Transition from intravenous epoprostenol to oral or subcutaneous therapy in pulmonary arterial hypertension: A retrospective case series and systematic literature review

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BACKGROUND: Intravenous epoprostenol, a prostaglandin analogue, has been a mainstay of therapy for patients with advanced pulmonary arterial hypertension (PAH) since the early 1990s. This medication has multiple side effects, and sudden discontinuation is potentially associated with severe sequelae. Several recent case series have described the transition from intravenous to newer oral or subcutaneous therapies. A case series detailing the authors' experience with such transitions, and a systematic literature review is presented.

METHODS: All consecutive PAH patients seen at the Vancouver Pulmonary Hypertension Clinic (Vancouver, British Columbia) between June 1995 and July 2009 were reviewed for cases in which weaning or transition from intravenous epoprostenol was attempted. The Cochrane Collaboration, Cochrane Register of Controlled Trials, Journals@Ovid, MEDLINE, EMBASE and Papers First were searched using predefined key words for publications describing transition of PAH patients from parenteral prostanoids to oral or subcutaneous agents.

RESULTS: Of the six patients who attempted, all transitioned successfully to oral or subcutaneous agents, having been on intravenous epoprostenol for a mean of 3.8 years (range 1.8 to 9.75 years). Five are living, surviving a mean of 5.5 years after transition. The literature search yielded nine studies and, of 127 patients described, 82 transitioned successfully. The length of pretransition prostanoid treatment (range 1.7 to 7.6 years) and the post-transition follow-up period (range two months to 70 months) were shorter than for patients described in the present study.

CONCLUSIONS: Given the rarity of PAH, the absolute numbers of patients transitioned from intravenous epoprostenol are still low. With the advent of new therapies, these numbers will hopefully increase; continued study is necessary to identify factors that are predictive of success.

Key Words: *Epoprostenol; Pulmonary hypertension; Transition*

Pulmonary hypertension is defined as a mean pulmonary arterial pressure of greater than 25 mmHg at rest (1). Pulmonary arterial hypertension (PAH) is characterized by an increased pulmonary vascular resistance (greater than $250 \text{ dyn} \cdot \text{cm}^{-5}$), with a pulmonary capillary wedge pressure of lower than 15 mmHg. PAH can be idiopathic, heritable or develop in association with other conditions (2). The underlying pathogenesis is believed to be abnormal vasoconstriction coupled with remodelling of small pulmonary arteries, leading to elevated vascular resistance (3,4).

There is currently no cure for PAH and, untreated, it is associated with a poor prognosis (5,6). In the early 1990s, epoprostenol, a prostaglandin analogue, was approved for treatment of patients with severe disease (7). After it was shown to improve hemodynamics, exercise tolerance and survival, epoprostenol represented a breakthrough in the

La transition de l'époprosthénol par voie intraveineuse vers la thérapie orale ou sous-cutanée en cas d'hypertension pulmonaire artérielle : une série rétrospective de cas et une analyse bibliographique

HISTORIQUE : Depuis le début des années 1990, l'époprosthénol par voie intraveineuse, un analogue de la prostaglandine, est le traitement normal auprès des patients atteints d'hypertension artérielle pulmonaire (HAP) avancée. Ce médicament s'associe à de nombreux effets secondaires, et un arrêt soudain peut s'associer à de graves séquelles. Plusieurs études de cas récentes portent sur la transition entre les traitements intraveineux et les traitements oraux ou sous-cutanés, plus récents. Une étude de cas détaille l'expérience de ces transitions par les auteurs, et une analyse bibliographique systématique est présentée.

MÉTHODOLOGIE : Les auteurs ont analysé les dossiers de tous les patients consécutifs atteints d'HAP vus à la clinique d'hypertension pulmonaire de Vancouver (à Vancouver, en Colombie-Britannique) entre juin 1995 et juillet 2009 pour déterminer les cas qui avaient fait l'objet d'une tentative de sevrage ou de transition de l'époprosthénol par voie intraveineuse. Ils ont effectué des recherches dans Collaboration Cochrane, le registre Cochrane d'essais cliniques, Journals@Ovid, MEDLINE, EMBASE et Papers First au moyen de mots-clés prédéfinis pour les publications décrivant la transition des patients atteints d'HAP des prostanoides par voie parentérale aux agents par voie orale ou sous-cutanée.

