Review Article

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A systematic review of transition studies of pulmonary arterial hypertension specific medications

Avraham Sofer[1], Michael J. Ryan[2], Ryan J. Tedford[3], Joel A. Wirth[4] and Wassim H. Fares[1]

[1]Section of Pulmonary, Critical Care & Sleep Medicine, Department of Internal Medicine, Yale University, New Haven, CT, USA; [2]French Hospital Medical Center, San Luis Obispo, CA, USA; [3]Johns Hopkins University School of Medicine, Baltimore, MD, USA; [4]Tufts University, Boston, MA & Maine Medical Center, Portland, ME, USA

Abstract

Pulmonary arterial hypertension (PAH) is a progressive potentially fatal disease. Multiple pharmacologic options are now available, which facilitated transitions between different therapeutic options, although the evidence for such transitions has not been well described. We sought to review the evidence supporting the safety and/or efficacy of transitioning between PAH-specific medications. We performed a systematic review of all published studies in the Medline database between 1 January 2000 and 30 June 2016 reporting on any transition between the currently Food and Drug Administration (FDA)-approved PAH-specific medications. Studies reporting on three or more adult patients published in the English language reporting on transitions between FDA-approved PAH medications were extracted and tabulated. Forty-one studies met the selection criteria, nine of which included less than eight patients (and thus were reported separately in the supplement), for a total of 32 studies. Transitioning from parenteral epoprostenol to parenteral treprostinil appears to be safe and efficacious in patients who have less severe disease and more favorable hemodynamics. Transitioning from a prostacyclin analogue to an oral medication may be successful in patients who have favorable hemodynamics and stable disease. There is conflicting evidence supporting the transition from a parenteral to an inhaled prostacyclin analogue, even in patients who are on background oral therapy. Currently, the only evidence in support of transitioning between oral PDE5 inhibitors is from sildenafil to tadalafil. Patients on higher doses of sildenafil are more likely to fail. In patients with liver abnormalities due to bosentan or sitaxentan, the transition to ambrisentan appears to be safe and can result in clinical improvement. Studies regarding PAH medication transitions are limited. Patients who have less severe disease, better functional status, and are on lower medications doses may be more successful at transitioning.

Keywords

pulmonary hypertension, transition, pulmonary arterial hypertension, pulmonary vascular disease, pharmacotherapy

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Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary vasculature that, if left untreated, has a very poor prognosis.[1–3] Since the introduction of infused epoprostenol in 1996, the number and routes of PAH-specific therapies have dramatically increased.[4,5] Currently, there are 14 therapies for PAH approved by the United States Food and Drug Administration (FDA) that are available through the intravenous (IV), subcutaneous (SQ), inhaled (IH), and oral routes. These drugs target three main pathways: the nitric oxide, endothelin-1, and prostacyclin pathways; and they currently include five families of drugs: phosphodiesterase type-5 inhibitors (PDE5-I), guanylate cyclase stimulator, endothelin receptor antagonists (ERA), prostacyclin analogues, and selective prostacyclin receptor agonists.[5–7] The availability of different classes of medications, different routes, and total number of available PAH-specific medications makes the

Corresponding author:
Wassim H. Fares, Yale University, 15 York Street, LCI 105-C, New Haven, CT 06510, USA.
Email: wassim.fares@yale.edu

number of potential transitions within the same class or between classes relatively large. These transitions are already occurring not uncommonly in clinical practice, and there may be pressure by external forces (i.e. third-party payers) to switch medications, often in the absence of high quality data about long-term clinical outcomes/consequences.

Despite the development of newer oral and IH therapies, most patients with advanced disease or rapidly progressive disease still require continuously infused parenteral prostacyclin analogues. Additionally, there is new interest in both upfront and sequential combination therapies.[4] Over 50% of patients with PAH are on more than one PAH-specific therapy.[8] At several large PAH centers, approximately 10% of patients on parenteral prostacyclin have attempted to transition to other therapies.[8,9] Typically, patients will attempt to transition therapies because of complications such as line infections[10] or vein stenosis in the case of IV therapies, site pain caused by SQ therapies, intolerable side effects from therapy, or to improve medication compliance relative to the simplicity of dosing with some newer agents.

