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Treatment Barriers in Portopulmonary Hypertension

Batool AbuHalimeh, MD [Postdoctoral fellow],
Pathobiology Division, Lerner Research Institute. Cleveland Clinic, OH, USA. abuhalb@ccf.org

Michael J Krowka, MD [Staff], and
Department of Gastroenterology and Hepatology and Department of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minnesota, USA. krowka.michael@mayo.edu

Adriano R. Tonelli, MD MSc [Staff]
Department of Pulmonary, Allergy and Critical Care Medicine. Respiratory Institute, Cleveland Clinic, Cleveland, OH, USA. tonella@ccf.org

Abstract

Portopulmonary hypertension (PoPH) is a form of pulmonary arterial hypertension (PAH) that can develop as complication of portal hypertension. Treatment of PoPH includes PAH-specific therapies and in certain cases, such therapies are necessary to facilitate a successful liver transplantation. A significant number of barriers may limit the adequate treatment of patients with PoPH and explain the poorer survival of these patients when compared to other types of PAH. Until recently, only one randomized controlled trial has included PoPH patients and the majority of treatment data is derived from relatively small observational studies. In the present manuscript we review some of the barriers in the treatment of patients with PoPH and implications for liver transplantation.

Keywords

portopulmonary hypertension; cirrhosis; treatment; side effects; liver transplantation

Address for correspondence: Adriano Tonelli MD, 9500 Euclid Avenue A-90, Cleveland, Ohio, 44195, Tel: +1 (216) 444-0812, Fax: +1 (216) 445-6024, tonella@ccf.org.

Contributions of authors:

Batool AbuHalimeh MD: Participated in the conception, design, writing and critical revision of the manuscript for important intellectual content and final approval of the manuscript submitted.

Michael J Krowka MD: Participated in the writing and critical revision of the manuscript for important intellectual content and final approval of the manuscript submitted.

Adriano R. Tonelli MD MSc: Participated in the conception, design, writing and critical revision of the manuscript for important intellectual content and final approval of the manuscript submitted. Dr Tonelli is the guarantor of the paper, taking responsibility for the integrity of the work as a whole, from inception to published article.

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Introduction:

Portopulmonary hypertension (PoPH) is defined as pulmonary arterial hypertension (PAH) associated with portal hypertension of intra or extrahepatic origin (1, 2). Pulmonary arterial hypertension requires a specific hemodynamic profile that includes a resting mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg, a pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg and a pulmonary vascular resistance (PVR) > 3 Wood units (3, 4). Meanwhile, portal hypertension is defined as a portal venous gradient of ≥ 6 mmHg (5). The prevalence of PoPH is 1 – 6% in patients with portal hypertension (6–8) and 5% in candidates for liver transplantation (9).

Patients with PoPH have worse survival than individuals with other types of PAH (10, 11). In fact, the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL registry) showed a 5-year survival of 40% for patients with PoPH (n=174) compared with 64% for individuals with idiopathic or heritable PAH, even when the pulmonary hemodynamic profile appeared more favorable in PoPH subjects (10). Interestingly, at the time of enrollment in this registry, patients with PoPH were less likely to be treated for PAH (10). In the United Kingdom National PAH registry, treatment-naïve patients with a recent diagnosis of PoPH (n=110) had a 5-year survival of 35%; worse than patients with idiopathic PAH.

PAH-specific treatment is indicated for patients with PoPH (2, 12); however, the long-term impact of this approach remains vastly unexplored (13, 14) with some studies questioning its efficacy (11, 15). Importantly, the liver transplant mortality increases in patients with PoPH, particularly in subjects with a mPAP ≥ 35 mmHg and PVR > 3 Wood units (16, 17). In patients with this unfavorable hemodynamic profile, PAH-specific therapies are used to improve pulmonary hemodynamics and right heart function, with the expectation of decreasing the perioperative mortality of liver transplantation (18, 19).

