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# Long-term experience after transition from parenteral prostanoids to oral agents in patients with pulmonary hypertension

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## KEYWORDS

Pulmonary hypertension;  
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Transitioning;  
Bosentan;  
Sildenafil

## Summary

**Background:** Long-term follow-up after transition to oral agents from parenteral prostanoid therapy has not been well characterized.

**Methods:** We reviewed our long-term experience after oral transitioning in patients with pulmonary hypertension. Patients were weaned off parenteral therapy based on a pre-determined outpatient protocol. Data were collected retrospectively after transition had taken place.

**Results:** Twenty-one transitioned patients were identified. Fifteen patients (71.4%) were successfully transitioned (ST): 7 to bosentan, 5 to bosentan and sildenafil, and 3 to sildenafil. Six patients failed transition (FT). None of the patients in the FT group received sildenafil. Prior to transition attempt, patients in the ST group were treated with parenteral agents for a mean of 26 months vs. 16 months in the FT group ( $p = 0.12$ ). Maximal epoprostenol dose was low in both groups (ST 17.8 ng/kg/min vs. FT 14.5 ng/kg/min). Mean duration of oral therapy prior to transition was 11 months. After a mean follow-up of 24 months, most patients on both groups were able to maintain stable 6 min walk distance and hemodynamics. FT was not associated with short- or long-term adverse events.

**Conclusions:** Oral transition from parenteral prostanoid agents can be safely done in a selected group of patients. Most patients are able to maintain stable functional class and hemodynamics at long follow up regardless of success of transition attempt. Combination

**Abbreviations:** 6MWD, 6-min walk distance; 6MWT, 6-min walk test; BNP, type-B natriuretic peptide; CI, cardiac index; CO, cardiac output; FT, failed transition; PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; PGI<sub>2</sub>, parenteral prostanoid agents; RVSP, right ventricular systolic pressure; ST, successful transition; WHO, World Health Organization.

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therapy with sildenafil appears to be associated with higher likelihood of successful transitioning.

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## Introduction

Pulmonary arterial hypertension (PAH) is a disease characterized by progressive pulmonary vasculopathy that results in right heart failure and death.<sup>1</sup> Patients with severe pulmonary hypertension (PH) and poor functional class (World Health Organization [WHO] class III and IV) are considered candidates for treatment with parenteral prostanoid agents (PGI<sub>2</sub>). Although parenteral therapy has been shown to improve hemodynamics and survival in patients with severe PAH,<sup>2</sup> treatment with these agents poses numerous challenges including an elevated cost, the need for central venous access, risk of thrombosis and infections, and several common adverse drug effects.<sup>3,4</sup> Moreover, drug interruption can result in unfavorable outcomes such as need for hospitalization or even death.<sup>5</sup>

The development of oral agents such as the endothelin receptor antagonists and phosphodiesterase inhibitors, offers new treatment options. Physicians currently face the challenge of determining if some patients on intravenous therapy can be safely transitioned to oral medications. Previous reports have shown that epoprostenol can be transitioned to oral therapy in carefully selected patients and that some patients discontinuing PGI<sub>2</sub> may exhibit clinical and hemodynamic stability after short- and medium-term follow up.<sup>6–8</sup> Despite these promising reports, there is lack of understanding about the factors that would predict a successful transition to oral agents and there are no guidelines to safely direct this process. Attempts at transition remain guided by scant literature especially as it relates to long-term outcomes after transition.<sup>9,10</sup> In addition, little is known about the risks of an unsuccessful transition and if this is associated with worse outcomes. Our report is an attempt to further investigate these unanswered questions.

## Methods

The study was approved by our Institutional Review Board. We performed a retrospective chart review to identify patients in whom an attempt was made to wean off PGI<sub>2</sub> with the addition of oral therapy. Transition from PGI<sub>2</sub> was attempted only in patients who were clinically stable (WHO class I–III, no evidence of overt right heart failure (exertional syncope, worsening lower extremity edema, jugular venous distension, hepatomegaly), stable 6-min walk distance (6MWD), and stable dose of PGI<sub>2</sub> for the preceding month) and was based on patient's preference for oral therapy, or severe or recurrent delivery device complications such as catheter-related infections or severe infusion site pain.