To evaluate the evidence supporting the efficacy and safety of transitions between PAH-specific medications, we performed a systematic review of published studies of adult patients who were transitioned between the currently FDA-approved PAH therapies.

Materials and methods

Search and selection criteria

We utilized the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[11] to perform a systematic review of all published studies in the Medline database between 1 January 2000 and 30 June 2016 reporting on any transition between the currently FDA-approved PAH-specific medications. Studies were identified using the following search strategy: [''switch'' or ''switched'' or ''switching'' or ''conversion'' or ''converted'' or ''transition'' or ''transitioned'' or ''transitioning''] AND ''pulmonary'' AND ''hypertension''; dates limit: 01/01/2000 through 06/30/2016.

We excluded case reports (reporting on less than three patients), studies including pediatric patients (age < 18 years), studies without a published English translation, and studies exclusively reporting on currently non-approved PAH medications (e.g. sitaxsentan) (e-Table 1). We report the studies that had less than eight patients in the supplement only, and we tabulate the studies separately based on their study design: retrospective versus prospective to reflect the differential quality level of the different studies presented. Three of the studies were reported as a ''transition'' from IH to infused prostacyclin analogues; however, we consider these ''transitions'' as escalation of care rather than transition, so we report them separately.

Data extraction and assessment of risk of bias

To avoid bias, three investigators (WHF, AS, and JAW) independently reviewed the literature and identified the potential studies for inclusion in this systematic review (e-Table 1). All five investigators performed data extraction/abstraction.

Results

A total of 32 studies are included in the systematic review (Fig. 1). Additional nine studies had less than eight patients and thus were reported separately in the supplement (e-Tables 2–4).

Intra-class PAH medication transitions: from one infused prostacyclin analogue to another infused prostacyclin analogue

There were 11 studies involving the transition from one infused prostacyclin analogue (either IV or SQ) to another infused prostacyclin analogue (Table 1), with a total of 377 patients studied. Two of the 11 studies were retrospective; eight of the studies were prospective open-label studies; and one study[12] was a prospective, randomized controlled trial. The duration of the studies were in the range of 1–12 months. Five out of the nine prospective studies involved transition from IV epoprostenol to either IV or SQ treprostinil, with a total of 108 transition patients studied. The rate of successful transition in these five studies was 86/108 (80%). In general, patients who were successfully transitioned had less severe disease (New York Heart Association [NYHA]) functional class I or II, or World Health Organization [WHO] functional class II or III) and more favorable hemodynamics at baseline. Overall, there was no worsening in WHO functional class or significant differences in 6-minute walk distance (6MWD) in patients who completed the transition.

Only three small studies involved the transition from either SQ or IV treprostinil to IV epoprostenol (Table 1 and e-Table 2), with a total of 18 patients studied and a success rate of 67%. In one of these studies,[13] two of the four ''transition'' patients died; however, these four patients were transitioned (escalation of care) specifically to try to mitigate clinical worsening of their PAH, rather than for reasons of intractable medication side effects or non-adherence.

Four out of the 11 studies involved the transition from a traditional formulation of IV epoprostenol to a thermostable form, with a total of 254 patients studied and a success rate of 76%. Patients who transitioned successfully tended to have improved quality of life and treatment satisfaction scores. In one of these studies,[14] which was a prospective, open-label registry, freedom from hospitalization rates were higher in patients who transitioned to thermostable IV epoprostenol.

There were no significant safety events in the majority of the studies. In the study by Benza et al.,[15] in which 31

Table 1. Intra-class PAH medication transitions: infused prostacyclin analogue to another infused prostacyclin analogue.