RÉSULTATS : Sur les six patients qui l'ont tentée, tous ont réussi la transition vers les agents par voie orale ou sous-cutanée, après avoir pris de l'époprosthénol par voie intraveineuse pendant une moyenne de 3,8 ans (plage de 1,8 à 9,75 ans). Cinq sont vivants, ayant survécu une moyenne de 5,5 ans après la transition. L'analyse bibliographique a permis d'extraire neuf études, et des 127 patients décrits, 82 ont réussi la transition. La durée du traitement au prostanoides avant la transition (plage de 1,7 à 7,6 ans) et de la période de suivi après la transition (plage de deux à 70 mois) était plus courte que celle des patients décrits dans la présente étude.

CONCLUSIONS : Compte tenu de la rareté de l'HAP, les chiffres absolus de patients qui font la transition de l'époprosthénol par voie intraveineuse demeurent faibles. Avec l'arrivée de nouveaux médicaments, on espère que ces chiffres augmenteront. La poursuite des études s'impose pour établir les facteurs prédictifs d'une transition réussie.

treatment of PAH (8); however, its use presents many challenges. It must be administered continuously through a central line (9), placing patients at increased risk of infection (10). Side effects include jaw pain, hypotension and flushing; severe rebound pulmonary hypertension can occur if the infusion is abruptly stopped (7). Thus, although epoprostenol can represent life-saving therapy, it is not without risks (11).

Two additional classes of oral medications for PAH – endothelin receptor antagonists and phosphodiesterase inhibitors – have been approved in the past decade. More recently, a subcutaneous form of prostanoid therapy (treprostinil) has also become available and, although it still requires continuous infusion via a portable pump, it circumvents the need for an indwelling venous catheter (12,13). With the development of these therapies, the concept of transitioning patients from intravenous (IV) to oral or subcutaneous agents has emerged.

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TABLE 1
Baseline characteristics of patients who were transitioned from intravenous epoprostenol to oral or subcutaneous therapy

Patient	Etiology of PH	WHO class at presentation	Pressure, mmHg		PVR [†] , dyn·s·cm ⁻⁵	Cardiac output [†] , L/min	PCWP, [†] mmHg
			Pulmonary artery* [†]	Right atrial [†]			
1	Idiopathic	3	82/36/55	Not reported	1086.0	3.4	8.3
2	Idiopathic	4	88/32/57	12	1461.5	2.9	Not reported
3	Idiopathic	3	75/35/50	6	1266.7	2.4	12
4	SLE	3	69/39/49	Not reported	697.3	1.5	27–30
5	SLE	2	100/54/68	1	1180.0	2.5	4
6	Idiopathic	3	54/38/45	17	Not reported	2.8	10

*Pressures presented as systolic/diastolic/mean; [†]Measured by right heart catheterization. PCWP Pulmonary capillary wedge pressure; PH Pulmonary hypertension; PVR Pulmonary vascular resistance; SLE Systemic lupus erythematosus

TABLE 2
Characteristics of patients before and after transition from epoprostenol

Patient	Duration of epoprostenol treatment	Dose of epoprostenol before transition, ng/kg/min	WHO class at time of transition	Transition to	Reason for transition	WHO class after transition*	RVSP after transition [†] , mmHg	Most recent 6MWT [‡] , m	Survival after transition to July 2009 [§]
1	9.75 years	31	1	Bosentan [¶]	Recurrent line infections in context of stable RVSP	1	40	479	4.5 years
2	2.1 years	20	1	Sildenafil**	Jaw pain, flushing, patient preference	1	78	444	1.6 years
3	2.8 years	9.5	2	Bosentan ^{††}	Recurrent line infections, remote location	1 to 2	95	125	4.4 years
4	1.8 years	27	2	Treprostinil + bosentan ^{††}	Patient preference in context of clinical stability	1	82	457	4.2 years
5	3.5 years	20	1	Treprostinil	Central venous thrombosis	2	68	555	3.1 years
6	2 years	N/A	1	Amlodipine	Patient preference in context of clinical stability	1	N/A	N/A	13 years