All but one of the randomized studies that led to the FDA approval of current PAH-specific medications excluded patients with PoPH (20). Relatively small observational studies reported on the use of PAH-specific medications to treat patients with PoPH (21, 22). These data remain insufficient to adequately guide evidence-based treatment decisions (Table 1). In addition, patients with PoPH appear to have frequent side effects with recommended doses of PAH medications, particularly prostacyclin analogues. In this manuscript, we examine the available literature and question whether a) the presence of advanced liver disease increases the incidence of side effects in patients treated with PAH-specific therapies and b) the worse outcomes observed in patients with PoPH are in part related to barriers in receiving an adequate PAH treatment.

a) Establishing the diagnosis of PoPH

An accurate diagnosis of PoPH is essential since patients with advanced liver disease have other reasons for pulmonary hypertension (PH) such as volume overload and hyperdynamic state; conditions that may not necessarily impact liver transplant outcomes (23). A right heart catheterization is required, both to confirm the diagnosis of PH (mPAP ≥ 25 mmHg) and establish the origin. In cases of volume overload and/or hyperdynamic state the PAWP

(> 15 mmHg) and/or cardiac index (≥ 4 L/min/m^2) are elevated while the PVR remains below 3 Wood units (or 240 dynes.s.cm^{-5}) (24). Volume overload is treated with diuresis with careful attention to renal function. A hyperdynamic state is inherent to the liver disease given splanchnic vasodilation and intrahepatic and/or mesenteric arteriovenous shunts (25); hence, there are no specific treatments for this condition apart from for liver transplantation (26). Importantly, other comorbidities (anemia, obesity, arteriovenous connections, Beriberi and hyperthyroidism) that increase the cardiac index need to be recognized (27).

b) Effect of PAH-specific therapies in PoPH

The goals of treating patients with PoPH are to alleviate symptoms, facilitate liver transplantation and ultimately, improve outcomes. A meta-analysis of 12 studies that included patients with PoPH showed that PAH-specific therapies improved pulmonary hemodynamics and functional capacity (28). Observational studies suggest that PAH-specific treatment may improve outcomes when compared to historical data (12) and potentially increase the eligibility and reduce the risks associated with liver transplantation (29, 30). However, it remains unclear whether PAH-specific treatment impacts the transplant free survival; particularly since any potential survival advantage may be curtailed by the advanced liver disease and associated comorbidities (11, 15).

Recent analyses on three PH registries suggest that PAH patients who sustain or achieve a low-risk category (31) during follow-up have better prognosis (32–34). However, one registry (33) excluded patients with PoPH, and the other two (32, 34) included a limited number of patients with this condition (2.6% and 5.6% of the entire cohort). It remains unclear whether an aggressive PAH-specific treatment, aimed at achieving low risk criteria is beneficial in PoPH patients; particularly when the hemodynamic goals for liver transplant are achieved. Moreover, the parameters used to define these risk criteria; i.e. World Health Organization (WHO) functional class, six-minute walk distance (35), N-terminal prohormone of brain natriuretic peptide (36), and hemodynamic determinations (37, 38), are inherently affected in patients with liver cirrhosis and therefore may not change with PAH treatment.

c) PAH-specific therapies used in PoPH:

1. Phosphodiesterase-5 inhibitors—Sildenafil was found to be effective in improving functional class, exercise tolerance and hemodynamics in PoPH (Table 1). Limited information exists on the use of once-a-day tadalafil in PoPH (39).

2. Soluble guanylate cyclase stimulator—The PATENT-1 study randomized patients with PAH to the soluble guanylate cyclase stimulator riociguat or placebo and included a limited number of PoPH patients (n=13, 11 subjects received riociguat and 2 placebo) (20). Riociguat appeared to improve functional and hemodynamic determinations in patients with PoPH; however, some patients experienced side effects (headaches (n=3) and peripheral edema (n=3)). In addition, one patient died of sepsis related to bronchopneumonia, an event not ascribed to the study drug (40).