Prostanoid analogs were weaned according to an outpatient weaning protocol (epoprostenol 3 ng/kg/min per week and treprostinil 4–6 ng/kg/min per week) until

patients were at a dose of  $\leq 8$  ng/kg/min or  $\leq 30\%$  of baseline dose. Clinicians were advised to wait for at least 2 months after addition of the oral agent(s) prior to initiation of prostanoid weaning and to perform right-sided heart catheterization prior to discontinuation of the PGI<sub>2</sub>. After initial reduction of the prostanoid doses and once patients reached the goals mentioned above, patients were admitted to an intensive care unit and the PGI<sub>2</sub> was titrated down at the rate of 1 ng/kg/min every hour as long as hemodynamics remained stable. During the weaning period and after discontinuation of PGI<sub>2</sub>, frequent telephone contact was maintained with the patients and they were evaluated clinically and underwent 6-min walk test (6MWT), transthoracic echocardiography, and type-B natriuretic peptide (BNP) testing every 2–3 months. Patients able to successfully transition to oral agents alone and not require re-institution of PGI<sub>2</sub> therapy at the time of data collection, were included in the successful transition (ST) group, whereas those not able to tolerate the discontinuation of parenteral prostanoids initially or those requiring the re-institution of parenteral prostanoids were included in the failed transition (FT) group. Those who failed within 3 months of discontinuation were categorized as 'early failures' and those who failed more than 3 months after discontinuation were categorized as 'late failures'.

Patients were followed and evaluations were performed prospectively, however, data were not captured or recorded until the summer of 2006 after institutional review board approval. At that point, an attempt at transition from PGI<sub>2</sub> therapy to oral agents had been made in 21 patients with PH.

## Statistical analysis

All quantitative variables are summarized as mean  $\pm$  standard deviation (SD). Group comparisons were performed by  $\chi^2$  tests or Fisher's exact test with respect to categorical variables. Group comparisons with respect to quantitative and ordinal variables were performed using Wilcoxon rank sum test and *T*-test.

## Results

### Clinical features prior to transition (Table 1)

We identified 21 patients who had received treatment with PGI<sub>2</sub> [intravenous epoprostenol ( $n = 17$ ) and treprostinil (2 intravenously and 2 subcutaneously)] in whom transition to oral agents was attempted. Fifteen patients (age  $47.3 \pm 12.6$ , mean  $\pm$  SD; 11 female/4 male) were successfully transitioned (ST group) to oral agents and 6 patients (age  $36.2 \pm 5.9$ , mean  $\pm$  SD; 4 female/2 male) failed to be transitioned (FT group) and required continuation or re-institution of therapy with parenteral agents. Demographics, etiology

**Table 1** Demographics and pulmonary hypertension targeted therapy at baseline and during transition.

Patient no.	Age	Sex	Diagnosis	Drug d/c	Reason for d/c	PGI2 (mo)*	Max PGI2 dose	Oral tx† (mo)	Tx at d/c
<i>Successful transition (ST) group</i>									
1	39	M	HIV	EPO	Intolerable PGI2 side effects	28	19	11	B
2	38	F	SLE	EPO	Thrombocytopenia	9	18	0	B
3	34	F	SLE	EPO	Recurrent line infection	37	13	24	B
4‡	61	F	Appetite-suppressant	EPO/TREP	Patient preference	28	17	13	B+S
5	55	F	IPAH	EPO	Intolerable PGI2 side effects	26	16	11	B+S
6	35	F	IPAH	EPO	Intolerable PGI2 side effects	8	10	4	B
7	54	F	SLE	TREP	Severe site pain	20	42	3	B
8‡	27	F	Familial	EPO/TREP	Patient preference	83	29	16	B+S
9	60	F	CHD	EPO	Intolerable PGI2 side effects	34	21	44	B
10	46	F	SLE	EPO	Intolerable PGI2 side effects	4	10	0	S
11	45	M	CTEPH	EPO	Patient preference	38	13	5	S
12	41	M	Porto-pulmonary	EPO	Patient preference	8	14	1	B
13	52	M	Porto-pulmonary	EPO	Patient preference	42	8	1	S
14	76	F	IPAH	EPO	Patient preference	19	32	17	B+S
15	47	F	Sarcoidosis	EPO	Recurrent line infection	28	29	15	B+S
Mean ± SD	47.3 ± 12.6					26 ± 17	18 ± 7.6	11 ± 12	
<i>Failed transition (FT) group</i>									
1	42	F	IPAH	EPO	Intolerable PGI2 side effects	8	5	3	B
2	38	F	SLE	EPO	Patient preference	35	13	26	B
3	39	F	IPAH	TREP	Patient preference	15	42.5	14	B
4	35	M	Scleroderma	EPO	Patient preference	12	17	6	B
5	38	M	CHD	EPO	Patient preference	16	24	5	B
6	25	F	IPAH	EPO	Intolerable PGI2 side effects	8	13.5	5	B
Mean ± SD	36.2 ± 5.9					16 ± 10	14.5 ± 6.9	10 ± 9	

Abbreviations: d/c: discontinued; PGI2: prostanoid analogues; mo: months; Tx: treatment; F: female; M: male; EPO: epoprostenol (in ng/kg/min); TRE: treprostinil (in ng/kg/min); B: bosentan; S: sildenafil; and NA: not available.

