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ORIGINAL ARTICLE

Initial Experience With Tadalafil in Pediatric Pulmonary Arterial Hypertension

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Abstract This study aimed to investigate the safety, tolerability, and effects of tadalafil on children with pulmonary arterial hypertension (PAH) after transition from sildenafil or after tadalafil received as initial therapy. A total of 33 pediatric patients with PAH were retrospectively evaluated. Of the 33 patients, 29 were switched from sildenafil to tadalafil. The main reason for the change from sildenafil was once-daily dosing. The average dose of sildenafil was 3.4 ± 1.1 mg/kg/day, and that of tadalafil was 1.0 ± 0.4 mg/kg/day. For 14 of the 29 patients undergoing repeat catheterization, statistically significant improvements were observed after transition from sildenafil to tadalafil in terms of mean pulmonary arterial pressure (53.2 ± 18.3 vs. 47.4 ± 13.7 mmHg; $p < 0.05$) and pulmonary vascular resistance index (12.2 ± 7.0 vs 10.6 ± 7.2 Units/m^2; $p < 0.05$). Clinical improvement was noted for four patients treated with tadalafil as initial therapy. The side effect profiles were similar for the patients who had transitioned from sildenafil to tadalafil including headache, nausea, myalgia, nasal congestion, flushing, and allergic reaction. Two patients discontinued tadalafil due to migraine or allergic reaction. One patient receiving sildenafil had no breakthrough syncope after transition to tadalafil. Tadalafil can be safely used for pediatric patients with PAH and may prevent disease progression.

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Pulmonary arterial hypertension (PAH) is characterized by endothelial and smooth muscle cell proliferation and pulmonary vascular remodeling, resulting in progressive elevation of pulmonary arterial pressure, an increase in pulmonary vascular resistance, right heart failure, and death [14]. The mechanism of progressive vascular dysfunction is caused in part by an overexpression of vasoconstrictors, including endothelin-1, and a reduction in vasodilators, including prostacyclin and nitric oxide. Conventional therapies such as calcium-channel blockers have been used to improve the symptoms of patients with PAH. However, calcium-channel blocker use has been limited because few patients have been candidates for this therapy [2].

Currently, specific targeted therapies have been approved for treatment including prostanoids [1, 8, 9, 11, 17], endothelin receptor antagonists [5, 10], and phosphodiesterase type 5 inhibitors (PDE-5i) [4, 7, 13, 15]. Two oral PDE-5i agents (sildenafil and tadalafil) currently are used for the treatment of PAH in adults. Tadalafil is a once-daily-dosing drug and has a longer half-life (about 17 h) than sildenafil (4 h) [16].

In 2009, Galiè et al. [6] reported on a double-blind, placebo-controlled study of 405 adult patients with PAH during 16 weeks. They concluded that 40 mg of tadalafil was well tolerated, improved exercise capacity and quality of life measures, and reduced clinical worsening. Based on this study, tadalafil was approved by the Food and Drug Administration for the treatment of adult patients with PAH. However, little is known concerning the use tadalafil for children with PAH. Our objective was to investigate the safety, tolerability, and effects of tadalafil for children with

PAH after transition from sildenafil or after tadalafil received as initial PDE-5i therapy.

Methods

This single-center study was a retrospective cohort investigation using clinical data from patients with PAH after transition from sildenafil or after tadalafil received as initial PDE-5i therapy. We enrolled 33 patients who were started with tadalafil from March 2008 to December 2010 and followed until March 2011 at Children's Hospital Colorado, Denver. Of the 33 patients, 29 were switched from sildenafil to tadalafil. For the remaining four children, tadalafil was the initial PAH therapy or added as initial PDE-5i therapy in combination with other targeted therapy.

All the patients were enrolled in an institutional review board–approved protocol entitled A Prospective Evaluation of Adolescents and Children With Pulmonary Arterial Hypertension. The clinical impact of tadalafil was evaluated by plasma brain natriuretic peptide levels, echocardiography, exercise capacity, cardiac catheterization, and World Health Organization (WHO) functional class before and after initiation of tadalafil.

The two-dimensional echocardiographic data included tricuspid regurgitant jet velocities for estimating right ventricular systolic pressure and right ventricular diastolic diameter. Using right heart catheterization via a flow-directed Swan-Ganz catheter and a systemic arterial line for blood pressure monitoring, we measured mean right atrial pressure, mean pulmonary arterial pressure, mean systemic blood pressure, and pulmonary capillary wedge pressure. Accordingly, we calculated the pulmonary vascular resistance index and the pulmonary vascular resistance-to-systemic vascular resistance ratio.

