Oral treprostinil for the treatment of pulmonary arterial hypertension in patients transitioned from parenteral or inhaled prostacyclins: case series and treatment protocol

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Abstract: Oral treprostinil (TRE) is a prostacylin approved for the management of pulmonary arterial hypertension (PAH). Few data exist to guide the use of oral TRE as a replacement for parenteral or inhaled prostacyclins. Therefore, the purpose of this report was to describe our experience with oral TRE to transition patients from parenteral or inhaled TRE. We describe a case series of patients admitted for a 4-day hospital stay to transition from parenteral or inhaled TRE. Appropriate criteria for transition included stable patients with improved symptoms/functional capacity, patients who could not tolerate intravenous prostacyclin due to infection or subcutaneous prostacyclin due to pain, and patient preference for transition. The dosing protocol for transition is described. A total of 9 patients generally representative of a typical PAH demographic and background medical therapy were included. Patients were initiated at either 0.5 or 1 mg 3 times daily and discharged on a median dose of 8 mg 3 times daily. Our protocol resulted in 6 of 9 patients who successfully transitioned at a median follow-up of 47 weeks. Two patients had to return to their previous prostacyclin therapy based on the presence of clinical worsening and adverse events ($n = 1$) and adverse events alone ($n = 1$). Another patient discontinued therapy due to plans for hospice care. Oral TRE may serve an important role in prostacyclin transitions in carefully selected, stable patients who receive background oral therapy for PAH.

Keywords: prostacyclin, oral treprostinil, transition, switch, pulmonary hypertension.

Pulm Circ 2016;6(1):132-135. DOI: 10.1086/685111.

Parenteral prostacyclins are the mainstay of treatment for patients with advanced symptoms of pulmonary arterial hypertension (PAH) as they have made a significant impact on exercise capacity, symptoms, and hemodynamics.[1] However, their use is fraught with complications related to their administration, such as injection-site pain with subcutaneous (SQ) use or line-related bloodstream infections with intravenous (IV) use.[1] Oral treprostinil (TRE) was approved in 2013, although clinical trial evidence demonstrated a modest improvement in 6-minute walk distance (6MWD) when given as monotherapy and no improvement as part of combination therapy.[2-5] These results, however, were likely confounded by subtherapeutic dosing and suboptimal dosing titration that resulted in a high proportion of adverse events (AEs) and premature study discontinuation.[3-5] Efforts to improve patient tolerability and reach optimal dosing have resulted in administration requirements and titration schedules that can be relatively complex.[2] Nonetheless, careful attention to dosing and monitoring have generated interest among clinicians and patients in the potential to replace parenteral prostacyclins with oral TRE. However, data to guide such prostacyclin transitions have thus far been limited.[6]

CASE DESCRIPTION

At University of Pittsburgh Medical Center Presbyterian University Hospital, we developed guidelines for use of oral TRE, including suggested parameters for transition of appropriate patients from parenteral or inhaled prostacyclins. Our center's criteria for transition to oral TRE include the following: stable patients with improved symptoms/functional capacity, patients who cannot tolerate IV prostacyclin due to infection or SQ prostacyclin due to pain, and patient preference for transition based on factors such as youthful lifestyle. Once patients are determined to be appropriate candidates for transition, they are scheduled for an inpatient admission during which they undergo a right heart catheterization to establish a pretransition baseline. The protocol for transition specifies a 4-day overlap, during which the oral TRE is initiated at either 0.5 mg or 1 mg 3 times daily (TID) depending on the maintenance prostacyclin dose from which the patient is being converted. Patients are then up-titrated by 0.5–1-mg increments 3 times daily over the course of their hospitalization. Furthermore, with each progressive up-titration of oral TRE, the dose of the IV/SQ or inhaled prostacyclin is down-titrated

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Submitted September 2, 2015; Accepted October 18, 2015; Electronically published January 29, 2016.

in consistent increments. The average rate of down-titration for IV/SQ treprostinil was approximately 10 ng/kg/min per day. For inhaled treprostinil, the average rate of down-titration was 3 breaths 4 times daily (QID). The starting dose of oral TRE and the increments of up-titration were determined by the total oral TRE dose, based on the conversion from total daily IV or SQ exposure. Our target dose at the time of discharge was approximately 10 mg TID and was estimated to achieve an equivalent parenteral TRE dose of approximately 40–50 ng/kg/min. The median parenteral TRE dose at the time of transition in our cohort was 42 ng/kg/min, and our median patient weight was approximately 75 kg. The conversion formula we used took into account these numbers and the absolute bioavailability of oral TRE of approximately 17%.[2] From this calculation, we determined the total daily oral TRE dose (mg per day). This total daily dose was then divided into TID dosing and rounded to the nearest 0.5 mg for the goal starting dose. The dosing conversion we used was similar to pharmacokinetic (PK) data reported by White et al.,[6] in which a dose of 1 mg by mouth TID was approximately equivalent to a dose of 5 ng/kg/min for TRE exposure in a typical 70-kg patient.