\*Total duration of parenteral prostanoid therapy prior to discontinuation.

†Duration of bosentan and/or sildenafil prior to discontinuation of parenteral prostanoids.

‡Patients originally on epoprostenol and then switched to treprostinil.

of PH, reason for discontinuation of PGI2, and oral therapy used prior to transition are shown in Table 1. The majority of patients had PAH (90.5%) with idiopathic pulmonary arterial hypertension (IPAH) and systemic lupus erythematosus associated PAH (SLE-PH) accounting for 29% and 24% of the group, respectively. One patient had PH associated with sarcoidosis and another had PH secondary to chronic thromboembolic disease. Patients in the ST group were older than patients in the FT group (47.3 ± 12.6 vs. 36.2 ± 5.9 years old, respectively;  $p = 0.013$ ). Eight patients (6 ST and 2 FT) were started on PGI2 before bosentan was commercially available (December 2001). Of these, 6 patients had significant hemodynamic compromise and poor functional class and would have been started on PGI2 even if bosentan had been available.

### Transition process (Tables 1 and 2)

The most common reasons for attempted transition included patient preference ( $n = 10$ ) and intolerable prostanoid side effects ( $n = 9$ ). Patients in the ST group tended to have longer duration of prostanoid therapy prior to transitioning, but this difference did not reach statistical significance (26 ± 17 months in the ST group vs. 16 ± 10 months in the FT group,  $p = 0.12$ ). The weaning period prior to discontinuation attempt was similar between the groups (1.6 ± 1.5 in the ST group vs. 1.7 ± 0.4 in the FT group,  $p = 0.42$ ). The maximal epoprostenol dose (17.8 ± 7.6 ng/kg/min in the ST group vs. 14.5 ± 6.9 ng/kg/min in FT group,  $p = 0.2$ ) was similar between the 2 groups. The duration of oral therapy before transition was similar in both groups

**Table 2** Clinical data and hemodynamics of ST group and FT group before transition.

Patient	WHO baseline	WHO d/c	6MWT baseline	6MWT d/c	BNP baseline	BNP d/c	mPAP baseline	mPAP d/c	CI baseline	CI d/c	PVR baseline	PVR d/c
<i>Successful transition (ST) group</i>												
1	III	II	419	608	62	5	50	26	2.7	4.1	6.5	2
2	IV	III	133	335	1070	618	48	36	1.7	2.8	11	4
3	III	II	404	433	NA	142	45	22	2.1	3.4	9	NA
4	III	III	258	277	204	183	72	46	1.7	2.37	15.5	8.45
5	III	II	265	530	NA	239	63	53	1.5	2.2	17	9.7
6	IV	II	422	456	NA	NA	43	54	2.06	3.46	8	6
7	III	II	472	515	NA	NA	59	NA	2.8	NA	9	NA
8	IV	II	367	401	NA	192	110	NA	1.2	NA	12	NA
9	IV	II	303	465	1160	184	72	29	2.3	3.8	9.3	3
10	III	III	244	287	86	80	50	34	1.8	NA	10	NA
11*	II	II	479	523	125	85	85	49	2.4	2.9	7.8	5.5
12	II	II	NA	479	NA	81	38	NA	3.9	NA	3	NA
13	II	II	419	561	9	41	50	36	2.2	4.4	8	2.225
14	III	III	323	224	580	355	65	36	1.7	3.58	14	2
15*	IV	III	192	322	580	9	65	NA	1.6	NA	15	9
Mean	II 20%, III 47%, IV 33%	II 67%, III 33%	336 ± 107	428 ± 115	431 ± 442	170 ± 167	61 ± 19	38 ± 11	2.1 ± 0.7	3.3 ± 0.7	10 ± 4	5.2 ± 3
<i>Failed transition (FT) group</i>												
1	III	II	392	430	NA	61	64	52	2.2	3.2	16.0	10.0
2	III	II	354	456	NA	319	55	NA	1.7	NA	13.0	NA
3	III	II	454	564	NA	33	40	50	2.1	3.4	10.0	7.0
4	III	III	338	384	NA	NA	61	17	1.5	3	17.1	2.0
5	IV	II	399	460	138	65	58	59	1.8	2.1	45.4	31.1
6	III	II	378	521	135	23	35	36	2.1	2.7	3.4	5.0
Mean	III 83%, IV 17%	II 83%, III 17%	386 ± 41	469 ± 64	137	100 ± 124	52 ± 12	43 ± 17	1.9 ± 0.3	2.8 ± 0.5	17.5 ± 14	11 ± 11.6

