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Different Efficacy of Inhaled and Oral Medications in Pulmonary Hypertension

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Abstract

Pulmonary arterial hypertension (PAH) is progressive disorder characterized by elevated pulmonary vascular resistance that can lead to right heart failure and death. One of the main therapeutic options for PAH are medications targeting the prostacyclin pathway. Treprostinil is a prostacyclin analogue and selexipag is a selective IP receptor agonist. Treprostinil can be delivered by a variety of routes including oral, inhaled, subcutaneous and intravenous. Selexipag is currently approved as an oral formulation. The impact of the route of deliver and the optimal dosing for transitioning inhaled treprostinil to oral treprostinil or selexipag is unknown. More importantly, given the different selectivity for prostacyclin receptors, it is uncertain whether treprostinil and selexipag can be substituted. We present two patients with PAH who received medications targeting the prostacyclin pathway and were transitioned from inhaled treprostinil to either oral treprostinil or selexipag. In both cases, we noted clinical, functional and hemodynamic

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deterioration. These cases highlight that the route of delivery (inhaled versus oral) and/or the specific PH medication (treprostinil versus selexipag) matter; therefore close monitoring during transitions is imperative.

Keywords

Pulmonary arterial hypertension; treprostinil; selexipag; route of delivery; bioavailability

Pulmonary arterial hypertension (PAH) is progressive disorder that if left untreated leads to right heart failure and death (1). Abnormalities in the prostacyclin pathway play an important role in the pathobiology of PAH. Patients with PAH have a marked reduction in prostacyclin synthase (2) and expression of prostaglandin I₂ receptors in the lungs (3). Hence, the prostacyclin analogues such as treprostinil(4, 5) and prostacyclin IP receptor agonists(6) constitute a major therapeutic option to treat PAH.

Treprostinil is a chemically stable, tricyclic analogue of prostacyclin(7) which is available in three different formulations and can be administer by four different routes: Remodulin® (treprostinil sodium, given by intravenous and subcutaneous administration), Tyvaso® (treprostinil sodium, given by inhalation), and Orenitram® (treprostinil diolamine given by oral route). Inhaled treprostinil is Food and Drug Administration (FDA) approved for the treatment of PAH patients in New York Heart Association (NYHA) class III, based on results of the TRIUMPH study (4). Oral treprostinil is FDA approved for the treatment of PAH patients in NYHA class II-III based on results of the FREEDOM-M study (5). Selexipag (Uptravi®) is an oral selective prostacyclin IP receptor agonist which is currently available as an oral formulation. Selexipag is FDA approved for the treatment of PAH patients in NYHA class II and III, based on the results of the GRIPHON study (6).

Scarce data from small case series is available to guide the transition among different treprostinil products (4, 8–12). A case report exists on the transition of inhaled treprostinil to oral selexipag (13). It remains unknown whether PH therapies that act in the prostacyclin pathway are similarly efficacious when delivered orally or by the inhaled route. We present two patients in whom transition from inhaled treprostinil to either oral treprostinil or selexipag had a major impact on clinical, functional and hemodynamic parameters, stressing that caution must be exercised when considering switching routes of delivery of treprostinil or transitioning treprostinil to selexipag.

Case 1 description

A 51-year-old man with heritable PAH received treatment with sildenafil 20 mg every 8 hours. Given persistent symptoms inhaled treprostinil was added (9 inhalations (54mcg) four times a day). The patient noticed symptomatic improvement with an increase in six-minute walked distance (6MWD) and a pronounced decrease in pulmonary vascular resistance (PVR). The patient's condition remained stable during a 4-year period; however, he reported difficulties in adhering with inhaled treprostinil 4 times a day. Therefore, he was switched to oral treprostinil with the dose titrated up to maximum tolerated (3 mg three times daily). Both before and after this transition he was also treated with tadalafil 40mg daily and

bosentan 125mg twice a day. A few months after receiving oral treprostinil he started having progressive dyspnea, nausea, leg pain, and fatigue. An echocardiogram revealed dilation of the right ventricle (RV) and a right heart catheterization (RHC), repeated after 15 months of receiving oral treprostinil, showed hemodynamic deterioration. Since the patient declined parenteral prostacyclin analogues, he was transitioned back to inhaled treprostinil (9 inhalations (54 mcg) 4 times a day) with improvement of his hemodynamic profile (table 1).