*First documented measurement after transition (3 days to 18 months post-transition); [†]Measured by echocardiogram one to six months after epoprostenol discontinuation; [‡]Measured one to six months after transition (except patient 4, at 18 months); [§]Patient 5 deceased from accidental cause, all other patients were alive at July 2009; [¶]Later switched to sildenafil due to elevated transaminase levels; **Bosentan subsequently added; ^{††}Treprostinil added nine months later; ^{‡‡}After four years, sildenafil added and remodulin discontinued due to intolerable site pain. 6MWT 6 min walk test; N/A Data not available; RVSP Right ventricular systolic pressure

Although there have been several reports of such attempts (14–19), the indications and long-term outcomes of this practice have not been fully characterized (20). The present retrospective case series reviews the experience of our centre in transitioning patients from IV therapy, highlights the rationale for doing so and the outcomes attained. We also present a systematic literature review describing the transition of PAH patients from IV to oral or subcutaneous therapies.

METHODS

Following institutional research ethics board approval, the charts of all consecutive patients seen at the Vancouver Pulmonary Hypertension Clinic (Vancouver, British Columbia) between June 1995 and July 2009 were reviewed. All cases in which weaning from IV therapy or transition to subcutaneous or oral therapy was attempted were identified. The catchment area of the Vancouver clinic includes the province of British Columbia, population 4.1 million (21).

To identify publications describing the transition of PAH patients from parenteral prostanoids to oral or subcutaneous agents, a literature search was performed by two independent reviewers (JS and KP). The following databases were searched from inception to May 16, 2010: CDSR, ACP Journal Club, DARE, CCTR, CLCMR, CLHTA, CLEED, Journals@Ovid, Ovid MedLine(R), Embase and Papers First. The following search terms were used: pulmonary hypertension, epoprostenol, Flolan, treprostinil, remodulin, bosentan, Tracleer, sildenafil, Viagra, endothelin receptor antagonist, prostanoid, phosphodiesterase inhibitor, transition and weaning. Studies not published in English were excluded. Studies involving transition to inhaled prostacyclin, or from one IV prostanoid to another, those involving short-term epoprostenol infusion or studies that were published only in abstract form were also excluded.

RESULTS

Case 1

In 1995, a 53-year-old woman with idiopathic PAH presented with a five-year history of progressive exertional dyspnea. She was WHO functional class 3 (22). She previously underwent cardiac catheterization, which revealed normal coronary arteries and a pulmonary artery systolic pressure of 104 mmHg. A vasodilator challenge and measurement of other cardiac parameters had not been performed. IV epoprostenol was initiated at the Vancouver Pulmonary Hypertension Clinic, and her functional capacity improved to WHO class 1. Right heart catheterization six months later showed a pulmonary arterial pressure of 82/36 mmHg (mean 55 mmHg) and pulmonary vascular resistance of 1086.0 dyn·s·cm⁻⁵ (Table 1).

Her functional class and right ventricular systolic pressure (RVSP) (measured by echocardiography) remained stable with gradual titration of epoprostenol to 31 ng/kg/min. After being on epoprostenol for eight years and, in light of clinical stability, repeated line infections and limitations in central venous access, transition from epoprostenol to bosentan was attempted. This decision was initiated by her physician, with strong patient endorsement.

Bosentan 62.5 mg twice/day was given orally for four weeks, then increased to 125 mg orally twice/day, without changing the epoprostenol dose. After four months, her RVSP remained stable; however, she experienced side effects related to epoprostenol. The infusion was decreased by 1 ng/kg/week and stopped six months later, at which time she remained WHO class 1 (Table 2).

She remained stable on oral bosentan 125 mg twice/day for more than three years. Elevated transaminase levels then necessitated switching to oral sildenafil 50 mg three times/day. Her liver enzyme

levels normalized. Thirteen years after initial presentation, she remains WHO class 1 on sildenafil, with no signs of right heart failure, although serial echocardiograms demonstrated a gradual increase in her RVSP to 77 mmHg. She declines restarting epoprostenol.