No.	Original drug	Drug transitioned to	Publication year/ Authors	Study design	PAH patients	Time	Outcome (transition success)	Comments
Prospective								
1	IV epoprostenol	SQ treprostinil	2007 / Rubenfire et al.[12]	Prospective randomized placebo-controlled trial	22	8 weeks	Successful in 13/14 patients randomized to transition to SQ treprostinil	Patients had stable WHO FC II or III disease 6MWD worsened by 35 m after transition to SQ treprostinil
2	IV epoprostenol	IV treprostinil	2005 / Gomberg-Maitland et al.[27]	Prospective open-label	31	3 months	Successful in 27/31 patients	WHO FC, 6MWD were unchanged Hemodynamics worse
3	IV epoprostenol	IV treprostinil	2007 / Sitbon et al.[28]	Prospective open-label	12 (NYHA class I or II)	3 months	Successful in 12/12 patients	Epoprostenol dose 28 ± 14 ng/kg/min Treprostinil dose 62 ± 30 ng/kg/min Fewer adverse events and all remained on treprostinil
4	IV epoprostenol	IV treprostinil	2013 / Benza et al.[15]	Prospective open-label	31 transition patients (out of total of 47 patients reported, 16 of which are de novo)	11 months	Successful transition (defined as freedom from death, lung transplantation, atrial septostomy, or discontinuation of IV treprostinil) in 77% of transition patients	No change in exercise capacity, WHO FC or hemodynamics at 11 months Two transition patients died and six discontinued the study due to adverse events
5	IV epoprostenol	IV treprostinil	2013 / Minai et al.[29]	Prospective open-label	10	8 weeks	Successful in 10/10 patients	No change in 6MWD; no worsening WHO FC; improved QOL and satisfaction, less time on drug prep activities
6	IV epoprostenol	IV thermostable epoprostenol	2013 / Tamura et al.[30]	Prospective open-label	8	12 weeks	Successful in 8/8 patients	No safety events or change in hemodynamics, improved satisfaction scores

(continued)

Table 1. Continued

No.	Original drug	Drug transitioned to	Publication year/ Authors	Study design	PAH patients	Time	Outcome (transition success)	Comments
7	IV epoprostenol	IV thermostable epoprostenol	2014 / Sitbon et al.[31]	Prospective open-label	41	3 months	Successful in 37/41 patients	TSQM scores showed an improvement in treatment convenience at 3 months
8	IV epoprostenol	IV thermostable epoprostenol	2015 / Provencher el al.[32]	Prospective open-label	16	4 weeks	Successful in 16/16 patients	No change in SF-36 HRQoL, WHO FC, 6MWD, NT-proBNP Most patients preferred the thermostable product
9	IV epoprostenol	IV thermostable epoprostenol	2015 / Frantz et al.[14]	Prospective open-label registry	189 transition patients (out of a total cohort of 336 patients)	12 months	Successful in 132/189 PAH transition patients	Freedom from hospitalization: 57.1 ± 3.7%; 1-year survival: 87.7 ± 2.5%
Retrospective								
10	IV epoprostenol	SQ treprostinil	2002 / Vachiéry et al.[33]	Retrospective	8	4–11 months	Successful in 7/8 patients	Transition achieved in 21–96 h, with no major adverse effects or worsening in clinical status All patients reported improved comfort at follow-up
11	SQ treprostinil	IV treprostinil or IV epoprostenol	2014 / Alkukhun et al.[34]	Retrospective	9 (7 with PAH, 2 with CTEPH)	12 months	Successful in 8/9 patients	Reasons for SQ to IV switch were site pain (n = 6), major surgery (n = 2) and septic shock (n = 1) SQ treprostinil to IV treprostinil: dose = 84.9 to 70.8 ng/kg/min SQ treprostinil to IV epoprostenol: dose = 24.5 to 13.3 ng/kg/min

6MWD, 6-minute walk distance; FC, functional class; HRQoL, health-related quality of life; IV, intravenous; mPAP, mean pulmonary artery pressure; N/A, not applicable; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; QOL, quality of life; SF-36, short form (36) health survey; SQ, subcutaneous; TSQM, treatment satisfaction questionnaire for medication; WHO, World Health Organization.

