric patients with an improved administration safety profile compared with IV prostacyclins. Adequate site maintenance and pain management strategies are critical to administer SubQ treprostinil effectively. In recent years, the use of pharmacologic and nonpharmacologic systemic and topical therapies, as well as careful consideration of site placement, have made SQ treprostinil an effective and manageable therapy for most pediatric patients.[9] However, long-term administration of this therapy is not always successful, and the mechanism of site pain is poorly understood. This study is the first description of a cohort of pediatric patients that failed to tolerate SubQ treprostinil.

The most common reason for failure to tolerate SubQ treprostinil was intractable site pain, with 73.2% observed to have this as the cause for discontinuation. Severe localized site reactions (not infection) and the need for frequent SubQ site changes were leading contributors to the discontinuation

TABLE 3 Reason for SubQ failure and associated pulmonary vasodilator therapies ($n = 41$).

Reason(s) are attributable to SubQ treprostinil failure:	$n = 41$
Frequent SubQ site changes	23 (56.1)
Intractable SubQ site pain	30 (73.2)
Infection(s) (cellulitis, abscess)	11 (26.8)
Severe localized site reactions	22 (53.7)
Prostacyclin side effects (headaches, jaw pain, nausea/vomiting, diarrhea, extremity pain, flushing, musculoskeletal pain)	0
Noncompliance/depression/anxiety	7 (17.1)
Concomitant pulmonary vasodilator therapies:	
Phosphodiesterase type 5 inhibitor (PDE5)	39 (95.1)
Endothelin receptor antagonist (ERA)	35 (85.4)
Soluble guanylyl cyclase (sGc) stimulator	0
Calcium channel blocker (CCB)	3 (7.3)
Other	2 (4.9)
(1) Chinese herbs	
(1) Diuretics	
Patient transitioned to another prostacyclin analog or prostacyclin receptor agonist	39 (95.1)
Intravenous (Flolan®, Veletri®, Remodulin®)	23 (56.1)
Inhaled (Tyvaso®, Ventavis®)	5 (12.2)
Oral (Orenitram®)	5 (12.2)
Prostacyclin receptor agonist (Uptravi®)	7 (17.1)
Underwent a Potts procedure	2 (4.9)
Underwent a lung transplant	3 (7.3)
Failure of/discontinuation of SQ treprostinil resulted in clinical deterioration	10 (24.4)

of SubQ therapy as well. Of note, patients could have multiple reasons attributable to the failure to tolerate SQ treprostinil therapy, and intractable site pain was associated with severe localized site reactions and/or frequent SubQ site changes in some patients. Narcotics were required by 43.9% of patients for SQ treprostinil site pain, further illustrating the degree of discomfort patients can experience with this therapy. It is preferable for pediatric patients to be treated with opioid-sparing analgesic techniques, and this is of even greater importance in hemodynamically tenuous patients with PH whereby narcotics may suppress respiratory drive, result in retention of carbon dioxide and further increase PAp. Additionally, there are potential long-term negative consequences as well. Data in young adults suggest use of opioids long-term is associated with a significant increase in opioid misuse later in life.[12] Anecdotally adolescents fail to tolerate SubQ treprostinil at higher rates; however, our data suggest that school-aged pediatric patients, with a mean age of 8.6 years (range 0.1–18 years) at initiation, were most likely to fail to tolerate SubQ treprostinil. More specifically, 2 patients were aged 0–1 year (0.5%), 5 patients were aged greater than 1–3 years (13.9%), 10 patients were aged greater than 3–6 years (27.8%), 4 patients were aged greater than 6–10 years (11.1%), 8 patients were aged greater than 10–15 years (22.2%), and 7 patients were greater than 15 years of age (19.4%). Unfortunately, we lacked age data for five patients due to patient age/date of birth restrictions on data sharing by some centers. The reason that school-aged patients are more likely to fail to tolerate subQ treprostinil is likely multifactorial, involving the developmental stage of school-aged children, their understanding of the pain, and their ability to cope with physical discomfort and stressors.

Patients who failed to tolerate SubQ therapy did not do so right away; in fact, patients were treated for an average of 22.6 months and achieved an average dose of 95.8 ng/kg/min before discontinuing therapy. A variety of SubQ treprostinil site maintenance and pain management strategies were utilized, and an array of SQ catheters were employed (Table 2) in most patients, which likely speaks to patient/family/provider efforts to administer therapy effectively.

This study has several limitations, including the small sample size and use of patient data from only 11 select pediatric PH programs (which may not be representative of all patients who fail to tolerate SubQ treprostinil). Additionally, the total number of pediatric patients receiving SubQ treprostinil in the United States and Canada is unknown, making it difficult to understand the total impact/percentage of patients who failed SubQ treprostinil compared with all who are treated. This study is retrospective and represents a broad, 10-year timeframe. Patients receiving SubQ treprostinil in the earlier years may not have received the modern-era SubQ site maintenance and pain management strategies. Each center was asked if discontinuation of SubQ treprostinil resulted in clinical deterioration, and centers responded yes for 10 of 41 patients. The specific data resulting in perceived failure were not captured, for example, the study did not capture hemodynamic or echocardiographic data. Moreover, as the trajectory of PH is poorly understood it is unknown if the clinical deterioration was associated with discontinuation of SQ treprostinil or reflective of natural disease trajectory. Notably, this study does not investigate the role of family dynamics or the social-emotional coping mechanisms of a patient and their family.

Notwithstanding these limitations, this study describes a cohort of pediatric patients that could not tolerate SubQ

treprostinil despite recent advances in SubQ treprostinil site maintenance and pain management strategies. SubQ is the preferred method of prostacyclin administration in pediatrics as it has a superior safety profile and is not associated with the side effects and complications that can occur with IV prostacyclins and associated indwelling CVC. It is clear that further research is warranted to better understand SubQ site pain mechanism of action and potential factors contributing to severe localized skin reactions and the need for frequent SQ site changes.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

Written informed consent was not required for this study and was performed in accordance with Texas Tech University Institutional Review Board.

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