Case 2

In 2005, a 34-year-old woman with idiopathic PAH presented with a four-month history of progressive exertional dyspnea. She was WHO class 4. Right heart catheterization revealed a pulmonary artery pressure of 88/32 mmHg (mean 57 mmHg) and her pulmonary vascular resistance was $1461.5 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ (Table 1). There was no response to nitric oxide. She was started on IV epoprostenol, and improved to WHO class 1 with gradual titration to 20 ng/kg/min.

Eighteen months later, she remained WHO class 1. Her RVSP remained stable. Due to the side effects from epoprostenol, the patient desired to attempt transition to oral agents. Her physician agreed and oral sildenafil 25 mg three times/day was started. Epoprostenol was decreased by 1 ng/kg/week until 2 ng/kg/min was reached. After four months, oral bosentan was added at 62.5 mg twice/day for one month and subsequently increased to 125 mg orally twice/day. Her epoprostenol was discontinued two months later, at which time her RVSP remained stable (Table 2). After being on oral agents for more than one year, she remains WHO class 1.

Case 3

In 1999, a previously healthy, 59-year-old woman presented with rapidly progressive dyspnea over several weeks. Her RVSP was 70 mmHg. She was initially believed to have thromboembolic disease, and was treated with anticoagulation. She was first assessed at the Vancouver Pulmonary Hypertension Clinic one year later when she was WHO class 3, with an RVSP of 78 mmHg. Right heart catheterization showed a pulmonary arterial pressure of 75/35 mmHg (mean 50 mmHg) (Table 1), with a pulmonary vascular resistance of $1266.7 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$ and no response to nitric oxide. Extensive workup for secondary causes of pulmonary hypertension was negative. She was reclassified as idiopathic PAH and started on IV epoprostenol.

Within three months, her WHO functional class improved to class 1 on a dose of 11 ng/kg/min. Over the next two years, her functional class and RVSP remained stable. Given that she lived remotely and had experienced several line infections, a joint decision was reached between the patient and her physician to attempt transition to oral agents. Oral bosentan 62.5 mg twice/day was started, and was increased to 125 mg orally twice/day after four weeks. Epoprostenol was then weaned by 1 ng/kg/min each week over three months until discontinuation; her WHO functional class remained 1 to 2 (Table 2).

Unfortunately, she deteriorated over the next year to WHO class 3. She was admitted to hospital for initiation of subcutaneous treprostinil. She was discharged on 6.25 ng/kg/min and continued oral bosentan 125 mg twice/day. Her RVSP was 54 mmHg.

Six months later, an echocardiogram performed at an outside institution showed that her RVSP had risen to 95 mmHg; it remains at this level after two years of treprostinil therapy. She is WHO class 3.

Case 4

A 32-year-old woman with pulmonary hypertension secondary to systemic lupus erythematosus presented with dyspnea in 1999. RVSP by echocardiogram (performed at an outside hospital) was 59 mmHg. There were no other pulmonary manifestations of lupus. She was initially treated with oral verapamil 180 mg once/day. Two years later, she had progressed to WHO class 3. Right heart catheterization showed a pulmonary arterial pressure of 69/39 mmHg (mean 48.9 mmHg) (Table 1). Pulmonary vascular resistance was $697.3 \text{ dyn}\cdot\text{s}\cdot\text{cm}^{-5}$, with no response to nitric oxide.

She was started on bosentan, and within three months had improved to WHO class 1. After one year, she was again WHO class 4 and her RVSP had worsened to 98 mmHg. IV epoprostenol was started and bosentan was continued. Eighteen months later, her functional class had improved to WHO 3 and her RVSP was stable. The patient

desired to switch to subcutaneous treprostinil because she found the pump to be more convenient and because central venous access was not required. Her physician agreed to the attempt.

She was admitted to hospital, and epoprostenol was gradually weaned and treprostinil gradually increased over two days. She tolerated the transition well and was discharged on treprostinil 13 ng/kg/min and oral bosentan 125 mg twice/day (Table 2).

After 18 months of treprostinil therapy, she had improved to WHO class 1, with RVSP stable at 90 mmHg. Over the next two-and-a-half years, she remained clinically stable, but experienced severe site pain. After four years of treprostinil therapy, she was started on oral sildenafil 25 mg three times/day; bosentan was continued and treprostinil was discontinued. She remains on the oral agents and declines parenteral prostanooids. Her most recent echocardiogram showed an RVSP of 98 mmHg. Her lupus is quiescent.