Case 2 description

A 50-year-old woman with PAH due to connective tissue disease was treated with bosentan 62.5 mg twice a day immediately after diagnosis. Due to persistent symptoms (NYHA III), first Tadalafil 40mg daily and then inhaled treprostinil (9 inhalations (54 mcg) four times daily) were added. Under this combination, the patient had symptomatic and echocardiographic improvement. During the 4-year follow-up, the patient's condition remained stable; however, she encountered difficulties in using inhaled treprostinil 4 times a day. Therefore, the patient was switched to oral selexipag with a dose titrated up to the maximum tolerated, i.e. 1400 mcg twice daily. On oral selexipag the patient experienced diarrhea and progressive dyspnea through the course of a few months. In addition, an echocardiogram obtained 2 months after initiation of oral selexipag showed an increase in right ventricular basal diameter and estimated right ventricular systolic pressure. Thus, the patient was switched back to inhaled treprostinil (9 inhalations (54mcg) 4 times a day) which resulted in clinical and echocardiographic improvement of her condition (table 2).

Discussion

Our study highlights the challenges in transitioning PH medications that work on the prostacyclin pathway from the inhaled to oral route of administration, even when maximum tolerated doses of the oral medication were provided. The cases presented emphasize the critical need to closely monitor these patients both during and after transition to be able to promptly manage a potential deterioration of their disease. Interestingly, when patients were switched back from oral (treprostinil or selexipag) to inhaled treprostinil their condition improved.

Inhaled and oral treprostinil offer the advantage of avoiding certain risks associated with the parental administration of prostacyclin analogues, such as infusion site pain, line dislodgment, and skin and bloodstream infections (4). Inhaled treprostinil is generally well tolerated with side effects (occurring in 10 % of patients) including cough, headache, nausea, dizziness, flushing, throat irritation, pharyngeal/laryngeal pain and diarrhea (4). Bioavailability is around 64–72%, time to peak between 0.12 – 0.25 h and terminal half-life of 4 hours (package insert). Side effects of oral treprostinil (occurring in 10 % of patients) include headache, nausea, diarrhea, jaw pain, vomiting, flushing and pain on the extremities (5). Oral absorption of treprostinil is increased when administered after a high-fat, high calorie meal with a bioavailability of ~17% and a time to peak around 4–6 hours. Both the inhaled and oral routes of administration require up-titration. The inhaled form of treprostinil is given 4 times a day while the oral formulation is administered every 8 to 12 hours (14).

Limited information exists on transitioning inhaled to oral treprostinil or vice versa. Coleman et al.(15) reported their experience in 8 pediatric patients (10–20 years old) with clinically stable PAH (5 idiopathic and 3 associated with congenital heart disease) in whom 5 subjects were transitioned from inhaled to oral treprostinil. These transitions were successful, but one patient later discontinued oral treprostinil due to migraines (15). Jorgensen et al.(11) transitioned 6 pediatric patients (7–21 years old) with PAH from inhaled (average dose of 172 mcg/day) to oral treprostinil (average dose of 3.5 mg/day) and of them, 3 experienced side effects (nausea, diarrhea, and loss of appetite) and one had sudden death (unclear if related to the transition or other factors) (11). Coons et al. (10) transitioned 2 patients with PAH from inhaled (72 mcg 4 times a day) to oral treprostinil (2.5 mg for one and 4 mg for the other subject, given every 8 hours). Both patients had side effects including headache, jaw pain, diarrhea and flushing. In one subject the dose was increased to 7mg every 6 hours (week 52 from initial transition), while the other patient was later enrolled in hospice (10). Khan et al. (12) transitioned 2 PAH patients from inhaled (54 and 72 mcg 4 times a day) to oral treprostinil (3 mg every 8 hours). In both patients the 6MWD improved and NYHA functional class remained stable (12). These data suggest that the transition from inhaled to oral treprostinil is feasible and that headaches and gastrointestinal side effects are expected. At the end of the transition the oral dose of treprostinil was usually around 2.5–4 mg every 8 hours. Our patient, in case 1, was transitioned from inhaled (54mcg every 6 hours) to oral treprostinil 3 mg every 8 hours, a dose that falls in the range described (10–12, 15). Treprostinil was initially given as 4 mg twice a day, but rapidly increased to 3 mg thrice a day. Chakinala et al. transitioned patients from parenteral to oral treprostinil and noted that the oral dose of the medication appears to be better tolerated when given 3 instead of 2 times a day, possibly by reducing the peak:trough fluctuations (16).