3. **Endothelin receptor antagonists—**Hoeper et al. (41) reported improvements in symptoms, exercise capacity and hemodynamics in PoPH patients treated with bosentan, a medication that was well tolerated. Similar results were reported by other investigators (Table 1). Bosentan causes an elevation of liver transaminases ≥ three-fold the upper limit of normal in ~11% of the patients; however, ambrisentan and macitentan, rarely cause hepatotoxicity. Ambrisentan has been associated with dramatic improvements in hemodynamics and WHO functional class in PoPH patients (42). A randomized, double-blind clinical study (PORTICO, NCT02382016), testing macitentan in patients with PoPH has recently finished enrollment. The primary outcome of the study is change in PVR at 12 weeks.

4. **Prostacyclin analogues and prostacyclin receptor (IP) agonist—**Intravenous epoprostenol has been used in PoPH patients as a mean to improve their hemodynamic profile to facilitate liver transplant (Table 1). Treprostinil is a chemically stable analogue of prostacyclin and its intravenous formulation has been used in PoPH patients with success (43). Continuous intravenous infusions of epoprostenol and treprostinil require active participation of the patient and/or caregiver. This fact is important since 30–45% of the patients with advanced liver disease develop hepatic encephalopathy, a condition associated with difficulties in performing activities of daily living (44, 45), which can make difficult the treatment with parenteral medications. For instance, subjects may accidentally disconnect their intravenous access or may not be able replace medication cassette reservoirs given agitation, confusion and/or somnolence. Furthermore, inadequate manipulation of vascular catheters can lead to catheter malfunction, bleeding and/or bloodstream infections.

Inhaled iloprost has been associated with long-term improvements in symptoms and exercise tolerance in PoPH (46, 47). Limited data exit on the use of inhaled treprostinil in patients with PoPH (48). Oral treprostinil has not been studied in patients with PoPH. Selexipag, an oral prostacyclin receptor (IP) agonist, has not been examined in patients with PoPH. Beraprost, an oral prostacyclin analog not available in the US, was used in a patient with POPH who exhibited improvements in symptoms, functional capacity and hemodynamic determinations (49). We use inhaled treprostinil or oral treprostnil or selexipag very carefully, paying particular attention to side effects and considering longer dosing intervals, lower doses and slower titration.

Interestingly, a retrospective study in PoPH patients compared treatment with inhaled iloprost (n=13) versus oral bosentan (n=18) and showed that both treatments were safe; however, patients treated with bosentan had a distinct improvement in functional capacity and pulmonary hemodynamics, with better overall and event free survival at 1-, 2- and 3-year (46).

d) Influence of liver disease on the metabolism of PAH medications:

Except for epoprostenol, the liver is the predominant metabolic site for PAH-specific medications (Table 2); therefore, PAH medications are expected to have a longer half-life and higher serum concentration in patients with liver disease; factors associated with more frequent medication side effects (50). In addition, the capacity of the liver to metabolize

drugs depends on its blood flow and enzyme activity, both of which can be affected in patients with liver disease (51). In support of this, Savale et al. noted that the plasma concentration of bosentan in patients with PoPH (Child-Pugh class B cirrhosis) was higher than individuals with idiopathic PAH, possibly due to a decrease in the liver uptake of bosentan, given lower efficiency of the organic anion transporter peptide (52). Frey et al. demonstrated a higher riociguat exposure (after a single oral dose) in individuals with Child-Pugh class B cirrhosis than healthy controls (53).

Phosphodiestearase-5 inhibitors are metabolized by the cytochrome P450 system (CYP3A4) and rarely cause liver injury (54). Endothelin receptor blockers are also metabolized by the cytochrome P450 system (CYP3A4, CYP2C9 and CYP2C19). A dose-dependent rise in liver function tests was observed in individuals receiving bosentan in its landmark trial (BREATHE-1) (55), possibly due to accumulation of cytotoxic bile that leads to liver cell damage (56). A relatively small study in patients with POPH treated with ambrisentan (n=13) showed no changes in hepatic transaminases (42). McGoon et al. (57) found that ambrisentan, at lower than the FDA approved dose, was well tolerated (without significant increases in liver function tests) in patients (n=36) who had experienced liver function test abnormalities while receiving bosentan or sitaxsentan.