**Abbreviations:** baseline: values at the time of original diagnosis of PH; d/c: last values prior to discontinuation of parenteral prostanoid therapy; 6MWT: 6-min walk test (in m); BNP: B-type natriuretic peptide (pg/mL); mPAP: mean pulmonary artery pressure (mmHg); CI: cardiac index (L/min/m<sup>2</sup>); and PVR: pulmonary vascular resistance (Woods units).

\*These patients additionally had a left heart catheterization that confirmed a normal pulmonary capillary wedge pressure (<18 mmHg) and normal LVEDP <12 mmHg).

(11 ± 12 months in the ST vs. 10 ± 9 months in the FT group;  $p = 0.78$ ). All 8 (of 15; 53%) patients receiving sildenafil alone ( $N = 3$ ) or in combination with bosentan ( $N = 5$ ), were ST off parenteral therapy ( $p = 0.0456$ ).

Table 2 depicts relevant clinical and hemodynamic features at the time of original diagnosis of PH prior to initiation of PGI<sub>2</sub> (baseline) and during the transition period. At baseline, both groups had severe PH (mPAP 61 and 52 mmHg [ $p = 0.31$ ], and mean CI 2.1 and 1.9 L/min/m<sup>2</sup> [ $p = 0.64$ ] in the ST and FT groups, respectively). When the decision to discontinue PGI<sub>2</sub> was made, 10 out of 15 (67%) in the ST group and 5 out of 6 patients (83%) in the FT group were functional class II. No significant differences were noted between the ST and FT groups for 6MWD, BNP, or right ventricular systolic pressure (RVSP) at the time the decision to transition was made ( $p = >0.05$  for all measures). Similarly, in patients who underwent right heart catheterization just prior to discontinuation of PGI<sub>2</sub>, no significant differences were noted between the ST and FT groups in terms of cardiac index, mean pulmonary artery pressure, or pulmonary vascular resistance ( $p = >0.05$  for all measures).

### Follow up data after transition (Table 3)

Follow up data on both groups is shown in Table 3 and Figures 1 and 2. Total follow up was 24.7 ± 13.6 months in the ST group and 30 ± 5.6 months in the FT group. Most patients who were ST experienced stable 6MWD and RVSP throughout follow up. The same was true for patients who did not tolerate weaning off prostanoid therapy. In the ST group, 5 patients showed a decline in their 6MWD and/or their WHO functional class during follow-up. In 3 of these patients, the deterioration was not felt to be significant by the treating physician and 1 (patient no. 15) patient refused re-initiation of PGI<sub>2</sub> therapy. The last patient (patient no. 5) remained stable after transition for approximately 3 years and subsequently moved to high altitude, against medical advice, and died of pneumonia. There were no statistically significant differences in these clinical parameters between the ST and FT groups throughout follow up ( $p > 0.05$  for all comparisons). None of our patients have required discontinuation of bosentan due to elevation in liver function tests.