Case 5

In 1998, a 20-year-old woman with pulmonary hypertension secondary to systemic lupus erythematosus presented with exertional dyspnea and presyncope. Her RVSP was 54 mmHg. There were no other pulmonary manifestations of lupus. She was evaluated at the Vancouver Pulmonary Hypertension Clinic three months later, at which time she was WHO class 2. She was subsequently lost to follow-up for 18 months and her function deteriorated to class 4. Right heart catheterization was then performed, showing a pulmonary arterial pressure of 100/54 mmHg (mean 69 mmHg) and a pulmonary vascular resistance of $1180.0 \text{ dyne}\cdot\text{sec}\cdot\text{cm}^{-5}$ (Table 1). There was no response to nitric oxide. She was started on IV epoprostenol, and her functional class improved to WHO 1 within two months.

She remained clinically stable on epoprostenol, with doses of between 15 ng/kg/min and 22 ng/kg/min. After 3.5 years, she was found to have extensive central venous thrombosis. With concern surrounding venous access, she was transitioned to subcutaneous treprostinil (Table 2). This was performed in hospital over three days, with the epoprostenol being gradually decreased and treprostinil concomitantly increased.

Unfortunately, this patient experienced significant site pain from treprostinil, and could not tolerate doses above 15 ng/kg/min. Bosentan was avoided because of elevated transaminase levels (secondary to autoimmune hepatitis). Oral sildenafil 25 mg three times/day was added, enabling a slight reduction in treprostinil dose. She continued to experience significant pain. Her functional class varied between WHO class 2 and 3, with an RVSP of 65 mmHg. She died from a cause unrelated to PAH the following year.

Case 6

In 1992, a 24-year-old man presented with exertional dyspnea and syncope, and was diagnosed with idiopathic PAH. Right heart catheterization showed a pulmonary arterial pressure of 54/38 mmHg (mean 45 mmHg). A nitric oxide challenge was not documented. He was treated with IV epoprostenol for two years at an experienced outside pulmonary hypertension centre, after which time his pulmonary pressures had normalized, and he was WHO class 1.

Because of his stable functional status and right ventricular function, the possibility of weaning the epoprostenol was considered by both the patient and physician. He discontinued the medication independently; he was subsequently treated with oral amlodipine 5 mg twice/day (Table 2). He was well for six years when exertional dyspnea recurred. He was then assessed at the Vancouver Pulmonary Hypertension Clinic, where his RVSP was estimated to be 43 mmHg. He has remained on amlodipine; his most recent echocardiogram showed an RVSP 51 mmHg. He is WHO class 1.

SYSTEMATIC LITERATURE REVIEW

Our initial database search yielded 420 citations. A review of titles and abstracts excluded 405 citations that did not fulfill the inclusion criteria. Fifteen publications were extracted for full review. Nine articles contained relevant information and were included in the final evaluation.

TABLE 3
Characteristics of patients reported to date who have attempted transition from parenteral prostanoids to oral or subcutaneous therapy