Epoprostenol is metabolized by rapid hydrolysis and causes limited (< 1%) hepatic side effects. Treprostinil and iloprost are metabolized by the liver (CYP2C8 and beta oxidation, respectively). Some studies suggest that prostacyclin analogues exert a cytoprotective action on liver cells, an effect that might be beneficial in patients with PoPH (58, 59). Peterson et al. showed that the clearance of a single dose of oral treprostinil decreased with the severity of the hepatic impairment, resulting in higher plasma levels (~8-fold higher in patients with severe hepatic impairment) and more side effects (60).

e) The side effects of PAH-specific medications overlap with the clinical manifestations of liver disease

Patients with advanced liver disease have characteristic clinical manifestations, inherent to their disease and treatments, including nausea, vomiting, diarrhea, abdominal distension, anorexia, fatigue, malaise, weight loss, and fluid retention (61, 62). Patients with liver disease who develop PoPH might present with fatigue, dyspnea, dizziness, ascites and peripheral edema, especially as right heart failure ensues (63). These clinical manifestations may overlap with common side effects of PAH-specific medications such as nausea, vomiting, anorexia, and edema (Table 3); making it difficult to correctly attribute the origin of certain signs and symptoms to underlying medical conditions or side effects of PAH medications.

In order to prevent or reduce side effects, PAH medications can be started at lower doses or titrated slowly; in addition, combination therapy can be initiated sequentially instead of concurrently to be able to ascribe side effects to a particular PAH medication. However, a gentle initiation and titration of PAH-specific medications may extend the time needed to achieve the pulmonary hemodynamic goals for liver transplantation; potentially delaying listing and increasing the risk of complications due to the underlying liver disease.

f) Effect of PAH-specific medications on portal hypertension:

There are limited data on the effect of PAH-specific medications on portal hypertension. The hepatic sinusoidal resistance is in part regulated by the nitric oxide-cyclic guanosine monophosphate system (64). Portal pressure may increase when there is a decrease in nitric oxide release by the liver sinusoidal endothelial cells (65, 66); an effect that could be mitigated by phosphodiesterase-5 inhibitors (67). Phosphodiesterase-5 inhibitors decrease the hepatic sinusoidal resistance (68) but also increase the splanchnic blood flow (69); accounting for the variable effects on the hepatic venous pressure gradient (39, 70, 71). Riociguat reduced the portal pressure in an animal model of biliary cirrhosis (72) but no data are available in humans.

Endothelin increases the intrahepatic vascular resistance, leading to portal hypertension (73, 74). In rats with biliary cirrhosis, bosentan decreased the portal pressure by reducing the hepatocollateral vascular resistance (75). In a mice model of cirrhosis, the chronic administration of endothelin receptor antagonists caused a reduction in liver fibrosis and portal pressure (76). Prostacyclin analogues increase the hepatic blood flow (77, 78). In an animal model of biliary cirrhosis, prostacyclin administration did not affect portal pressure (77). In patients with PoPH (n=8), Melgosa et al. showed that the hepatic venous pressure gradient and hepatic blood flow did not change at 30 and 60 minutes after the inhalation of iloprost (47).

g) Factors to consider in the selection of PAH-specific therapies:

When prescribing PAH-specific medications to patients with PoPH it is important to consider the presence of certain signs and symptoms as well as underlying medical conditions (e.g. renal failure). Patients with severe fluid retention may not be good candidates for endothelin receptor antagonists and patients with pronounced nausea and dyspepsia may not tolerate prostacyclin analogues. In addition, certain interactions are important to consider: ethanol may enhance the hypotensive effects of phosphodiesterase-5 inhibitors and increase the absorption of oral treprostinil, organic nitrates may increase the vasodilatory effect of phosphodiesterase-5 inhibitors, and cyclosporine may increase the serum concentrations of bosentan and ambrisentan.