Selexipag is an oral selective IP prostacyclin receptor agonist. Side effects noted in more than 10% of the patients include headache, diarrhea, nausea, jaw pain, vomiting, pain in extremities, myalgia, flushing (6). Selexipag is titrated to the highest tolerated or the maximum dose of 1,600 mcg twice daily (6). Oral selexipag is characterized by rapid absorption (maximum plasma concentration within 1–3 hours), bioavailability of 50% and terminal half-life of 0.8–2.5 hours which is extended by an active metabolite to 6.2–13.5 hours (17) (package insert). A recent case report described a successful (defined by stable NYHA functional class and estimated RVSP) transition from inhaled treprostinil (12 inhalations (72 mcg) 4 times daily) to oral selexipag (1600 mcg twice daily) over a period of 8 weeks (13). Future results from an ongoing study (NCT02471183, TRANSIT-1: study to assess the tolerability and the safety of the transition from inhaled treprostinil to oral selexipag in patients with PAH) will help guide this transition.

It remains unclear whether the route of administration and the type of medications that work on the prostacyclin pathway may influence the treatment efficacy. In the cases presented, inhaled treprostinil was transitioned to either oral treprostinil or selexipag with associated worsening of PAH that then partially improved after switching back to inhaled treprostinil. These different responses may suggest either a reduced gastrointestinal absorption with lower systemic levels of the medication in certain patients, a preferential (local) effect of the inhaled medication directly on the pulmonary vasculature, and/or intrinsic differences between treprostinil and selexipag that have differential effects on prostacyclin receptors

(18). We believe that our patients were compliant in taking either the inhaled or oral PAH medications. We have no reason to believe that they preferentially did not take to oral formulation. Further research is needed to better understand the discordant response noted between inhaled and oral medications in these 2 patients.

Conclusions

Pulmonary arterial hypertension medications may have different effectiveness depending on the route of administration (inhaled versus oral) and/or the type of medication used (treprostinil versus selexipag). Further investigations are needed to better guide these transitions and identify patients in whom switching from inhaled to oral formulation might not be appropriate.

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Abbreviations

6WMD	six-minute walk distance
PAH	pulmonary arterial hypertension
RVSP	right ventricular systolic pressure
FDA	Food and Drug Administration
BMI	body mass index
NYHA	New York Heart Association
WHO	World Health Organization
RHC	right heart catheterization

References

1. Tonelli AR, Arelli V, Minai OA, Newman J, Bair N, Heresi GA, et al. Causes and circumstances of death in pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2013; 188(3):365–9. [PubMed: 23600433]
2. Tuder RM, Cool CD, Geraci MW, Wang J, Abman SH, Wright L, et al. Prostacyclin synthase expression is decreased in lungs from patients with severe pulmonary hypertension. *Am J Respir Crit Care Med*. 1999; 159(6):1925–32. [PubMed: 10351941]
3. Falcetti E, Hall SM, Phillips PG, Patel J, Morrell NW, Haworth SG, et al. Smooth muscle proliferation and role of the prostacyclin (IP) receptor in idiopathic pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2010; 182(9):1161–70. [PubMed: 20622039]
4. McLaughlin VV, Benza RL, Rubin LJ, Channick RN, Voswinckel R, Tapson VF, et al. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. *J Am Coll Cardiol*. 2010; 55(18):1915–22. [PubMed: 20430262]
5. Galie N, Corris PA, Frost A, Girgis RE, Granton J, Jing ZC, et al. Updated treatment algorithm of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2013; 62(25 Suppl):D60–72. [PubMed: 24355643]

