Transitioning Between Treprostinil Formulations: Evidence and Strategies

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BACKGROUND

- The prostacyclin treatment pathway is an essential pathway for treating pulmonary arterial hypertension.
- Each formulation of treprostinil, a prostacyclin analogue, is associated with advantages and limitations. Because every patient is different, each formulation may benefit a different type of patient.
- Transitions between treprostinil formulations occurs frequently in clinical practice.
- No consensus or guideline exists on how to perform transitions between treprostinil formulations.

Remodulin® (treprostinil) infusion is initiated at low doses and titrated to the maximum tolerable dose. Parenteral treprostinil may be administered as a continuous subcutaneous or intravenous infusion and requires administration via a patient-specific pump. It has a terminal elimination half-life of 4 hours.[43]

The primary limitations associated with parenteral treprostinil are injection site pain, line-related bloodstream infections, and infusion pump complexity.[1,7,8,12]

Tyvaso® (treprositinil) inhalation solution is initiated at 3 breaths four times daily (QID) and titrated to a target dose of 9-12 breaths QID. There is no maximum dose.[44] It is administered through a product-specific device; management of which may be cumbersome for some patients.

Inhaled treprostinil is administered direct-to-lung, resulting in less systemic exposure; however, the dose-limiting adverse event is often cough.[44]

Orenitram® (treprostinil) extended-release tablets are initiated at a dose of 0.125 mg TID or 0.25 mg BID. Oral treprostinil is titrated to the highest tolerated dose in 0.125 mg TID or 0.25-0.5 mg BID increments not more frequent than every 3-4 days.[42]

The most frequently reported dose-limiting adverse events associated with oral treprostinil are headache, diarrhea and nausea.[42]

METHODS

- A literature search was performed to identify publications reporting transitions between treprostinil formulations in patients receiving treatment for PAH and PH-ILD.
- Formulations included treprostinil injection, trepositinil inhalation solution, and treprostinil extended-release tablet.
- Tyvaso DPI® (treprostinil) inhalation powder was not included given paucity of transition data.
- Published materials included manuscripts, congress materials and specialty pharmacy data.
- Publications reporting pediatric data, Delphi analyses or transitions to multiple agents without differentiating outcomes were not included.
- Data collected included the reason for the transition, setting of transition, type of transition, adverse events, and outcomes.

RESULTS

Table 1. Number of Publications Included by Type of Transition and Type of Analysis[1-4, 6-14, 17-18, 22-41]

Type of transition	Number of prospective analyses	Number of retrospective analyses	Number of case reports	Total number of publications
Remodulin to Orenitram	3	5	7	15
Remodulin to Tyvaso	1	4	5	10
Tyvaso to Orenitram		2	3	5
Tyvaso to Remodulin		1	1	2
Orenitram to Remodulin		1	3	4
Orenitram to Tyvaso		1		1
Total number of publications				**37**

Figure 1. Reasons for Transition
n=28 publications

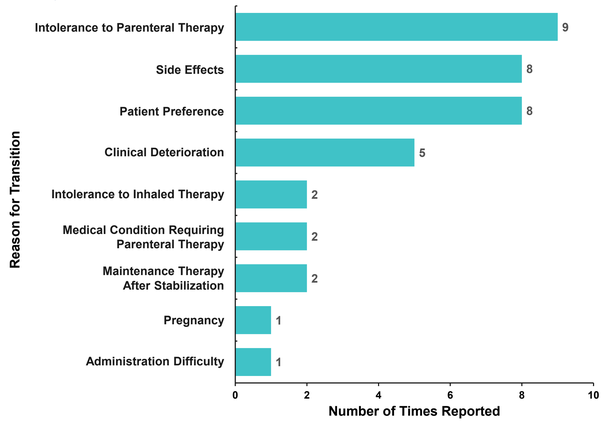

Figure 2. Setting of Transition
n=252 patients

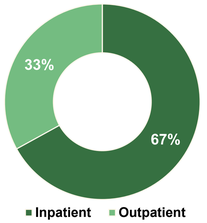

Figure 3. Type of Transition
n=310 patients

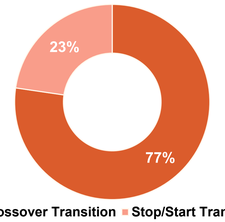

Figure 4. Transition Outcome
n=350

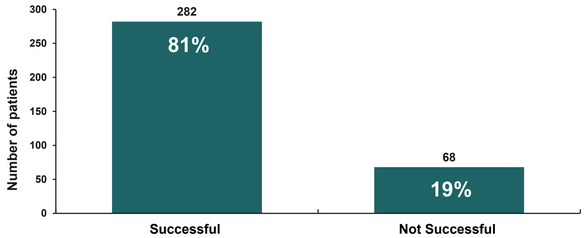

Table 2. Frequently Reported Adverse Events Following Transition

Adverse Event	Number of times reported (%) n=37 publications
Headache	13 (35.1%)
Nausea	9 (24.3%)
Diarrhea	7 (18.9%)
Cough	5 (13.5%)
Dyspnea	5 (13.5%)
Vomiting	5 (13.5%)
Fatigue	4 (10.8%)
Flushing	4 (10.8%)
Jaw pain	3 (8.1%)
Dizziness	3 (8.1%)

LIMITATIONS

- The definition of a successful transition differs across publications. For this analysis, a successful transition was that as outlined by the publishing author.
- Not all clinical parameters were available in all publications.
- Most data are derived from case reports and retrospective analyses.
- A limited number of publications evaluated treprostinil transitions in patients with PH-ILD.