Before making treatment decisions, it is essential to assess the living conditions, social support, adherence to other treatments, patient’s capacity to be educated on the use of different PAH-specific medications, insurance drug coverage, copays and eligibility for medication assistance programs.

h) Factors affecting the treatment of PoPH:

Certain factors germane to patients with PoPH (Table 3) may affect the intensity (1–3) and hence the effectiveness of PAH-specific therapies (79). Importantly, studies have shown that appropriate dosing as well as the use of combination therapy improve outcomes in PAH patients (80–82). The REVEAL registry included 118 patients with PoPH of whom 56% were treated with phosphodiesterase-5 inhibitors, 29 % with IV or SQ prostacyclin analogues, 14% with inhaled or PO prostacyclin analogues, 7% with endothelin receptor antagonists and 16% received no PAH-specific therapy at the time of inclusion. The

proportion of treatment naïve patients decreased at 90 (11%) and 365 (5%) days from enrollment. Interestingly, patients with PoPH were less likely to receive PAH-specific treatment both at enrollment and 90 days compared to subjects with idiopathic or heritable PAH (10). In our experience, side effects of PAH medications appear to be more pronounced in patients with PoPH that other types of PAH.

Swanson et al. proposed to divide PoPH patients in two groups based on PAH severity. Patients with stable liver disease and mild to moderate PAH could be treated with oral therapies, with drug escalation based on response. Meanwhile, patients with moderate to severe PAH, particularly those with unstable liver disease, need to be treated more aggressively with parenteral prostacyclin therapy (83). The intensity of treatment depends on the severity of PAH and the degree of hemodynamic improvement required for liver transplantation. We particularly focus on decreasing the PVR since the mPAP may remain elevated due to a high PAWP in the setting of volume overload, or high cardiac output from the inherent hyperdynamic state– a key point to remember especially in liver transplant candidates.

i) Impact of PAH-specific therapies on liver transplantation eligibility:

There is no standardized approach for the management of PoPH, particularly in patients that are considered for liver transplantation. The general goals of treatment are as guidelines would recommend for other PAH types (84, 85). The hemodynamic treatment goal for safe liver transplantation (mPAP < 35 mmHg and PVR < 5 Wood units or PVR < 3 Wood units irrespective of mPAP with satisfactory right ventricular function by echocardiogram (22)) espoused by ILTS guidelines, can be attained via numerous medication options (17). This hemodynamic target for liver transplantation fluctuates among the institutions based on their multidisciplinary evaluation, comorbidities, inclusion of PVR in the hemodynamic evaluation and prior experiences with similar patients. Although predictors of waitlist mortality exist, i.e. PVR and MELD score (96), there are no clear predictors of treatment response. Until prospective studies address this issue, it may be prudent to use intravenous prostacyclin analogues and or combination therapies in the most severe cases of PoPH, especially if liver transplantation is to be considered (86). For example, in a liver transplant candidate with normal right ventricular function, a mPAP of 40 mmHg, cardiac index of 4.3 L/min and PVR of 3.5 Wood units, treatment with an oral PAH-specific therapy might be sufficient to achieve the goal of a mPAP < 35 mmHg or PVR < 3 Wood units. In contrast, in a liver transplant candidate with dilated and dysfunctional right ventricle with mean PAP of 50 mmHg, cardiac index of 2.2 L/min and PVR of 9 Wood units, parenteral prostacyclin analogues, sometimes in combination with oral agents, offer the best chance be able to meet the hemodynamic goals and list the patient for liver transplantation. Importantly, regardless of therapies, transplant in the setting of POPH remains higher risk and resolution of PoPH post-transplant is unpredictable. In addition, attaining an improvement and ideally a normalization of right ventricular function is of great importance, especially in transplant candidates.

