Case Report

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Impact of four times daily dosing of oral treprostinil on tolerability and daily dose achieved in pulmonary hypertension

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Abstract

Oral treprostinil (TRE) is a prostacylin that is approved for the treatment of patients with pulmonary arterial hypertension (PAH). Dosing is approved for two or three times daily (t.i.d.); however, adverse effects, including gastrointestinal-related symptoms, may limit the ability to reach optimal doses. We report our experience with a four times daily (q.i.d.) regimen of oral TRE for goal-directed therapy of PAH. We describe three patients that were transitioned from infusion or inhaled TRE to oral TRE with initial t.i.d. dosing over a four-day hospital stay. All patients were subsequently further dose-adjusted in the outpatient setting; however, adverse effects limited additional up-titration despite persistent dyspnea. In a carefully monitored outpatient setting, patients were switched from t.i.d. to q.i.d. dosing of oral TRE. All three patients were successfully dosed q.i.d., having achieved a higher total daily dose compared with a t.i.d. dose regimen. Furthermore, patients were able to maintain functional class II symptoms with mitigation of adverse effects using the q.i.d. dose regimen.

Keywords

prostacyclin, dosing, pulmonary arterial hypertension

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Oral treprostinil (TRE) was approved in 2013 for the treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity.[1] Clinical studies showed a modest improvement in 6-min walk distance (6MWD) when given to treatment-naïve patients, but no improvement in patients on background therapy.[2–4] Additionally, a single-center, open-label, study of 37 patients enrolled in the FREEDOM extension study found no change in functional class, 6MWD, or hemodynamics with long-term oral TRE compared to baseline.[5] However, these results were possibly confounded by sub-therapeutic dosing and premature discontinuation due to adverse events (i.e. headache, nausea, diarrhea, jaw pain, flushing).[2–4] In fact, the median doses with long-term follow-up were only 9 and 11 mg per day at 12 and 24 months, respectively, and there was a modest yet significant inverse relationship between

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dose and change in pulmonary vascular resistance (PVR).[5] The introduction of lower tablet strengths for titration and a protocol amendment which allowed for three times daily (t.i.d.) dosing attenuated adverse effects, but did not lead to an increased total daily dose for patients in long-term follow-up.[5] Pharmacokinetic data indicate that t.i.d. dosing may improve tolerability by more closely simulating a continuous infusion schedule, in comparison to two times daily (b.i.d.) dosing which provided higher peak and lower trough concentrations.[6,7] Current product labeling recommends initiation with either b.i.d. or t.i.d. dosing, with a strong preference for t.i.d. dosing based on expert consensus.[1,8]

Continued interest in determining the optimal dosing of oral TRE has been driven by a study which highlights the feasibility of transitioning to this formulation as an alternative to parenteral (intravenous [IV] or subcutaneous [SQ]) treprostinil therapy in carefully selected, stable patients on background PAH therapy.[7] However, the majority of patients (97%) experienced at least one adverse event (with 23/33 patients having received t.i.d. dosing).[7] Similarly, in our program, some patients have been unable to tolerate effective t.i.d. dosing due to adverse effects. Therefore, we report our experience with four times daily (q.i.d.) dosing of oral TRE for goal-directed therapy of PAH.

Our protocol for switching patients to t.i.d. oral TRE has typically been up to a four-day hospitalization in which IV or inhaled TRE is weaned off while oral therapy is up-titrated to an initial goal, followed by further outpatient titration.[9] Patient criteria for transition include: clinical stability with improved symptoms/functional capacity; intolerance of IV prostacyclin due to infection or SQ prostacyclin due to pain; and patient preference for transition in consideration of the aforementioned factors. The details of our dosing protocol have been published elsewhere.[9] In three patients, prostacyclin-related adverse effects limited further up-titration with oral TRE despite significant dyspnea suggesting that an effective dose had not been reached. In a carefully monitored outpatient setting, these patients were switched from t.i.d. to q.i.d. dosing by dividing the total daily dose of oral TRE into four equal dosages administered at evenly spaced intervals throughout the day. The PAH nurse provided telephone follow-up with each patient every two days to monitor response to therapy and adverse effects. Each dose was then up-titrated as tolerated in 0.25–0.5 mg increments on a weekly basis. The details of each case are summarized below.

Case descriptions

Patient 1 is a 45-year-old man with idiopathic PAH (IPAH) diagnosed in 2012 after presenting with syncope and World Health Organization (WHO) functional class (FC) IV symptoms. Treprostinil SQ was then started urgently. Tadalafil was added three months later. After two years, his 6MWD had increased to 515 m and he improved to FC II symptoms. At that point in June 2014, the patient was switched to oral TRE 10 mg t.i.d. due to persistent and severe site pain. Hemodynamics just before the switch are provided in Table 1. In October 2014, his dose was changed to 8 mg q.i.d. due to headache, flushing, jaw pain, and dyspnea. Over the subsequent three months his dose was up-titrated to 10 mg q.i.d., a higher total daily dose achieved compared to the t.i.d. dose that he received previously. Since that time, the patient has remained in FC II.