Author (reference), year	Attempted, n (number successful)	Etiology of PH*	Medications*	Reason for attempt*	Functional class before transition	Mean duration of prostanoid before transition, years	Mean duration of follow-up, months	Reason for failure
Vachieri et al (26), 2002	8 (8)	PPH (4), PPH/HIV (1), VSD/PDA(1), portal hypertension (1), CTD (1)	IV epoprostenol → SC treprostinil	Life-threatening complications of IV epoprostenol (sepsis [5], recurrent syncope [1], cerebral emboli with hemiplegia [1], headache [1])	NYHA III–IV	2.2	4 to 11 [†]	N/A
Kim et al (19), 2003	4 (4)	PPH (3), scleroderma (1)	IV epoprostenol → PO nifedipine (1); bosentan/diltiazem/sildenafil (1); bosentan/nifedipine (1); bosentan (1)	Catheter-related infections (1), decreased pulmonary artery pressure (4), side effects of epoprostenol (1)	WHO 1–2	5.7	11	N/A
Ivy et al (17), 2004	8 (3)	Idiopathic (8)	IV epoprostenol → PO bosentan	Side effects of epoprostenol (8)	WHO 2–3	7.6	24	Increasing PH; elevated liver enzymes
Suleman and Frost (18), 2004	23 [‡] (9 [§])	PPH (15), CVD (7), ASD (1)	IV epoprostenol (17) or IV/SC treprostinil [¶] (6) → PO bosentan	Patent preference in context of clinical stability (23)	WHO 2–3	3.1	9.6	Clinical deterioration; elevated liver enzymes
Steiner et al (16), 2006	22 ^{**} (7 ^{††})	Idiopathic (13), CTD (5), sarcoidosis (2), HIV (1), FPAH (1)	IV epoprostenol (17) or SC treprostinil (5) → PO bosentan	Patient preference in context of clinical stability (22)	WHO 2–3	3.2	17.7	Exertional dyspnea; PH symptoms
Johnson et al (15), 2007	13 (13 ^{‡‡})	Idiopathic (7), SLE (3), HIV (1), CHD (1), FPAH (1)	IV epoprostenol → PO bosentan (11), sildenafil (2), amlodipine (1)	Improved to WHO 1–2 (13) and decreased PAP (7), line infection (2), subclavian vein thrombosis (1), difficulty managing infusion system due to dementia (1)	WHO 1–2	3.8	29.9	Worsening functional class
Keogh et al (23), 2007	14 (10)	Idiopathic (7), thromboembolic disease (3), scleroderma (2), postsurgical reparation VSD (2)	SC treprostinil → PO sildenafil	Patient preference due to injection site pain (14)	NYHA III–IV	1.7	3	Clinical deterioration
Rubenfire et al (25), 2007	14 (13)	Idiopathic (10), scleroderma (2), portopulmonary hypertension (1), congenital systemic-to-pulmonary shunt (1)	IV epoprostenol → SC treprostinil	Clinical stability; randomized, controlled trial (14)	WHO 2–3	3.2	2	Clinical deterioration (syncopal event)
Diaz-Guzman et al (14), 2008	21 (15)	Idiopathic (6), SLE (5), portopulmonary (2), CHD (2), scleroderma (1), HIV (1), familial (1), sarcoidosis (1), appetite suppressant (1), CTEPH (1)	IV eprostenol (17), IV treprostinil (2), SC treprostinil (2) → PO bosentan (7), sildenafil (3), both (5)	Clinical stability (21) plus: intolerable side effects (7), severe site pain (1), thrombocytopenia (1), recurrent line infection (2), patient preference (10)	WHO 2–3	2	26.2	Clinical deterioration

*Parentheses indicate number of patients; [†]No mean value reported, therefore range quoted; [‡]Seventeen patients on intravenous epoprostenol, six on subcutaneous (SC) treprostinil. [§]Four other patients transitioned successfully but experienced failure at seven weeks to 12 months due to progressive symptoms of pulmonary hypertension. Two patients developed liver enzyme abnormalities necessitating change back to parenteral medication. Subsequent five-year follow-up of 11 patients who were initially successfully transitioned (mean follow-up 70 months) (24) showed that seven patients had required resumption of prostanoids due to clinical deterioration; [¶]Not specified by authors whether treprostinil was administered intravenous (IV) or SC; ^{**}Seventeen patients on intravenous epoprostenol, five on subcutaneous treprostinil; ^{††}Three other patients transitioned successfully but required reinstitution of prostacyclin at two, six and 12 months (two of these patients subsequently died); ^{‡‡}Four patients suffered late failure (14 to 38 months off epoprostenol), three required re-institution of epoprostenol or iloprost, and one died of causes unrelated to right heart dysfunction. ASD Atrial septal defect; CHD Congenital heart disease; CTD Connective tissue disease; CTEPH Chronic thromboembolic pulmonary hypertension; CVD Collagen vascular disease; FPAH Familial pulmonary artery hypertension; HIV Human immunodeficiency virus; N/A Not applicable because all patients were successful; NYHA New York Heart Association; PAP Pulmonary arterial pressure; PDA Patent ductus arteriosus; PH Pulmonary hypertension; PO Per oral; PPH Primary pulmonary hypertension; SLE Systemic lupus erythematosus; VSD Ventricular septal defect

Eight studies described transition from parenteral to oral therapies (14,19,23), and two described transition to subcutaneous therapies (25,26) (Table 3). A 10th study (24) revisited outcomes from a subset of patients in one of the original studies (18) but was not included in the analysis (Table 3 legend).