Conclusions:

Treatment of PoPH patients is challenging and needs to be individualized. In comparison with treatment in other types of PAH, patients with PoPH have frequent side effects that limited the use of certain medications and the dose achieved. Furthermore, in patients with PoPH it is critical to optimize their clinical condition and hemodynamic status to minimize the perioperative risk associated with liver transplantation.

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Abbreviations:

mPAP	mean pulmonary artery pressure
MELD	Model for End-stage Liver Disease
PAH	pulmonary arterial hypertension
PAWP	pulmonary artery wedge pressure
PH	pulmonary hypertension
PoPH	portopulmonary hypertension
PVR	pulmonary vascular resistance
REVEAL	Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management
WHO	World Health Organization

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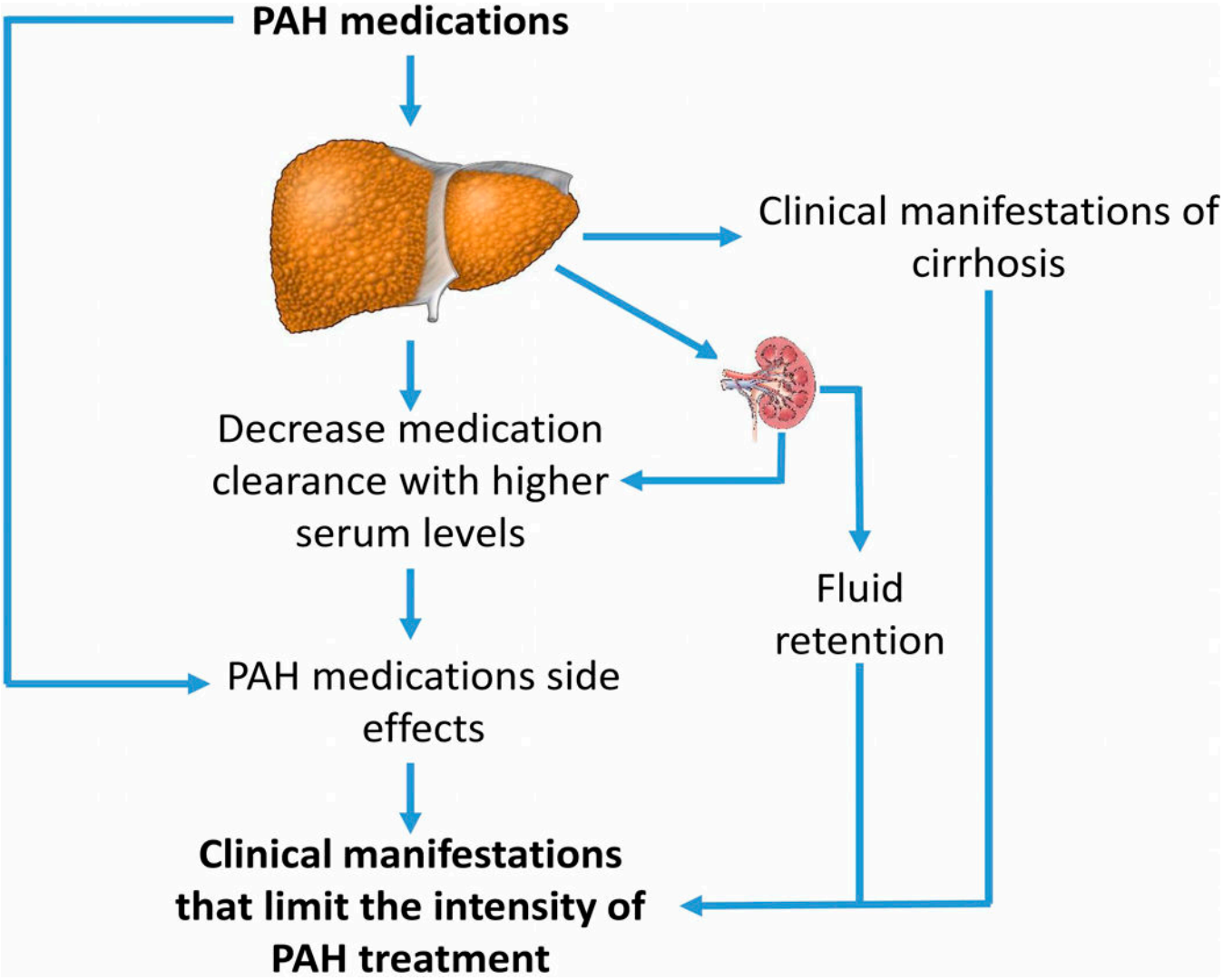