**Table 3** Follow up variables and outcomes of ST (N = 15) and FT (N = 6) groups.

Patient no.	F/u Mo*	WHO			6MWT			RVSP			BNP			Outcome	
		At d/c	6 mo	Last	At d/c	6 mo	Last	At d/c	6 mo	Last	At d/c	6 mo	Last		
<i>Successful transition (ST) group</i>															
1	41	II	II	II	608	NA	448	50	41	38	62	16	11	Alive	
2	41	III	III	III	335	NA	197	48	NA	54	1070	NA	285	Alive	
3	29	II	II	II	433	370	410	65	34	34	NA	109	14	Alive	
4	42	III	III	III	277	196	162	81	80	86	204	161	67	Alive	
5	34	II	II	IV	530	487	343	72	93	79	NA	128	361	Dead <sup>†</sup>	
6	49	II	II	II	456	454	506	45	50	59	NA	11	14	Alive	
7	14	II	II	II	515	565	535	22	26	25	NA	154	80	Alive	
8	27	II	II	II	401	NA	436	103	NA	120	NA	NA	51	Alive	
9	17	II	III	II	465	419	447	43	37	38	1160	125	264	Alive	
10	14	III	III	III	287	260	261	97	NA	73	86	NA	78	Alive	
11	11	II	II	II	523	586	587	70	69	83	125	42	52	Alive	
12	12	II	II	II	479	NA	447	52	57	92	NA	70	157	Alive	
13	13	II	II	II	561	548	549	54	69	28	9	17	22	Alive	
14	12	III	III	II	224	335	335	51	43	43	580	129	129	Alive	
15	14	III	IV	IV	322	213	213	41	62	87	580	5	477	Alive	
Mean ± SD		24.7 ± 13.6	II 67%, III 33%	II 60%, III 33%, IV 7%	II 67%, III 20%, IV 13%	428 ± 115	403 ± 140	392 ± 134.5	60 ± 22	55 ± 20	63 ± 28	431 ± 442	81 ± 60	137.5 ± 144	
<i>Failed transition (FT) group</i>															
1 <sup>‡</sup>	50	II	II	II	430	Na	337	100	82	87	61	18	73	Alive	
2	25	II	II	II	456	444	590	69	81	64	319	261	72	Alive	
3	14	II	II	I	564	559	552	70	48	36	33	69	45	Alive	
4 <sup>‡</sup>	44	III	I	IV	384	428	251	NA	NA	101	NA	22	274	Dead	
5	22	II	III	III	460	407	404	56	78	92	65	60	60	Alive	
6	25	II	III	II	521	543	598	56	65	45	23	13	5	Alive	
Mean ± SD		30.0 ± 5.6	II 83%, III 17%	I 17%, II 50%, III 33%	I 17%, II 50%, III 17%, IV 17%	469 ± 64	476 ± 70	455 ± 146	70 ± 18	71 ± 14	71 ± 26	100 ± 124	74 ± 95	88 ± 94	

**Abbreviations:** WHO: World Health Organization functional class; 6MWT: 6-min walk test (m); RVSP: right ventricular systolic pressure (mmHg); BNP: B-type natriuretic peptide (pg/mL); DC: last value prior to discontinuation of parenteral prostanoids; and Last: most recent value.

\*Total follow up time in months after prostanoid therapy discontinuation.

<sup>†</sup>Patient moved to high altitude and died with pneumonia approximately 34 months after prostanoid therapy was discontinued.

<sup>‡</sup>These patients failed approximately 39 and 24 months after epoprostenol discontinuation, respectively.

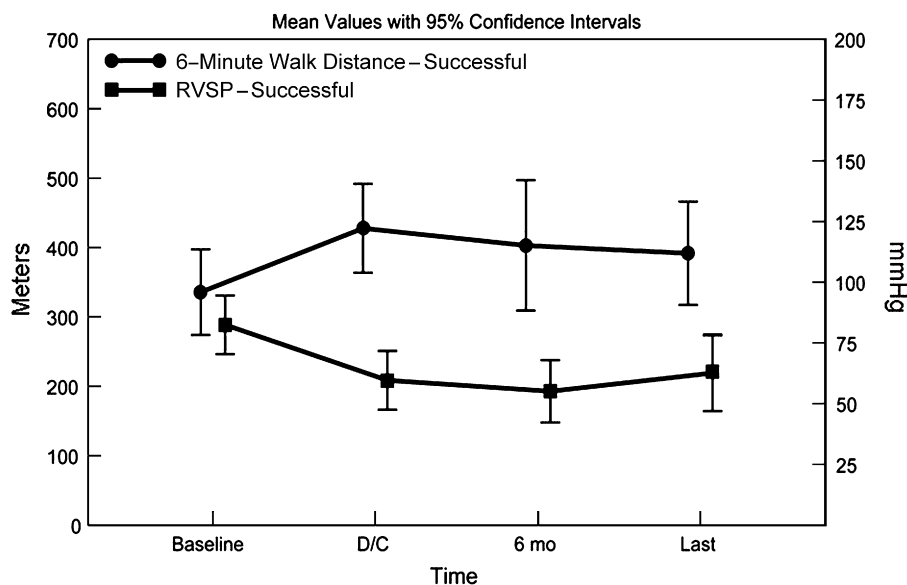


Figure 1 Six-minute walk distance and RVSP-successful: mean values with 95% confidence intervals.