DISCUSSION

- The most common reasons for transitions were intolerance to parenteral therapy, adverse events and patient preference.
- The majority of transitions occurred in the inpatient setting as a crossover transition.
- The most frequent adverse events were headache, nausea, diarrhea, cough and dyspnea, reported in 35%, 24%,19%, 14%, and 14% of publications, respectively.
- 81% of transitions were considered successful.

KEY TAKEAWAYS

- Failure of one treprostinil formulation does not constitute failure of other treprostinil formulations.
- Multiple transition protocols have demonstrated success. Healthcare providers should consider patients' individual clinical needs when devising a transition plan.
- Future clinical decision making for treprostinil transitions will likely rely on case reports, case series, and expert opinion.

REFERENCES

1. Ackerbauer KA et al. *Journal of Pharmacy Practice.* 2017;31(2):163-166; **2.** Ali R et al. *CHEST* 2019 156:4*Supplement* (A1704-A1705). **3.** Ataya A et al. *Pulm Pharmacol Ther.* 2016;40:39-43; **4.** Balasubramanian VP et al. Pulm Circ. 2018;8(2):2045894018770654; **5.** Bourge RC et al. *J Am Coll Cardiol.* 2013;31(1):38–44; **6.** Bryan LG et al. Presented at PHA's PHPN Symposium. October 5-7, 2017. North Bethesda, Maryland; **7.** Chakinala MM et al. *J Heart Lung Transpl.* 2017;36(2):193-201; **8.** Coons JC et al. *Pulm Circ.* 2017;8(1):1-4. Coons JC, *Pulm Circ.* 2016;6(1):132-135; **9.** D'Albini L et al. Presented at American Thoracic Society International Conference. May 19-24, 2017. Washington, DC. A2298; **10.** de Jesus Perez VA et al. *Am J Cardiol.* 2012;110(10):1546-1550; **11.** Enderby CY et al. *J Clin Pharm Ther.* 2014;39(5):496-500; **12.** Fearon-Clarke J et al. Presented at PHA's International PH Conference. June 29 – July 1, 2018. Orlando, Florida. Abstract 1073; **13.** Felder A et al. Presented at PHA's PHPN Symposium. October 5 – 7, 2017. North Bethesda, Maryland. Abstract 1043; **14.** Gleason JB et al. *Case Rep Pulmonol.* 2015;2015:498981; **15.** Humbert M et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J.* 2022. 11;43(38):3618-3731; **16.** Hoeper MM et al. *N Eng J Med.* 2023;338:1478-1490; **17.** Jarrett H et al. *J Heart Lung Transplant.* 2018;37(4S):S494; **18.** Kimmig LM et al. *Lung.* 2020;198(1):53-58; **19.** Kingrey JF et al. *Pulm Circ.* 2023; 13:e12255; **20.** Kumar P et al. *Clin Pharmacokinet.* 2016;55(12):1495-1505; **21.** Lim A et al. *J Clin Pharm Ther.* 2013;28(6):450–5; **22.** Maestas T et al. *Pulm Circ.* 2018;8(4):2045894018797270; **23.** McLaughlin VV et al. *J Am Coll Cardiol;* **24.** 2010 May 4;55(18):1915–22; **25.** Migliore C et al. Presented at American Thoracic Society International Conference. May 19-24, 2017. Washington, DC. A2280; **26.** Miller CE et al. *Respir Med.* 2023;218:107374; **27.** Nathan SD et al. *Am J Respir Crit Care Med.* 2013;187:A3276; **28.** Nelsen AC et al. *Am J Respir Crit Care Med.* 2010;181:A338; **29.** Oudiz R et al. *Pulm Circ.* 2016;6(4):532-538; **30.** Pan IZ et al. *Front Med* (Lausanne). 2020;7:81. 2020 Mar 31; **31.** Parikh, R et al. *ERJ Open Research.* 2024;10(1), 00659-2023; **32.** Preston IR et al. *Pulm Circ.* 2014 Sep;4(3):456-61; **33.** Raina A et al. *Pulm Circ.* 2013;3(1):116-120; **34.** Sargent T et al. *Pulm Circ.* 2020;10(3):2045894020931324; **35.** Singh M et al. *Chest.* 2010;138 (4_MeetingAbstracts):369A; **36.** Smith ZR et al. *Journal of Pharmacy Practice.* 2018;32(5):599-604; **37.** Suliman SA et al. *Am J Respir Crit Care Med.* 2018;197:A5681; **38.** Traiger G. Presented at the 2011 PH Professional Network Symposium; September 22-24, 2011; Arlington, VA (abstract); **39.** Waxman A et al. *N Engl J Med.* 2021;384:325-334; **40.** Wilson M et al. PHPN Symposium (PHPN) 2011. Crystal City, VA. Sept 23-24, 2011; **41.** Zwicke DL et al. *Pulm Circ.* 2021;11(1):2045894021998203. **42.** Orenitram US Prescribing Information. United Therapeutics Corporation. Research Triangle Park, NC 27709; **43.** Remodulin US Prescribing Information. United Therapeutics Corporation. Research Triangle Park, NC 27709; **44.** Tyvaso US Prescribing Information. United Therapeutics Corporation. Research Triangle Park, NC 27709.

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