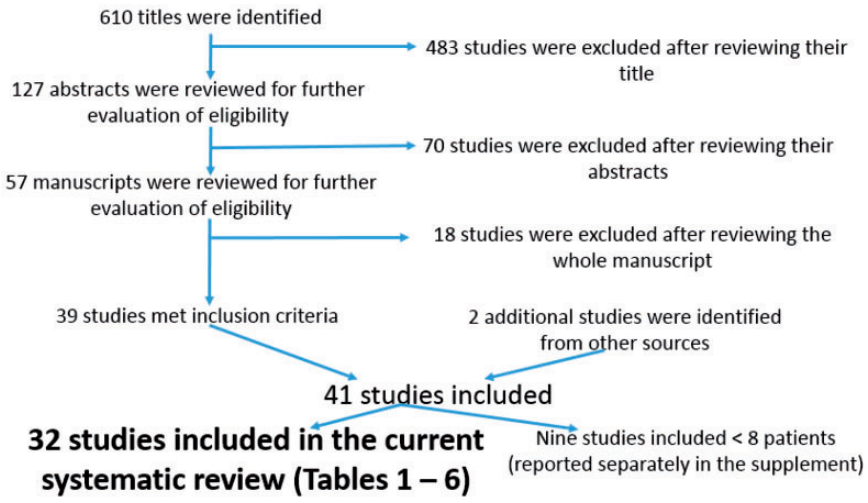

Fig. 1. PRISMA diagram of the selection of the studies included in the systematic review.

patients were transitioned from IV epoprostenol to IV treprostinil, a total of eight transition patients died or discontinued the drug; however, the authors concluded that none of the deaths were related to treprostinil.

Intra-class PAH medication transitions: from a prostacyclin analogue via one route to a prostacyclin analogue via another route

There were five studies involving the transition from a prostacyclin analogue via one route (i.e. infused, IH, or oral) to another route (other than from infused to another infused medication or route) (Table 2), with a total of 170 patients studied. Three of the five studies were retrospective studies; two were prospective, open-label studies. The duration of most of the studies was in the range of 6–12 months. Three additional studies (Table 3) involved the "transition" from an IH prostacyclin analogue to either IV or SQ prostanoid, with a total of 63 patients studied. These were not true transitions, as such a "transition" is considered an escalation of care. In general, these patients had worse baseline functional status and hemodynamic impairment and were transitioned from inhaled to parenteral prostanoids as a form of rescue therapy. The transition resulted in clinical and hemodynamic short-term stabilization in a majority of the patients, but did not prevent subsequent disease progression, as many patients still died and others required lung transplantation (Table 3).

Two retrospective studies involved the transition from either IV or SQ prostacyclin analogue to an inhaled form, with 55 patients studied. The transition was considered successful in one of these studies.[9,16] In a study by Channick et al.,[9] in which 81% of patients remained free of clinical symptoms one year after transitioning, one of the major predictors of transition success was the use of background oral PAH therapy. In a small study by Enderby et al.[16] (e-Table 3), in which the transition was considered successful in 3/3 patients, all three patients were on oral PAH therapy prior to the transition. By contrast, in the study by de Jesus Perez et al.,[17] in which 18 patients on infused prostanoids as well as background oral PAH therapy were transitioned to IH treprostinil, there was a deterioration in WHO functional class as well as worsening of the 6MWD and NT-proBNP level in a minority of the patients. The authors raised concerns over the "amount of therapeutic control that can be achieved with inhaled therapies."

Two studies[18,19] (Table 2) examined the transition from either IV, SQ, or IH treprostinil to oral treprostinil in a carefully selected, stable cohort of patients. The transition was deemed successful in 37/42 patients (88%).

One study (20) involved the transition from IH iloprost to IH treprostinil. The authors reported an 89% "success" rate and concluded that the transition was "safe and well-tolerated with no apparent loss of clinical status," and resulted in an average time savings of approximately 1.4 h per day.

Inter-class PAH medication transitions: from a prostacyclin analogue to an oral non-prostacyclin analogue

There were seven studies involving the transition from a prostacyclin analogue to an oral non-prostacyclin analogue (Table 4). Two of the seven studies were prospective, open-label studies, five were retrospective studies. The duration of the studies was in the range of 3–60 months. All seven of these studies involved the transition from a parenterally administered prostanoid to either oral bosentan or sildenafil, with a total of 126 patients studied. In general, patients who were able to transition successfully had a more favorable hemodynamic profile and WHO functional class and were on lower doses of prostacyclin analogues prior to transitioning.

In a study[21] examining transitioning from SQ treprostinil to oral sildenafil, the change was deemed successful in 71%

Table 2. Intra-class PAH medication transitions: prostacyclin analogue from one route to another route (i.e. infused, inhaled, or oral) (other than switched from infused to another infused medication or route).