Reasons for transition to oral agents included sepsis, line infections (14,15,26), side effects of epoprostenol (14,17), difficult venous access (15) and patient preference (14,16,18). For transition from subcutaneous treprostinil, injection site pain was also cited (14,23). Time for transition from parenteral to oral agents ranged from four weeks (23) to one year (16).

DISCUSSION

We described six patients with PAH who successfully transitioned off of IV epoprostenol. Reasons for transition included recurrent line infections, medication side effects, compromised central access and patient preference in the context of clinical stability (Table 2). These were similar to the reasons that were cited in the literature.

Four of our patients have transitioned to oral agents, and have survived epoprostenol free for between four months and 13 years. This is longer than the mean follow-up period reported in the literature, which varied between eight weeks (25) and 70 months (15).

Although each case was unique, our patients had oral agents initiated for a period of at least one month before a reduction in parenteral prostanoïd dosing, which was then performed gradually over a period of up to six months, noting that the timeframe for dose reduction for the patient described in Case 6 was not available.

Where specified in the literature, oral agents were similarly initiated for at least four weeks before reduction in epoprostenol dose (16,18). In studies that specified rates, epoprostenol was downtitrated from between 1 ng/kg/week and 2 ng/kg/week (14,15,17), to between 1 ng/kg/min and 2 ng/kg/min every day or alternate day (16,18). In the two studies involving transition from treprostinil to oral agents (14,23), patients were either on oral agents for at least two months before treprostinil dose reduction (14) or started on sildenafil after treprostinil had been weaned to one-half dose (23).

Two previous studies reported transition from IV to subcutaneous prostanoïds. Vachieri et al (26) described eight patients who were successful, with a follow-up period of between four and 11 months. Rubenfire et al (25) performed a randomized placebo-controlled trial in which patients on IV epoprostenol were transitioned to subcutaneous treprostinil or placebo. Thirteen of 14 patients who were withdrawn from treprostinil did so without clinical deterioration when followed for eight weeks.

Two of our patients switched from IV to subcutaneous agents, with initiation performed in hospital for both over periods of days. This was similar to the series by Vachieri et al (26) in which patients were transitioned in hospital over 21 h to 96 h, and Rubenfire et al (25) who reported a mean transition period of seven days.

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Factors predictive of successful transition from epoprostenol are not well established. Ivy et al (17) noted that children who had been on epoprostenol longer were able to tolerate greater dose reductions when given bosentan. Kim et al (19) described two nonvasoreactive patients who became vasodilator responsive after several years of epoprostenol treatment. One of our patients (Case 1) successfully transitioned to oral medication after almost a decade of IV epoprostenol. Whether long-term epoprostenol treatment is beneficial before transition to oral or subcutaneous therapy remains unclear. Suleman and Frost (18) noted the opposite, with trends toward patients with longer duration of parenteral prostacyclin failing transition, although these patients also tended to exhibit higher pretransition pulmonary arterial pressures. Steiner et al (16) found that lower baseline RVSP was associated with more successful transition to bosentan. Finally, Diaz-Guzman et al (14) did not find pulmonary hemodynamics at diagnosis to be predictive of transition success.

Quality of life frequently played a role in decisions to transition. One study demonstrated improved quality-of-life scores in patients transitioned from subcutaneous treprostinil to oral sildenafil (23). In support of this, two of our patients refused to resume parenteral therapy, even when faced with the possibility of worsening disease.

CONCLUSION

We described six patients with PAH who successfully transitioned from IV prostanoïds to oral and/or subcutaneous agents. With the advent of new therapies, reports of such transitions are increasing. However, pulmonary hypertension is rare and absolute numbers are small. As our understanding increases, factors predictive of suitability for transition will hopefully become more evident.

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