DISCUSSION

We evaluated a total of 9 patients who were generally representative of a typical PAH demographic and baseline treatment regimen (Table 1). At the time of transition to oral TRE, all patients were receiving parenteral TRE and 8 of the 9 were on background therapy with a phosphodiesterase type-5 inhibitor (PDE5i) and/or an endothelin receptor antagonist (ERA; Table 1). Additionally, each patient was on stable parenteral prostacyclin therapy for more than 30 days prior to the transition. Our transition protocol was relatively rapid compared to the clinical trials but consistent with the protocol reported by White et al.[6] The majority of our patients (6/9) were started at 1 mg TID, and the median dose at discharge was approximately 8 mg TID (Table 2). This was the same median total daily dose (24 mg) also reached after transition in the White et al. study.[6] Our protocol did result in 7 of the 9 patients achieving a successful transition. Six of the 9 patients had some documentation of clinical follow-up data at a median of 47 weeks. One patient discontinued therapy due to plans for hospice care after a successful transition. The median total daily dose for the 6 patients with follow-up data was 28 mg. We did have documentation of 6MWD beyond 16 weeks after transition for 4 of the 6 patients. Two of the 4 patients had 6MWD documented at 10 months (1 patient declined from 515 to 457 m, and the other increased from 403 to 412 m). The other 2 patients had 6MWD documented at 6 months (1 patient declined from 311 to 256 m, and the other declined from 407 to 403 m).

Two patients in our cohort did not transition successfully and returned to their previous prostacyclin therapy (Table 2). In 1 case, the patient experienced both clinical worsening and significant AEs, whereas the other patient had AEs (Table 2). Another patient had documentation of clinical worsening but continued on oral TRE therapy at an increased dose. With regard to safety, the majority (8/9) of our patients did experience AEs. The most common AEs were gastrointestinal in nature and consistent with those reported in the clinical trials.[3-5] There were two patients whose dose after discharge had

Table 1. Demographic and clinical characteristics of patients transitioned to oral treprostinil

Characteristics	Value
No. patients (F/M)	9 (7/2)
Age, median (range), years	50 (34–72)
Actual body weight, median (range), kg	74.8 (50.9–115.7)
Type of PAH, *n*	
IPAH	5
PAH-CTD	2
PAH-CHD[a]	2
WHO FC prior to transition, *n*	
1	0
2	7
3	2
4	0
6MWD prior to transition, median (range), m[b]	338 (53–515)
Reason for transition, *n*	
Intolerance of IV prostacyclin due to infection	1
Intolerance of SQ prostacyclin due to pain	4
Patient preference	4
Concomitant PAH therapy at time of transition	
None, *n*	0
PDE5i monotherapy, *n*	5
ERA monotherapy, *n*	1
PDE5i + ERA combination, *n*	2
No background therapy, *n*	1
Inhaled prostacyclin, *n*	2
Dose, mcg × QID	72
SQ prostacyclin, *n*	5
Dose, median (range), ng/kg/min	40 (24–70)
IV prostacyclin, *n*	2
Dose, median (range), ng/kg/min	44 (39–50)

Note: ERA: endothelin receptor antagonists; F: females; IPAH: idiopathic PAH; IV: intravenous; M: males; PAH: pulmonary arterial hypertension; PAH-CHD: congenital heart disease–associated PAH; PAH-CTD: connective tissue disease–associated PAH; PDE5i: phosphodiesterase type-5 inhibitors; 6MWD: 6-minute walk distance; SQ: subcutaneous; WHO FC: World Health Organization functional class; QID = 4 times daily dosing.

[a] For the 2 patients with PAH-CHD, 1 had a ventricular septal defect repair and the other had a late atrial septal defect closure.

[b] 6MWD not documented prior to transition in 1 patient.