Cardiac output was obtained using thermodilution, and the cardiac index was calculated. If a significant intracardiac defect remained, cardiac output was obtained by the Fick method using LaFarge estimation. Exercise capacity was assessed by a 6-min walk distance during follow-up assessment. Plasma brain natriuretic peptide was assayed on an i-STAT system using the two-site enzyme-linked immunosorbant assay (Abbott Laboratories, IL, USA).

Safety evaluations included the recording of adverse events, hemodynamic change, and laboratory tests. At each clinic visit, we routinely asked about clinical worsening including chest pain with exercise, dyspnea with exercise, abdominal pain after meals, dizziness, stomach pain, syncope, presyncope, edema in the feet and hands, pallor, and cyanosis. In addition, after initiation of tadalafil therapy, all the patients were asked about side effects of tadalafil such as headache, nasal congestion, flushing, myalgia, and any allergic reaction. Children weighing more than 40 kg were treated with the adult dose. Children weighing 20–40 kg were treated with one half of the adult dose, and children weighing less than 20 kg were treated with one fourth of the adult dose.

All analyses included baseline and at least one post-baseline measure. All results are reported as median and range or mean ± standard deviation together with the 95% confidence interval as appropriate. Comparisons of 6-min walk distance, WHO functional class, natriuretic peptide levels, echocardiographic data, and hemodynamic variables before and after initiation of tadalafil were performed using Student *t* tests when the data had a normal distribution. If data did not show a normal distribution, a non-parametric test was used for analysis (Mann–Whitney *U* test). For evaluating the difference in clinical variables, we chose the last data on sildenafil and the first data on tadalafil. The level of statistical significance was defined as a p value of 0.05. Analyses were conducted using Statmate III for Windows (Atoms Co., Tokyo, Japan).

Results

Table 1 presents the clinical characteristics of the pediatric patients. Among 16 patients with congenital heart disease, 6 patients with significant intracardiac shunts were classified as having Eisenmenger syndrome because of mild to moderate desaturation. Whereas 15 patients received triple vasodilator therapy, 12 patients received double vasodilator therapy including tadalafil. The period for receiving concomitant therapies before initiation of tadalafil therapy was 54.3 ± 21.3 months.

Transition From Sildenafil to Tadalafil

The main reason for changing from sildenafil was once-daily dosing. One patient had an allergic reaction to sildenafil (rash and clitoral swelling) and was trialed with tadalafil but had a similar allergic reaction and tadalafil was discontinued. The mean follow-up period was 52.2 ± 21.8 months for sildenafil and 9.0 ± 7.2 months for tadalafil. The average dose of sildenafil was 3.4 ± 1.1 mg/kg/day and that of tadalafil was 1.0 ± 0.4 mg/kg/day.

Of 29 patients, 14 had catheterization on sildenafil and tadalafil during the follow-up period. The time from the previous catheterization on sildenafil to the last catheterization on sildenafil was 15.2 ± 8.8 months. The time from the initiation of tadalafil to the first catheterization on tadalafil was 7.6 ± 3.4 months. The duration from the last catheterization on sildenafil to the first catheterization on tadalafil was 23.5 ± 8.3 months.

Comparison of the previous catheterization data on sildenafil therapy with the last catheterization data on

Table 1 Patient demographics and clinical measurements

Total no. of patients	33
Transition/initial therapy (*n*)	29/4
Age (years): median (range)	10 (4–18)
Gender (male/female)	11/22
Race (*n*)	Caucasian (14)
	White (11)
	Hispanic (5)
	Asian (2)
	Black (1)
Median weight: kg (IQR)	33.9 (22.2–46.1)
Etiology (*n*)	Congenital heart disease (16)
	Idiopathic (14)
	Connective tissue disease (1)
	Others (2)
Concomitant therapy (*n*)	Treprostinil (13)
	Epoprostenol (3)
	Iloprost (2)
	Ambrisentan (13)
	Bosentan (6)
	Calcium-channel blocker (8)
WHO functional class (*n*)	Class 1 (11)
	Class 2 (13)
	Class 3 (8)
	Class 4 (1)
Median 6-min walking distance: m (range) (28 patients)	512.5 (419.2–559.5)
Median brain natriuretic peptide: pg/ml (range) (31 patients)	37.5 (15.0–607.0)
Echocardiographic data: median (range) (30 patients)	
Tricuspid regurgitation velocity (m/s)	3.9 (3.6–4.5)
Right ventricular diastolic dimension (mm/m^2)	23.5 (12.6–57.1)
Right heart catheterization: median (range) (30 patients)	
Mean right atrial pressure (mmHg)	7 (3–8)
Mean pulmonary arterial pressure (mmHg)	45 (37–58)
Mean systemic arterial pressure (mmHg)	64 (56–71)
Pulmonary vascular resistance index (Units/m^2)	8.3 (6.5–14.0)
Pulmonary/systemic vascular resistance ratio	0.64 (0.48–0.93)
Cardiac index (l/min/m^2)	4.2 (3.3–5.1)