6. Sitbon O, Channick R, Chin KM, Frey A, Gaine S, Galie N, et al. Selexipag for the Treatment of Pulmonary Arterial Hypertension. *N Engl J Med*. 2015; 373(26):2522–33. [PubMed: 26699168]
7. Kumar P, Thudium E, Laliberte K, Zaccardelli D, Nelsen A. A Comprehensive Review of Treprostinil Pharmacokinetics via Four Routes of Administration. *Clin Pharmacokinet*. 2016
8. Ataya A, Somoracki A, Cope J, Alnuaimat H. Transitioning from parenteral to inhaled prostacyclin therapy in pulmonary arterial hypertension. *Pulm Pharmacol Ther*. 2016; 40:39–43. [PubMed: 27470680]
9. Bourge RC, Tapson VF, Safdar Z, Benza RL, Channick RN, Rosenzweig EB, et al. Rapid transition from inhaled iloprost to inhaled treprostinil in patients with pulmonary arterial hypertension. *Cardiovasc Ther*. 2013; 31(1):38–44. [PubMed: 22970909]
10. Coons JC, Miller T, Simon MA, Ishizawa DC, Mathier MA. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients transitioned from parenteral or inhaled prostacyclins: case series and treatment protocol. *Pulm Circ*. 2016; 6(1):132–5. [PubMed: 27162621]
11. LOJ, RWD. Body mass index during transition from inhaled to oral treprostinil. *Pulm Circ*. 2015; 5(4):744–50.
12. Khan AA, Ackerbauer K, RT. Safety and tolerability of outpatient transmission of parental and inhaled treprostinil to oral treprostinil in patient with pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2016; 193:A3970.
13. El-Kersh K, Smith JS. Transition From Inhaled Treprostinil to Selexipag in Pulmonary Arterial Hypertension. *Am J Ther*. 2016
14. Park, RT., editor. Corp NUT. Orenitram (treprostinil) [prescribing information]. Research Triangle Park, NC: United Therapeutics Corp; Jan. 2016
15. BAC, MC, DDI. Initial Clinical experience with oral treprostinil (UT-15C) in pediatric pulmonary hypertension at a single center. *Pulm Circ*. 2015; 5(4):744–50.
16. Chakinala MM, Feldman JP, Rischard F, Mathier M, Broderick M, Leedom N, et al. Transition from parenteral to oral treprostinil in pulmonary arterial hypertension. *The Journal of heart and lung transplantation: the official publication of the International Society for Heart Transplantation*. 2016
17. Kaufmann P, Hurst N, Astruc B, Dingemanse J. Absolute oral bioavailability of selexipag, a novel oral prostacyclin IP receptor agonist. *Eur J Clin Pharmacol*. 2016
18. Mitchell JA, Ahmetaj-Shala B, Kirkby NS, Wright WR, Mackenzie LS, Reed DM, et al. Role of prostacyclin in pulmonary hypertension. *Glob Cardiol Sci Pract*. 2014; 2014(4):382–93. [PubMed: 25780793]