No.	Original drug	Drug transitioned to	Publication year	Study design	PAH patients	Time	Measures	Outcome
Prospective								
1	IH iloprost	IH treprostinil	2013 / Bourge et al.[20]	Prospective open-label	73	3–12 months	Likelihood of staying on treprostinil at 3 months, 6MWD, NT-proBNP, CAMPHOR, TSQM	Successful in 89% 6MWD (+16.0) NT proBNP (–74) Higher CAMPHOR/TSQM scores in treprostinil group
2	IV/SC treprostinil	Oral treprostinil	2016 / Chakinala et al.[18]	Prospective open-label	33	24 weeks	Investigator-determined clinical stability at week 24, 6MWD, hemodynamics, QOL, safety, pharmacokinetics, treatment satisfaction	Successful transition in 31/33 participants within first 4 weeks No change in 6MWD, WHO FC, hemodynamics or symptoms at week 24
Retrospective								
3	IV/SQ treprostinil or epoprostenol	IH treprostinil	2012 / de Jesus Perez et al.[17]	Retrospective	18 15 IV/SQ treprostinil 3 IV epoprostenol	7 months	WHO FC 6MWD Hemodynamics	Deterioration in WHO FC in minority
4	IV/SQ epoprostenol or treprostinil	IH iloprost	2013 / Channick et al.[9]	Retrospective	37	12 months	Likelihood of staying on iloprost Clinical worsening	Successful in 78.4% 19% experienced clinical worsening Use of background oral PAH therapy was associated with success
5	IV / SQ / IH treprostinil	Oral treprostinil	2016 / Coons et al.[19]	Case series	9	47 weeks (median follow-up)	Clinical symptoms, 6MWD, NT-proBNP level	Deemed successful in 6/9 patients (1 worsened, 1 could not tolerate side effects, and 1 transitioned to hospice care)

CAMPHOR, Cambridge Pulmonary Hypertension Outcome Review; IH, inhaled. Other abbreviations per Table 1 footnote.

Table 3. Intra-class PAH medication escalations: prostacyclin analogue from inhaled route to infused route.

No.	Original drug	Drug transitioned to	Publication year	Study design	PAH patients	Time	Measures	Outcome
Prospective								
1	IH iloprost	IV iloprost	2002 / Hoeper et al.[35]	Prospective open-label	16	3–16 months	WHO FC 6MWD	8 improved 1 alive but worsened 5 died 2 transplanted
2	IH iloprost	IV iloprost	2007 / Ewert et al.[36]	Prospective open-label	24	1–44 months	WHO FC 6MWD Hemodynamics	WHO FC and hemodynamics improved in subset of patients 5 on long-term medical therapy 7 deaths 12 transplantation
Retrospective								
3	IH treprostinil	IV or SQ treprostinil	2014 / Preston et al.[37]	Retrospective	23 (3 patients were WHO group 4 or 5)	3–18 months	WHO FC 6MWD NT-proBNP Hemodynamics	8 improved, 17 maintained their functional class, 1 deteriorated

of 14 patients based upon improvements in NHYA functional class and quality of life. In another study[22] of six patients (e-Table 4) with PAH due to Eisenmenger's syndrome who were transitioned from SQ treprostinil (n = 5) or oral beraprost (n = 1) to oral bosentan, patients had a non-significant decrease in 6MWD and no significant change in WHO functional class.

Intra-class oral PAH medication transitions: from one phosphodiesterase type5 (PDE5) inhibitor to another

There were five studies examining the transition between different PDE5 inhibitors and all involved the transition from sildenafil to tadalafil (Table 5). Three of the five studies were retrospective studies and two were prospective, open-label studies, with a total of 193 patients studied. The duration of follow-up was in the range of 3–12 months. The majority of the transitions were deemed successful (success rate = 86–97%), which was generally defined as the successful continuation of tadalafil without clinical deterioration. Patients who failed to transition successfully in one study[23] were noted to have more severe disease and were on a higher dose of sildenafil at baseline (180 versus 115.5 mg per day, $P = 0.06$).