IQR interquartile range, *WHO* World Health Organization

sildenafil showed an increase in mean pulmonary arterial pressure (49.0 ± 14.5 vs. 53.2 ± 18.3 mmHg; $p = 0.06$) and the pulmonary resistance index (9.9 ± 5.8 vs. 12.2 ± 7.0 Units/m^2; $p < 0.05$), as well as an increase in the pulmonary/systemic vascular index ratio (0.66 ± 0.27 vs. 0.89 ± 0.47; $p < 0.05$).

After the transition, statistically significant improvements were observed with tadalafil therapy compared with sildenafil therapy in terms of mean pulmonary arterial pressure (53.2 ± 18.3 vs. 47.4 ± 13.7 mmHg; $p < 0.05$), the pulmonary vascular resistance index (12.2 ± 7.0 vs. 10.6 ± 7.2 Units/m^2; $p < 0.05$), and the pulmonary/systemic vascular resistance ratio (0.89 ± 0.47 vs. 0.75 ± 0.35; $p < 0.05$) during the follow-up period (Fig. 1). No change in sildenafil versus tadalafil was observed in terms of tricuspid regurgitant jet velocity (4.1 ± 0.7 vs. 3.9 ± 0.8 m/s; $n = 21$), right ventricular diastolic dimension (24.5 ± 10.1 vs. 23.6 ± 8.8 mm/m^2; $n = 19$), mean right atrial pressure (6.7 ± 3.6 vs. 6.6 ± 2.4 mmHg; $n = 14$), cardiac index (4.4 ± 1.2 vs. 4.4 ± 1.3 l/min/m^2; $n = 14$), brain natriuretic peptide (102.2 ± 238.3 vs. 100.2 ± 160 pg/ml; $n = 24$), or 6-min walk distance (508.1 ± 102.4 vs. 516.3 ± 90.3 m; $n = 19$) according to the paired *t* test or the Mann–Whitney *U* test. With sildenafil therapy, 11 patients (38%) were class 1 or 2, 6 patients (21%) were class 3, and only 1 patient (3%) was class 4. During the follow-up period, four patients improved in functional class (class 2 to class 1 [$n = 1$], class 3 to class 2 [$n = 3$]), and four patients deteriorated in functional class (class 1 to class 2 [$n = 1$], class 2 to class 3 [$n = 3$]) with tadalafil therapy.

Tadalafil as Initial Therapy

All the patients had idiopathic PAH. Two patients had PAH therapy before initiation of tadalafil (inhaled treprostinil and ambrisentan, ambrisentan and epoprostenol), and two patients had tadalafil as their initial PAH therapy. Although statistical analysis was not performed due to the small number of the patients, tadalafil tended to improve the 6-min walk, tricuspid regurgitant jet velocity, brain natriuretic peptide, mean pulmonary arterial pressure, and the pulmonary vascular resistance index compared with baseline during the follow-up period of 10.5 ± 3.5 months (Table 2).

During the follow-up period of 13.3 ± 13.2 months, two class 3 patients improved to class 1 or 2, and the remaining two class 2 patients did not deteriorate in terms of functional class. None of the four patients changed the concomitant medications or added new vasodilator therapies after initiation of tadalafil.