Table 2. Oral treprostinil transition and evaluation of outcomes

Patient	Prostacyclin dose/route prior to transition	Oral treprostinil dose			Clinical worsening	Adverse events	Conversion failure
		Initiation, mg	Discharge, mg	Last clinic visit, mg (w after transition)			
1	40 ng/kg/min; SQ	1, TID	10, TID	10.25, QID (44)	Yes; mild increase in symptoms, decline in 6MWD, increase in BNP level; required increase in treprostinil dose	Yes; flushing	No
2	12 breaths QID; INH	0.5, TID	2.5, TID	7, QID (52)	No	Yes; headache, jaw pain, loose stool, flushing	No
3	24 ng/kg/min; SQ	0.5, TID	3.5, TID	2, BID (44)	No	Yes; nausea, vomiting, diarrhea, dyspnea, edema; required lowering of dose	No
4	50 ng/kg/min; IV	1, TID	10, TID	10, QID (55)	No	Yes; headache, nausea, diarrhea, flushing, jaw pain, dizziness	No
5	40 ng/kg/min; SQ	1, TID	8, TID	7, TID (50)	No	Yes; nausea, vomiting, edema; required lowering of dose	No
6	70 ng/kg/min; SQ	1, TID	13, TID	NA; discont. at 12	Yes; syncopal episode, decreased energy and exercise tolerance	Yes; headache, nausea, vomiting, flushing, syncope, dyspnea, dizziness	Yes; resumed SQ treprostinil but at higher dose (75 ng/kg/min vs. 70 ng/kg/min at baseline)
7	39 ng/kg/min; IV	1, TID	8.5, TID	NA; discont. at 2	No	Yes; headache, nausea, vomiting, edema, chest pain, shortness of breath, numbness/tingling	Yes; resumed SQ treprostinil at 40 ng/kg/min (same as baseline)
8	36 ng/kg/min; SQ	0.5, TID	5, TID	8, TID (27)	No	No	No
9	12 breaths QID; INH	1, TID	4, TID	NA; discont. at 2 due to plan for hospice care	No	Yes; headache, nausea, flushing	No
	Median SQ/IV dose (range)	Median (range), mg	Median (range), mg	Median total daily, mg (median [range] w after transition)	Total clinical worsening, *n*	Total adverse events, *n*	Total conversion failures, *n*
Total	42 (24–70) ng/kg/min	1 (0.5–1), TID	8 (2.5–13), TID	28; range: 4–41[a] (47 [27–55])	2	8	2

Note: Conversion failure defined as the need to discontinue oral treprostinil and transition back to the original prostacyclin therapy based on the presence of clinical worsening and/or adverse events. BID = twice daily dosing; BNP = brain-type natriuretic peptide; discont. = discontinued; INH = inhaled; IV = intravenous; NA = not applicable; 6MWD: 6-minute walk distance; SQ = subcutaneous; TID = 3 times daily dosing; QID = 4 times daily dosing; w = weeks.

[a] One patient received BID dosing; 2 patients received TID dosing; 3 patients received QID dosing.

to be reduced to manage AEs, whereas all others who successfully transitioned had an increase in dose. There was no obvious correlation between concomitant PDE5i use or background therapy in general among patients who experienced AEs. The only patient who did not experience any AEs happened to be receiving both a PDE5i and an ERA as background therapy. Dosing frequency was adjusted in an effort to minimize AEs. All patients at discharge were on TID dosing; however, the oral TRE dosing frequency at the most recent clinic visit varied. Two patients remained on TID dosing, whereas 3 others were switched to QID dosing, and 1 patient was decreased to twice-daily dosing. Each of these changes occurred in response to dose-limiting AEs. Although oral TRE dosing frequency greater than 3 times daily has not been previously reported to our knowledge, in each case the patient was able to better tolerate the medication at a higher total daily dose than was achieved with TID dosing (with stable-to-improved functional class at follow-up). The PK and clinical outcomes associated with this higher dosing frequency merit further investigation.

In conclusion, oral TRE adds to the growing number of therapeutic options for patients with PAH. Its precise application in the treatment of PAH remains to be firmly established, but accumulating evidence suggests that it may serve an important role in prostacyclin transitions in carefully selected, stable patients who are receiving background oral therapy with either a PDE5i and/or an ERA. Ongoing clinical trials will further evaluate longer-term effects of oral TRE on patient symptoms, quality of life, disease progression, and survival.

ACKNOWLEDGMENTS

No copyrighted text or trademarked material was used in this report. Therefore, permissions for any reproductions were not applicable. All ethical procedures were followed in accordance with the preparation of this report. This case report is a retrospective review. All patient identifiers have been removed.

Source of Support: Nil.

Conflict of Interest: DCI has served on an advisory board for United Therapeutics (relevant marketed products: treprostinil [Tyvaso, Remodulin, Orenitram]). All other authors: none declared.

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