In the study by Lichtblau et al.,[24] in which 13 patients who could not tolerate the side effects of sildenafil attempted to transition to tadalafil, the transition success rate was only 54%. Patients who were unable to transition successfully had discontinued the drug due to adverse events. The authors noted that "in almost half of these cases, adverse reactions were similar to those with sildenafil, in the other half, different side effects led to discontinuation of treatment."

Intra-class oral PAH medication transitions: from one endothelin receptor antagonist (ERA) to another

Transitioning from one ERA to another was reviewed in an uncontrolled, prospective open-label study[25] of 36 patients who had elevated liver function tests due to bosentan or sitaxsentan (Table 6). Patients were switched to ambrisentan with a follow-up period of 12 weeks. Only one patient had an elevation of liver function tests (>3 times upper limit of normal) at the end of the study. Additionally, there were significant improvements in several clinical parameters in patients transitioned to ambrisentan. The authors concluded that ambrisentan may be a "viable treatment option for patients with PAH who have previously had liver abnormalities during bosentan or sitaxsentan therapy."

Discussion

Certain PAH therapies, particularly those requiring parenteral administration, can pose a significant burden to patients. With the availability of newer and more convenient treatment options for PAH, there has been an increase in the

Table 4. Inter-class PAH medication transitions: prostacyclin analogues to oral non-prostacyclin analogue agents.

No.	Original drug	Drug transitioned to	Publication year	Study design	PAH patients	Time	Measures	Outcome
Prospective								
1	Epoprostenol or treprostinil	Oral bosentan	2004 / Suleman et al.[38]	Prospective open-label	23	12 months	Successful transition WHO FC 6MWD Echocardiogram	Only 9 patients (39%) were successfully transitioned to bosentan. In failure group, there was a trend toward higher doses and duration of PG therapy and higher PAP, though not statistically significant Half of failures in initial 8 weeks and half in subsequent 3–12 months
2	IV epoprostenol or IV treprostinil	Oral bosentan	2006 / Steiner et al.[39]	Prospective open-label	22	17.7 ± 5.3 months	Change 6MWD - primary changes in prostanoid dosing, BORG score, FC, changes in PAH therapy, RVSP by echo	10/22 patients were able to complete transition over 6 months (2–12 range) 3/10 late failures 41 m fall in 6MWD in transitioned patients at 1 year Borg unchanged Successful patients with lower RVSP, mPAP, better 6MWD, and FC and lower PG analogue doses vs. those who failed
Retrospective								
3	SQ treprostinil	Oral sildenafil	2007 / Keogh et al.[21]	Retrospective	14	3 months	Successful transition WHO FC 6MWD QoL Echocardiogram	71% stayed on Sildenafil Improved QOL No other significant changes
4	IV epoprostenol	Oral bosentan or oral sildenafil	2007 / Johnson et al.[40]	Retrospective	13 (2 failed epo wean and not transitioned)	29.9 ± 11.6 months	RHC, FC, 6MWD	9/13 unchanged FC 4/13 worse FC Normal pre-wean hemodynamics (mPAP < 30 mmHg or PVR < 4 WU) predicted successful transition 8 successful at end of study 1 death from SDH 4 worsened and restarted prostacyclin 6MWD unchanged All 4 who failed had abnormal hemodynamics pre-transition
5	Epoprostenol (17 patients) or treprostinil (4 patients)	Oral bosentan and/or sildenafil	2008 / Diaz-Guzman et al.[41]	Retrospective	21 (15 successful; 6 failed transition)	24.7 ± 13.6 months in ST 30 ± 5.6 in FT	6MWD, FC, BNP	Successful in 15/21 (71.4%) Low doses of prostanoids, mPAP < 40 mmHg, 6MWD > 400 m, SLE-PH, and use

(continued)