Table 1

Functional, echocardiographic and hemodynamic assessments in patient 1

	At time of diagnosis	Before inhaled treprostnil	On inhaled treprostnil	On oral treprostnil	Back on inhaled treprostnil
PAH therapies	Sildenafil 20mg every 8h	Sildenafil 20mg every 8h	Sildenafil 40mg every 8h & inhaled treprostnil 54mcg 4 times a daily	Tadalafil 40mg daily, bosentan 125mg every 12h & oral treprostnil 3mg three times daily	Bosentan 125mg every 12h, Tadalafil 40mg daily & inhaled treprostnil 54mcg 4 times a daily
NYHA class	III	II	II	I/II	I/II
6MWT (meters walked & % predicted)	479 (76%)	567 (92%)	631 (108%)	658 (112%)	N/A
Echocardiogram *					
TAPSE (mm)	7.0	16.6	15.4	15.8	N/A
RV basal diameter (mm)	47.8	42.7	37.3	52.6	
RVOT notching	Yes	N/A	No	Yes	
RVOT AT (ms)	22	N/A	34	20	
Tricuspid annular systolic velocity (S') (cm/s)	N/A	N/A	12	10	
Right Heart Catheterization					
RA (mmHg)	28	8	1	16	8
MPAP (mmHg)	78	70	24	73	39
PCWP (mmHg)	23	10	11	21	20
CI (L/min/m ²)	2.4	2.0	2.6	2.0	2.1
TPG (mmHg)	55	60	23	52	19
PVR (Wood units)	10.1	13.0	2.1	9.4	3.5

* RVSP could not be measured because of the inadequate envelope of the tricuspid regurgitation flow.

NYHA: New York Heart Association

PAH: pulmonary arterial hypertension

6MWT: 6-minute walk test

TAPSE: tricuspid annular plane systolic excursion.

RV: right ventricle

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RVOT: right ventricular outflow tract
RVOT AT: right ventricular outflow tract flow acceleration time
RA: right atrium
MPAP: mean pulmonary artery pressure
PCWP: pulmonary capillary wedge pressure
CI: cardiac index
TPG: transpulmonary pressure gradient
PVR: pulmonary vascular resistance

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Table 2

Functional, echocardiographic and hemodynamic assessments in patient 2.

	At time of diagnosis	Before inhaled treprostinil	On inhaled treprostinil	On oral treprostinil	Back on inhaled treprostinil
PAH therapies	Bosentan 62.5mg every 12h	Bosentan 125mg every 12h & tadalafil 40mg daily	Bosentan 125mg every 12h, inhaled treprostinil 54mcg 4 times a day & tadalafil 40mg daily	Bosentan 125mg every 12h, tadalafil 40mg daily & selexipag 1400mcg every 12h	Bosentan 125mg every 12h, tadalafil 40mg daily & inhaled treprostinil 54mcg 4 times a day
NYHA class	III	III	I/II	III	II
6MWT (meters walked & % predicted)	N/A	328 (60%)	379(69%)	241 (47%)	363 (69%)
Echocardiogram					
TAPSE (mm)	2.3	2.3	3.0	1.3	1.9
RV basal diameter (mm)	3.8	3.1	3.3	4.8	4.3
RVOT notching	Yes	Yes	Yes	Yes	Yes
RVOT AT (ms)	48	72	60	44	55
Tricuspid annular systolic velocity (S') (cm/s)	11	12	14	5	9
RVSP (mmHg)	86	62	38	102	77
Right Heart Catheterization					
RA (mmHg)	6	10	N/A	N/A	14
MPAP (mmHg)	60	52	N/A	N/A	60
PCWP (mmHg)	8	14	N/A	N/A	11
CI (L/min/m ²)	2.04	2.7	N/A	N/A	2.5
TPG (mmHg)	52	38	N/A	N/A	49
PVR (Wood units)	13	7	N/A	N/A	10

NYHA: New York Heart Association

PAH: pulmonary arterial hypertension

6MWT: 6-minute walk test

TAPSE: tricuspid annular plane systolic excursion

RV: right ventricle

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RVOT: right ventricular outflow tract
RVOT AT: right ventricular outflow tract flow acceleration time
RA: right atrium
MPAP: mean pulmonary artery pressure
PCWP: pulmonary capillary wedge pressure
CI: cardiac index
TPG: transpulmonary pressure gradient
PVR: pulmonary vascular resistance

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