Figure 1:
Barriers that limit the effectiveness of PAH therapy

Table 1:

Studies that included ≥ 3 patients and described the effect of PAH-specific therapies in PoPH.

First author, year, reference	n	WHO functional class	PVR (dyn*s*cm^{-5})	Medication	MELD / Child-Pugh score	Outcomes
Phosphodiesterase-5 inhibitors						
Hemmes et al, 2009(87)	10	I- IV	Mean ±SD 664 ± 336	Sildenafil 20–50mg three times daily.	MELD:mean ±SD 14±3.3	✓Improvement in functional class, exercise tolerance and cardiopulmonary hemodynamics. Three patients were listed for liver transplantation and one was successfully transplanted.
Reichenberger et al, 2006(48)	13	III- IV	Mean ±SD 759± 338	Sildenafil 50mg three times daily.	C-P: A,B,C	✓Improvement in functional class, exercise tolerance and cardiopulmonary hemodynamics.
Fisher et al, 2015(88)	20	III- IV	Mean ±SD 683± 259	Sildenafil 20–25 mg three times daily (n=19), tadalafil 40 mg daily (n=1)	C-P: A,B,C MELD: median,(range) 15 (13–18)	✓Improvement in functional class and cardiopulmonary hemodynamics. No change in exercise tolerance.
Gough et al, 2009(89)	11	I -III	Mean: 575	Sildenafil 25–50mg three times daily.	C-P: B,C MELD:mean ±SD 14±4.6	✓Improvement in cardiopulmonary hemodynamics. One patient had a successful liver transplant.
Endothelin receptor antagonists						
Hoeper et al (2005) (41)	11	II-IV	Mean ±SD 944 ±519	Bosentan 62.5 mg twice daily for 4–8 weeks, increased to 125 mg twice daily	C-P: A	✓Improvement in functional class, exercise tolerance and cardiopulmonary hemodynamics. One patient had worsening ascites. No evidence of liver toxicity.
Savale et al (2013) (52)	34	II-IV	Mean ±SD 696 ± 264	Bosentan 62.5 mg twice daily for 4 weeks, increased to 125mg twice daily	C-P: A, B	✓Improvement in functional class, exercise tolerance and cardiopulmonary hemodynamics. Three patients died of right heart failure. Elevation of liver enzymes was noted in several patients.
Cartin-Ceba et al (2011)(42)	13	II-III	Median (IQR) 445 (329–834)	Ambrisentan 5mg daily for 4 weeks, increased to 10mg daily	C-P: A,B,C MELD: median of 10 (IQR,8.5–15)	✓Improvement in cardiopulmonary hemodynamics and BNP levels. One patient underwent successful liver transplantation. One patient had periorbital bleeding, peripheral edema and 8 pounds weight gain. No