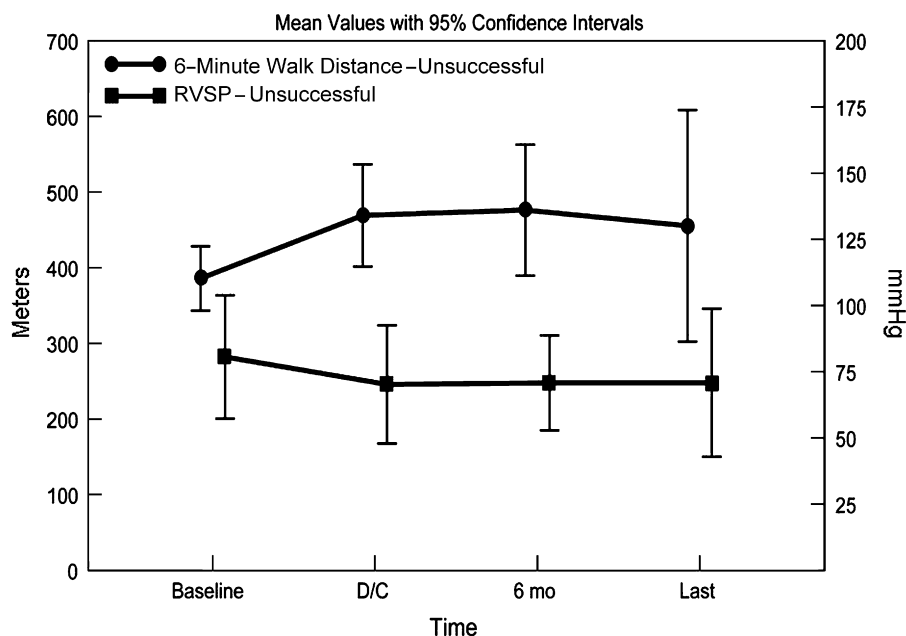


Figure 2 Six-minute walk distance and RVSP-unsuccessful: mean values with 95% confidence intervals.

### Transition failures (FT group) (Table 3)

Six patients failed to successfully transition to oral agents or required re-institution of PGI<sub>2</sub> after initial transition. Two patients could not tolerate discontinuation and were continued on PGI<sub>2</sub>. Two patients each, required re-institution of PGI<sub>2</sub> within 3 months (early failure) and more than 3 months (late failure) after transitioning to oral therapy, respectively. After transition, 1 patient in the FT group (patient no. 1) completely discontinued her bosentan for 22 months, against medical advice, after which she deteriorated and was started on PGI<sub>2</sub>. She has regained her baseline functional status and is currently WHO II. Patient no. 4 deteriorated clinically after being off PGI<sub>2</sub> for 25 months.

He died of worsening PH 28 months after the re-initiation of PGI<sub>2</sub> therapy.

### Discussion

Our study presents the results of a series of patients who were transitioned from prostanoid agents to oral agents according to a pre-determined out-patient weaning protocol. Our results indicate that selected patients with PH who are clinically stable on low doses of parenteral prostanoid agents may be safely transitioned to oral agents with good long-term results. We found that the use of sildenafil, alone or in combination with bosentan, was associated with a

higher likelihood of a successful transition. We also found that patients that FT were not affected adversely by the attempt, and were able to reach their baseline clinical status with the resumption of prostanoid therapy.

It is important to emphasize that transition to oral therapy from parenteral agents in patients with PH is a complex process that requires careful monitoring and close follow up and should only be attempted at experienced centers. There is currently no consensus about which patients should be candidates for transitioning to oral agents and such attempts remain guided by case reports or small case series. Table 4 summarizes the available adult experience with transition from prostanoid therapy to oral agents.