Patient 2 is a 38-year-old woman with PAH secondary to late ventricular septal defect repair, diagnosed in 2005, with FC II symptoms that was initiated on bosentan. In 2007, her 6MWD was 387 m and tadalafil was added to her regimen. Due to progressive dyspnea, inhaled TRE was started in 2010, but by 2012 she required transition to IV TRE due to continued FC III symptoms. In September 2014, the patient was switched from IV to oral TRE at 10 mg t.i.d. due to recurrent line-related infections and patient preference. She had FC II symptoms at that time with a 6MWD of 378 m. Her hemodynamics before the switch are shown in Table 1. In November 2014, her oral TRE dose was changed to 7 mg q.i.d. due to headache, flushing, and jaw pain that were experienced with the t.i.d. dose. She was subsequently up-titrated to 10 mg q.i.d. without any issues, a higher total daily dose than was attained with the t.i.d. dose. She has maintained FC II symptoms since that time.

Patient 3 is a 58-year-old man with IPAH diagnosed in 2003, FC II, who was initiated on TRE SQ in 2003. He was subsequently started on bosentan and sildenafil in May 2006. Treprostinil SQ was switched to inhaled TRE in 2010 due to patient request and desire to maintain a more active lifestyle. The patient was later transitioned to oral TRE at 2.5 mg t.i.d. in September 2014, again based on patient preference. At the time of switch to oral TRE, he had FC II symptoms. His pre-conversion hemodynamics are shown in Table 1. His dose of oral TRE was up-titrated to 9 mg t.i.d. due to dyspnea, then eventually to 7 mg q.i.d. due to headache, flushing, and jaw pain. He has since maintained FC II symptoms on this higher total daily q.i.d. dose regimen.

Three patients with PAH were successfully dosed with oral TRE using a q.i.d. dose regimen. All patients achieved a higher total daily dose (TDD) compared with a t.i.d. dose regimen with improved tolerability. Two of the three patients achieved a 33% increase in the TDD, whereas the other patient had only a slight increase in TDD with q.i.d. dosing. Furthermore, patients were able to maintain FC II symptoms with improvement in adverse effects using the q.i.d. dose compared to the t.i.d. dose that was initially prescribed. The 6MWD showed minimal change during follow-up, but is subject to limitations as a means of evaluating treatment response.[10] Transition to oral treprostinil requires vigilant monitoring due to the potential for clinical deterioration.[7] Therefore, ongoing evaluation of these patients with objective echocardiographic and/or

Table 1. Clinical characteristics of patients treated with oral TRE using a q.i.d. dosing schedule.

	Patient 1	Patient 2	Patient 3
Age, sex	45-year-old man	38-year-old woman	58-year-old man
Diagnosis	IPAH	Late VSD repair	IPAH
Baseline prostacyclin	TRE SQ 40 ng/kg/min × 2 years	TRE IV 50 ng/kg/min × 2 years	TRE INH 9 breaths q.i.d. × 4 years
Background oral therapy	Tadalafil	Bosentan, tadalafil	Bosentan, sildenafil
Switch to oral TRE			
Indication	Site pain/quality of life	Line infection/patient desire	Stable/patient desire
Baseline WHO FC	II	II	II
Baseline 6MWD (m)	515	387	403
Pre-conversion hemodynamics	RA 6 PAP 81/31/51 PCWP 8 CO 5.4 PVR 8	RA 10 PAP 67/26/41 PCWP 13 CO 6.9 PVR 4	RA 0 PAP 91/26/48 PCWP 5 CO 4.2 PVR 10
Oral TRE Maximum tolerated t.i.d. dose	10 mg t.i.d. (TDD = 30 mg)	10 mg t.i.d. (TDD = 30 mg)	9 mg t.i.d. (TDD = 27 mg)
Post-conversion WHO FC	II	II	III
Post-conversion 6MWD (m)	476	378	372
Oral TRE			
Initial q.i.d. dose	8 mg q.i.d. (TDD = 32 mg)	7 mg q.i.d. (TDD = 28 mg)	7 mg q.i.d. (TDD = 28 mg)
Final q.i.d. dose	10 mg q.i.d. (TDD = 40 mg)	10 mg q.i.d. (TDD = 40 mg)	7 mg q.i.d. (TDD = 28 mg)
Final WHO FC	II	II	II
Final 6MWD (m)	457	372	412

IPAH, idiopathic pulmonary arterial hypertension; VSD, ventricular septal defect; TRE, treprostinil; SQ, subcutaneous; IV, intravenous; INH, inhaled; q.i.d., four times daily dosing; WHO, World Health Organization; FC, functional class; 6MWD, 6-min walk distance; RA, right atrial pressure (mmHg); PAP, pulmonary artery pressure (mmHg); PCWP, pulmonary capillary wedge pressure (mmHg); CO, cardiac output (L/min); PVR, pulmonary vascular resistance (Wood units); t.i.d., three times daily dosing; TDD, total daily dose.

hemodynamic testing is critical in the event that a return to parenteral therapy is required. In summary, this is the first clinical report of a novel dosing regimen of oral TRE for the management of PAH and provides further illustration of the importance of achieving clinically effective doses in PAH.[11] Four times daily dosing may merit further study to evaluate the pharmacokinetic profile and to determine long-term clinical effects relative to t.i.d. or b.i.d. doses.

Conflict of interest

The author(s) declare the following conflicts of interest: James C. Coons has received grant funding from United Therapeutics; David C. Ishizawar has served on an advisory board for United Therapeutics. The remaining authors declare that there is no conflict of interest.

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