Adverse Events

Adverse events were assessed at each clinic visit. The number of clinic visits during the first year after initiation of tadalafil was 1.9 ± 1.2. Side effect profiles were similar between the patients receiving sildenafil and those

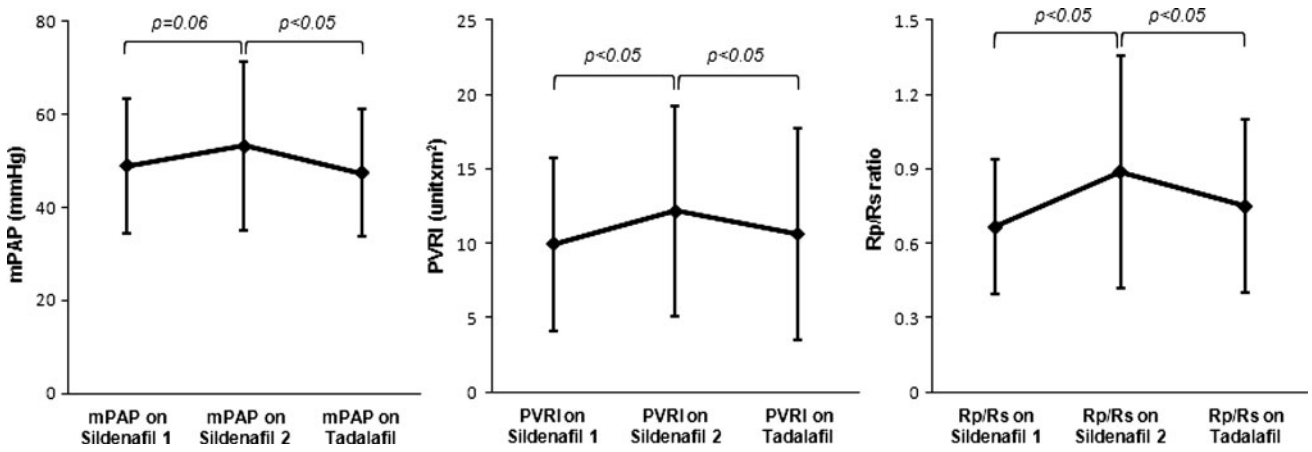

Fig. 1 Hemodynamic improvement after transition from sildenafil to tadalafil for 14 patients on Sildenafil 1; previous catheterization on sildenafil therapy, on Sildenafil 2; last catheterization on sildenafil therapy, on Tadalafil; initial catheterization on tadalafil therapy. For 14 patients, mPAP, PVRI, and the Rp/Rs ratio increased from the previous catheterization (with sildenafil 1) to the last catheterization with sildenafil therapy during the follow-up period of 15.2 ± 8.8 months. After transition to tadalafil, these hemodynamic data significantly improved compared with the last data on sildenafil therapy during the follow-up period of 23.5 ± 8.3 months. *mPAP* mean pulmonary arterial pressure, *PVRI* pulmonary vascular resistance index, *Rp/Rs ratio* pulmonary/systemic vascular resistance ratio with sildenafil

receiving tadalafil (Table 3). Nasal congestion and myalgia were observed after transition, but these were very mild. One patient reported erections as a side effect of sildenafil. He had received 40 mg/day of sildenafil for 3 years. After the sildenafil dose was increased to 60 mg/day, he reported several episodes of erections during the school day. The erections resolved after transition to tadalafil.

Of the 33 patients, 2 discontinued tadalafil due to migraines or allergic reaction. The tadalafil dose for these two patients were respectively 0.4 and 0.6 mg/kg/day, lower than the average tadalafil dose of 1.0 mg/kg/day in our population. Over all, the discontinuation rates were 6%. Three patients receiving sildenafil had episodes of chest pain, which resolved after transition to tadalafil. Only one patient had administration of other PAH drugs due to clinical worsening. This patient was started on subcutaneous treprostinil therapy due to worsening hemodynamic data and exercise intolerance after transition to tadalafil. No patients died or were hospitalized during the follow-up period.

Discussion

We found that orally administered tadalafil as a once-daily-dosing drug was well tolerated by pediatric patients. Most of the patients who switched from sildenafil (average dose, 3.4 ± 1.1 mg/kg/day) to tadalafil (1.0 ± 0.4 mg/kg/day) successfully continued tadalafil therapy without needing to switch back to sildenafil. Only two patients stopped tadalafil due to side effects including migraine and allergic reaction. Thus, the discontinuation rate for tadalafil therapy in the children was 6%.

Despite concomitant therapy, tadalafil statistically improved hemodynamic data including mean pulmonary arterial pressure, the pulmonary vascular resistance index, and the pulmonary-systemic vascular resistance ratio compared with sildenafil used for 14 of 29 patients who had repeated catheterization. Importantly, the clinical benefits of sildenafil were maintained in terms of echocardiographic data, brain natriuretic peptide level, 6-min walk distance, and WHO functional class after transition to tadalafil. There were no deaths during the short-term follow-up period.