Table 4. Continued

No.	Original drug	Drug transitioned to	Publication year	Study design	PAH patients	Time	Measures	Outcome
								of sildenafil could predict a higher likelihood of successful weaning
6	IV epoprostenol	Oral bosentan	2009 / Safdar[42]	Retrospective	11	3 months	Successful transition Adverse events WHO FC 6MWD	7/11 patients required resumption of infused prostanoid 57% remained stable for "substantial period of time" on oral therapy 2 discontinued due to abnormal LFTs
7	Parenteral epoprostenol or treprostinil	Oral ERA/PDE5i	2013 / Escolar et al.[43]	Retrospective	22	60 months	Successful transition Adverse events WHO FC 6MWD NT-proBNP Hemodynamics	Successful in 50% Failure associated with: Age > 55 years, idiopathic PAH, combination therapy, abnormal hemodynamics (RAP > 5 mmHg, mPAP > 40 mmHg, PASP > 70 mmHg, PVR > 6.5 WU

mPAP, mean pulmonary artery pressure; PG, prostaglandin; PASP, pulmonary artery systolic pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVSP, right ventricular systolic pressure; SDH, subdural hematoma; WU, Wood units.

number of patients transitioned between therapies. Despite this increase, there have been a limited number of studies examining the safety and/or efficacy of these transitions. To our knowledge, this is the first systematic review examining transitions between PAH-specific therapies.

The majority of the studies we reviewed involved the transition from a prostacyclin analogue to another medication (Tables 1–4). The studies consisted of both retrospective and prospective open-label studies. The transition from parenteral epoprostenol to parenteral treprostinil was successful in 80% of patients and generally well tolerated. Patients who were successfully transitioned tended to have less severe disease and more favorable hemodynamics at baseline. Overall, there was no worsening in WHO functional class or significant differences in 6MWD in patients who completed the transition. Conversely, there were only few studies reporting on the transition from parenteral treprostinil to parenteral epoprostenol; these studies had a lower success rate for transitioning; however, some of the patients were transitioned (from parenteral treprostinil to parenteral epoprostenol) to address clinical worsening rather than mitigation of drug side effects.

The transition from parenteral epoprostenol to a thermostable form was generally successful, and patients who transitioned tended to have improved quality of life, treatment satisfaction scores, and freedom from hospitalization.

There were limited studies examining the transition from an IH prostacyclin analogue to a parenteral prostanoid. Patients in these studies generally had more severe disease and were ''transitioned'' as a form of rescue therapy. Most of these patients were able to achieve short-term clinical and hemodynamic stabilization but had subsequent disease progression, including death or lung transplantation.

There is conflicting evidence involving the transition from a parenteral prostacyclin analogue to an IH form. Two studies examining this transition[9,16] in patients who were on background oral PAH therapy reported success, whereas one study[17] reported clinical deterioration in a minority of patients. Therefore, clinicians should carefully discuss the risks and benefits of this particular transition with their patients and ensure close monitoring during and after the transition period. The transition from parenteral to oral treprostinil was evaluated in two studies[18,19] and it appears to be feasible and safe in low-risk, clinically stable patients. The transition from inhaled iloprost to inhaled treprostinil was evaluated in one study[20] and appears to be safe and well tolerated, and can result in modest time savings.

The transition from a parenteral prostacyclin analogue to an oral non-prostacyclin analogue was evaluated in seven studies (Table 4), with variable success rates. Most of these patients were transitioned from either epoprostenol or treprostinil to bosentan or sildenafil. Patients who successfully transitioned tended to have more favorable hemodynamics, better functional class and higher 6MWD at baseline compared with those who failed, and were on lower doses of prostacyclin analogues prior to transitioning.

Table 5. Intra-class oral PAH medication transitions: PDE5 inhibitors.