Predictors of successful transition are difficult to identify since the criteria for attempting a transition have varied between reports. Despite these differences, all studies have tended to include patients that are 'clinically stable' in WHO classes I-III, on stable doses of prostanoid analogs, and

without evidence of overt right-sided failure. Most previous studies<sup>8,10</sup> have not reported results of right heart catheterization prior to initiation of PGI2 therapy for individual patients. Contrary to 1 previous report,<sup>9</sup> we found that hemodynamics at the time of initial diagnosis of PH ('baseline' in Table 2) were not useful as guides to differentiate between those who would or would not be able to make a successful transition. This stands to reason since many of these patients were on parenteral therapy for years prior to attempted discontinuation. Patients with normal<sup>6</sup> or near normal<sup>9,10</sup> hemodynamics with the use of prostanoid agents have been reported to have better long-term outcomes. Although we found no significant differences in hemodynamic parameters among the ST and FT groups, patients who made a successful transition had lower mPAP and PVR and a higher CI prior to discontinuation. At the time of PGI2 discontinuation, 5 patients in the ST group had a PVR ≤ 4 units and all but 4 had a mPAP ≤ 36 mmHg.

**Table 4** Transition from PGI2 to oral agents in adult patients: summary of the available literature\*.

	Kim et al. <sup>6</sup>	Suleman and Frost <sup>8</sup>	Steiner et al. <sup>9</sup>	Johnson et al. <sup>10</sup>	Current report
No. patients	4	23	22	15	21
No. ST (%)	4 (100%)	11 (47.8%)	7 (31.8%)	10 (66.6%)	15 (71.4%)
Design	Retrospective	Prospective	Prospective	Retrospective	Retrospective
Criteria prior to weaning	Normalization of PAP on epoprostenol	Infrequent increase in PGI2 dose, FC II,III, no heart failure	Stable FC, <10% decrease in 6MWD and no PGI2 dose changes	Stable FC, no increase in PGI2, oral therapy at least 3 months	FC I, II, or III, stable 6MWD, stable prostanoid dose, no right heart failure, oral therapy at least 2 months
Mean PGI2 duration (mo)	68.4	ST 35.2 FT 38.4	ST 41 FT 36	45.1	ST 26 FT 16
Mean max PGI2 dose (ng/kg/min)	40.5	ST 25.9 FT 40.1	ST 25.5 FT 37.67	23.2	ST 18 FT 14.5
At wean, mean:					
6MWD (m)	N/A	361.8	317.9/294	420	427.7/469.1
mPAP (mmHg)	21	65.8/84.1	38/56	35.8	38.2/42.8
CI (L/min/m <sup>2</sup> )	2.85	CO 4.4 (both)	NA	CO 4.9	2.1/1.9
PVR (units)	NA	NA	NA	6.2	10.3/17.5
Oral therapy	CCB = 1 CCB+Sild+ B = 1 CCB+B = 1 B = 1	Bosentan	Bosentan	Bosentan 11 Sildenafil 2	ST: B = 7 S = 3 B+Sild = 5 FT: B = 6
Mean oral therapy duration (mo)	10	3	6	4.5	11
Mean follow up (mo)	11	9.6	17.7	29.9	27.3
Adverse events of transitioning	None	2 late failures, no deaths	4 deaths, 2 were ST	2 late failures, no deaths	1 late death due to pneumonia in ST and 1 death in FT

**Abbreviations:** ST: successful transition; FT: failed transition; PGI2: prostanoid therapy; mo: months; Max: maximum; 6MWD: 6-min walk distance; mPAP: mean pulmonary artery pressure; CI: cardiac index; PVR: pulmonary vascular resistance; NA: non-available; CCB: calcium channel blockers; Sild: sildenafil; B: bosentan; and FC: functional class.

\*Data separated by "/" indicates ST/FT groups.

Johnson et al.<sup>10</sup> reported that their patients with mPAP < 30 mmHg and PVR < 4 units had good long-term outcomes on oral therapy. Other reports<sup>8,9</sup> have also found that patients able to make the transition successfully were more likely to have lower pulmonary arterial pressures than those who could not.

It is unclear if underlying disease has an impact on the rate of success during the transition process. Most of the literature relating to transition from parenteral prostanoids to oral agents is in patients with IPAH. Four of our successful transitions were patients with SLE and the only scleroderma patient failed to transition. Johnson et al.<sup>10</sup> attempted transition in 3 patients with SLE-PH and were successful in all 3 cases. This information is not provided in the other case series since patients are reported under the generic diagnosis of connective tissue diseases. Contrary to extensive experience with scleroderma-associated PAH,<sup>11,12</sup> we have recently reported<sup>13</sup> sustained long-term improvement in hemodynamics and functional capacity in patients with SLE-PH. Whether patients with SLE-PH represent a group that lends itself to favorable long-term outcomes after transition to oral agents requires further study.