The current study is helpful in guiding tadalafil therapy for pediatric patients with PAH because it suggests the safe use of tadalafil for these pediatric patients. In addition, disease progression was rare during the follow-up period with tadalafil. Recently, tadalafil has been approved in the United States for the treatment of adults with group 1 PAH [3]. In a large previous study, oral tadalafil at 40 mg once daily was effective in improving exercise capacity even for adult PAH patients receiving bosentan as background therapy [6].

Tadalafil has shown beneficial effects in a prospective cohort study involving patients with Eisenmenger syndrome [12]. Despite several recent reports on the use of tadalafil therapy, tadalafil is not approved to date for pediatric patients. The current report is the first to describe the clinical benefits and safety for a dedicated cohort of pediatric patients with PAH. Currently, no established dosing of sildenafil or tadalafil exists for pediatric patients

Table 2 Clinical profile of four patients treated with tadalafil as initial therapy with phosphodiesterase type 5 inhibitors (PDE-5i)

Case	Age (years)	Diagnosis	6 MWD (m)		WHO functional class		TR velocity (m/s)		BNP (pg/ml)		mPAP (mmHg)		PVRI (Units/m^2)	
			Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
1	5	IPAH			3	2	4.5	3.2	1,289	66	76		16.7	
2	8	IPAH			3	1	3.6	2.9	163	124	58		14.4	
3	8	IPAH	413	555	2	2	3.9	4.0	20	15	27	28	3.1	4.3
4	16	IPAH	581	652	2	2	3.9	3.1	46	15	38		8.2	
Mean ± SD			497 ± 118.8	603 ± 68.6	2.5 ± 0.6	1.5 ± 0.6	4.0 ± 0.4	3.3 ± 0.5	380 ± 609.5	55 ± 51.9	50 ± 21.7	28	11 ± 6.2	4.3

6 MWD 6-min walking distance, *WHO* World Health Organization, *TR* tricuspid regurgitation, *BNP* brain natriuretic peptide, *mPAP* mean pulmonary arterial pressure, *PVRI* pulmonary vascular resistance index, *IPAH* idiopathic pulmonary arterial hypertension, *SD* standard deviation

Table 3 Adverse events for 29 patients receiving sildenafil and tadalafil

	Sildenafil *n* (%)	Tadalafil *n* (%)
Symptoms due to PAH		
Fatigue	7 (24)	6 (21)
Chest pain	3 (10)	0 (0)
Dyspnea	1 (3)	1 (3)
Syncope	1 (3)	0 (0)
Side effects		
Headache[a]	4 (21)	4 (21)
Nausea	2 (7)	2 (7)
Flushing	1 (3)	1 (3)
Myalgia	0 (0)	1 (3)
Nasal congestion	0 (0)	1 (3)
Others	Erection 1 Clitoral and facial swelling 1	Clitoral and facial swelling 1

PAH pulmonary arterial hypertension

[a] Including migraine

with PAH. We extrapolated the pediatric dose for this study from adult studies. Although the tadalafil doses were empiric, they appeared to be safe and effective. Our study provides important information on the usefulness of oral tadalafil therapy as an additional targeted therapy for pediatric PAH.

The reasons for the hemodynamic improvement after transition to tadalafil from sildenafil are not clear, but it may be caused by differences in pharmacokinetics. Unlike sildenafil, the longer half-life of tadalafil makes serum levels more consistent [13], which may have an advantage with regard to hemodynamics in patients with PAH. In addition, sildenafil therapy may have a risk for worse compliance due to multiple daily dosing. Our results provide initial data showing that pediatric patients may switch from sildenafil to tadalafil as a once-daily-dosing drug with a tolerable safety profile.

The limitations of the current study were the small sample size and the relatively short observational duration. Due to the small number of patients, we could not assess the efficacy of tadalafil as initial therapy in the pediatric population. Therefore, the clinical findings for tadalafil administered to children remain to be confirmed in a larger study.

A further limitation also may have been the relative heterogeneity of the study population. However, most pediatric PAH studies are composed of children with idiopathic PAH and PAH associated with congenital heart disease. Thus, a larger study involving PAH patients is needed to determine whether the results we observed for children with PAH are generalizable to the larger pediatric

population. Finally, we did not perform a pharmacokinetic analysis, which should be performed in future studies.

Conclusions

The convenience of once-daily dosing prompted the transition from sildenafil to tadalafil for pediatric patients. Tadalafil can be safely used for pediatric patients with PAH and may prevent disease progression.

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