No.	Original drug	Drug transitioned to	Publication year	Study design	PAH patients	Time	Measures	Outcome
Prospective								
1	Sildenafil	Tadalafil	2008 / Tay et al.[44]	Prospective open-label	12	3–6 months	6MWD, Borg Dyspnea index, cardiac index, SF-36 score – physical function	No significant differences in 6MWD, NYHA class, Borg index and SF-36 physical function scores after transition to tadalafil. No significant adverse effects at 6 months
2	Sildenafil	Tadalafil	2014 / Frantz et al.[45]	Prospective open-label	35 (56% were receiving ≥ 2 PAH therapies)	6 months	Treatment Satisfaction Questionnaire for medication Adverse events	Successful in 86% Only 55% "satisfied" at 90 days. Patients taking >20 mg three times a day of sildenafil were successfully transitioned to tadalafil 40 mg once daily
Retrospective								
3	Sildenafil	Tadalafil	2012 / Shlobin et al.[23]	Retrospective	35 (5 non-group 1 PAH)	12 months	Likelihood of staying on therapy 6MWD	86% stayed tadalafil 6MWD $+37.04$ m Failure group had higher sildenafil dose (180 vs. 115.5 mg/day; $p=0.06$)
4	Sildenafil	Tadalafil	2013 / Shapiro et al.[46]	Retrospective	98 (The majority of patients [78%] were receiving sildenafil 80–100 mg three time a day)	8 ± 4.5 months	Likelihood of staying on therapy 6MWD BNP	97% stayed on tadalafil No changes. There was no pattern of response observed for the patients whose 6MWD improved or worsened in relation to the dose of sildenafil at the time of transition
5	Sildenafil	Tadalafil	2015 / Lichtblau et al.[24]	Retrospective	13 patients who did not tolerate side effects of sildenafil	11 ± 3 months	WHO FC 6MWD Echocardiogram NT-proBNP	Successful in 54% 5/13 patients had adverse events leading to discontinuation

Table 6. Intra-class oral PAH medication transitions: endothelin receptor antagonists.

No.	Original drug	Drug transitioned to	Publication year	Study	PAH patients	Time	Measures	Outcome
1	Bosentan or sitaxsentan	Ambrisentan	2009 / McGoon et al.[25]	Prospective open-label	36 (prior abnormal LFTs with therapy)	12 weeks	LFTs > 3x's ULN; Tx discontinuation, Δ in 6MWD) Borg dyspnea index, WHO FC functional class, health survey score	One out of 36 with LFTs > 3x's ULN; no discontinuations; improvements in other clinical endpoints

LFT, liver function tests; ULN, upper limit of normal.

In terms of intra-class oral PAH medication transitions, only sildenafil to tadalafil and bosentan or sitaxsentan to ambrisentan are supported by the available evidence. Most patients successfully transitioned from oral sildenafil to once daily tadalafil; patients who failed to do so were on a higher dose of sildenafil at baseline, thus raising concerns about the safety and efficacy of transitioning patients on higher doses of sildenafil. Other patients who may not transition successfully are those who have experienced intolerable side effects from sildenafil.

Limitations and potential biases

One major limitation of this systematic review is the heterogeneity of the studies reviewed and the heterogeneity of the patients included in these studies; including reasons for transitioning, inconsistency in defining ''successful transition,'' variable length of follow-up, and lack of standardized protocols for transitioning patients from one drug to another, especially in the case of infused prostanoids. For example, patients may have transitioned to a different medication as a form of rescue therapy in some studies rather than to reduce unwanted side effects of initial therapy, which would lead to significant bias. In addition, the PAH subtype and severity of disease, as well as background therapy and combination therapy are confounders that could not be accounted for in this analysis as they were not well described or characterized in many of the above studies. Additionally, most of these studies were retrospective reviews with small sample sizes (only one study was a prospective trial) limiting the generalizability of the data. It is also difficult to generalize our findings to the pediatric population, in which studies are severely limited. In addition, publication bias could not be accounted for, as unsuccessful transitions would be unlikely to be published.

Implications for clinical practice

Patients and clinicians may wish to transition between PAH therapies for a variety of reasons. We have provided a comprehensive review of the available evidence to guide clinicians in discussing transitions between PAH-specific therapies with their patients, as well as patient-specific characteristics that may help predict the likelihood of a successful transition. More studies[26] are expected to further guide clinicians when considering transitions between PAH medications.

Conclusion

In summary, data regarding transitions between PAH-specific therapies are limited and the quality of the available evidence is variable. Certain patient characteristics, such as severity of disease as well as baseline hemodynamic profile and clinical parameters may help clinicians predict the likelihood of a successful transition between different PAH

therapies. Patients will require careful monitoring during and after the transition period to ensure clinical stability and to monitor for adverse effects.

Conflict of interest

WHF is on the Speakers Bureau of Actelion, Gilead, & United Therapeutics/Lung; and advisory Board of Actelion, Bayer, Gilead, and United Therapeutics. JAW (Principal Investigator for Actelion, Bayer, Gilead, Lung LLC, and United Therapeutics). RJT serves as a hemodynamic core-lab for a Actelion phase II study.

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