Maximum prostanoid dose, duration of prostanoid therapy, and duration of oral therapy are quite variable between the various reports and their role in terms of predicting success or failure requires further clarification. In our study the mean duration of prostanoid therapy before transition was longer in the group that had a successful transition, although this difference was not statistically significant (26 months vs. 16 months,  $p = 0.12$ ). This suggests that longer duration of prostanoid therapy might be associated with successful weaning, maybe because longer exposure to these agents allows for some regression of pulmonary vascular remodeling. This, of course, remains highly speculative. Tendency for longer duration of prostanoid therapy to predict weaning success was seen by Steiner et al.<sup>9</sup> Contrary to this Suleman et al.<sup>9</sup> found an increased trend for longer duration of prostanoid use in patients failing to transition successfully. Duration of oral therapy prior to successful discontinuation of prostanoid therapy has varied among reports, ranging from 3 to 11 months. Our experience and the small series by Kim et al.<sup>6</sup> suggest that longer duration may be associated with better outcomes. However, Johnson et al.<sup>10</sup> had good results after only 4.5 months. Thus, the appropriate duration of oral therapy before transition attempt is yet to be determined. Although 4 of our patients were transitioned very quickly, based on the literature, it is the authors' recommendation that transition be attempted no less than 2 months after the initiation of oral therapy.

Previous studies have speculated that there may be an association between a lower mean prostanoid dose and higher weaning success since that may be reflective of less severe disease.<sup>8,9</sup> Overall our study seems to confirm this since most of the patients in our study were on lower doses of prostanoids than in other studies (Table 4). However, we did not find any significant difference in prostanoid dose between those in the ST and the FT groups and in fact, those in the ST group were on a higher mean dose of prostanoids than the FT group. Similar to the study by Johnson et al.<sup>10</sup> the mean 6MWD among our patients was > 400 m and among the available reports, these 2 series seem to have the highest success rate.

As shown in Table 4, success rate of transitioning has also been variable with earlier studies reporting a success rate of only 30–50% using bosentan alone. Our success rate was 70% and patients were transitioned to different single or a combination of oral agents. It is interesting to note that all our patients receiving sildenafil alone or in combination with bosentan, were able to successfully transition off parenteral therapy. Johnson et al.<sup>10</sup> reported using sildenafil in 2 patients, both of whom also transitioned successfully with adequate long-term hemodynamics. Although this could be one of the factors explaining our higher success rate, this finding requires further validation. It is possible that the combination of sildenafil with an endothelin receptor antagonist may allow for a higher success rate with transitions but this remains speculative.

Most of the transitioned patients were able to maintain good hemodynamic and functional parameters while on oral agents at least for an average of 2 years, making this only the second study<sup>10</sup> to report on long-term outcomes in these patients. Four of our patients in the ST group were doing well after 3 years follow-up.

In our study, most of the patients that failed to transition (FT group), did not experience severe long-term hemodynamic or functional deterioration secondary to this transition attempt. There was no mortality due to this transition attempt; however, 1 patient died 2 years after re-institution of parenteral therapy. Previous studies have reported worsening clinical status and even mortality in patients who failed to transition successfully.<sup>9,10</sup>

This study has several limitations. The patient population was small and although the transition process was done according to a predetermined protocol this was an observational, retrospective study. The small number of patients may have precluded statistical analysis with enough power to detect any differences. Many questions remain unanswered. Even though we report on relatively long-term outcomes, it is unclear if these patients will sustain the clinical and hemodynamic benefit going forward. It is also not known if the ST patients would have done better had they been continued on parenteral prostanoids and whether they will respond to re-institution of these agents should they deteriorate. Some of these questions may be answered by future studies.

In summary, carefully selected patients with PH, can be safely transitioned to oral agents and enjoy continued clinical stability after a mean follow up of 2 years. Low doses of prostanoids, mean PAP < 40 mmHg, 6MWD > 400 m, SLE-PH, and the use of sildenafil could predict a higher likelihood of successful weaning. These findings require further confirmation in prospective clinical trials. Since unsuccessful transition to oral agents may, at times, be associated with unfavorable outcomes, it is our recommendation that such transition be attempted only in carefully selected patients, by physicians with extensive experience in caring for patients with PH.

## Conflict of interest statement

Dr. Minai is on the Scientific Advisory Board and a Speaker for Actelion, Pfizer, United Therapeutics, and Gilead. The rest of the authors have no significant conflicts of interest with

any companies/organizations whose products or services may be discussed in this article.

The document represents original work that is not being considered or has been accepted for publication elsewhere. All authors have read and approved the manuscript for its submission.

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