First author, year, reference	n	WHO functional class	PVR (dyn*s*cm^{-5})	Medication	MELD / Child-Pugh score	Outcomes
						evidence of liver toxicity
Prostacyclin analogues						
Krowka et al (1999) (90)	15	II-IV	Mean ±SD: **Acute phase**: 525±286 **Long-term phase:** 373±191	**Acute phase**: IV epoprostenol 4–10 ng/kg/min over 60 min (n=14). **Long-term phase**: IV epoprostenol up to 48 ng/kg/min (n=10)	C-P: B,C	✓**Acute phase**: improvement in cardiopulmonary hemodynamics. Hypotension, headache and nausea were noted. ✓**Long-term phase:** no improvement in cardiopulmonary hemodynamics. One patient died of worsening heart failure and another had sudden death after successful liver transplantation.
Awdish et al, 2013(91)	21	I-III	Mean ±SD 537± 160	IV epoprostenol 20.8 ± 13.9 ng/kg/min	C-P: A,B,C MELD: mean ±SD: 12.5 ±5.1	✓Improvement in exercise tolerance and cardiopulmonary hemodynamics. Seven patients were transplanted successfully, and four patients were listed for liver transplantation.
Kuo et al, 1997(92)	4	II-IV	N/A	IV epoprostenol up to 28 ng/kg/min	C-P: B	✓Improvement in cardiopulmonary hemodynamics.
Melgosa et al, 2010(47)	21	I- IV	**Acute phase:** 564±282 **Long-term phase:** 802±313	**Acute-phase**: 21 patients were given 2.8 μg of inh iloprost. **Long-term phase:** inh iloprost 5 μg six times daily for 1 year (3 patients also received bosentan 125 mg twice daily)	MELD: mean ± SD **Acute-phase** 15.0±2.5 **Long-term phase** 11.1±5.3	✓**Acute-phase**: improvement in cardiopulmonary hemodynamics. ✓**Long-term phase**: improvement in exercise tolerance and functional class but no change in cardiopulmonary hemodynamics. Two patients worsened their pulmonary hypertension.
Sakai et al, 2009 (43)	3	N/A	249,304, 718	IV treprostinil : 45, 36 and 106 ng/kg/min	MELD: 22, 33, N/A	✓Improvement in cardiopulmonary hemodynamics in two patients who underwent successful liver transplantation.
Ashfaq et al,2006(30)	16	II-IV	Mean ±SD: **Moderate PoPH** (n=6) 402±87 **Severe PoPH** (n=10) 551±92	IV epoprostenol (n=15, 2 patients also received bosentan). One patient was treated with diltiazem.	C-P: B,C MELD: mean ±SD: **Moderate** 11.9 ± 4.5 **Severe** 15.2 ± 4.6	✓Improvement in cardiopulmonary hemodynamics. Eleven patients were successfully transplanted.
Sussman et al, 2006(93)	8	N/A	Mean 410	IV epoprostenol at 2–8 ng/kg/min	MELD: mean ±SD 17±6.4	✓Improved cardiopulmonary hemodynamics. Six patients were listed for liver transplantation

First author, year, reference	n	WHO functional class	PVR (dyn*s*cm^{-5})	Medication	MELD / Child-Pugh score	Outcomes
						(four were successfully transplanted)
Hoeper et al, 2007 (46)	31	II-III	812±337(iloprost) and 866±422 (bosentan)	Iloprost 5ug inh six times daily (n=13) or bosentan 125mg twice daily (n=18).	C-P: A,B MELD:mean ±SD 12±3 and 10±3	✓Bosentan was a safe. Compared with iloprost, patients treated with bosentan had better effects on exercise capacity, hemodynamics and higher survival and event-free survival.
Fix et al,2007(94)	19	II-IV	Mean 670 (95%CI: 556–784)	Epoprostenol (n=19). In 7 patients sildenafil was added.	C-P: A,B,C MELD: median, (range) 14 (7–26)	✓Improved cardiopulmonary hemodynamics. Two patients underwent liver transplantation. Epoprostenol was discontinued in 2 and sildenafil in 4 patients given side effects.

WHO: World Health Organization

N/A: not available

MELD: Model for End-stage Liver Disease

C-P: Child-Pugh score

SD: standard deviation

IQR: interquartile range

CI: confidence interval

mPAP: mean pulmonary artery pressure

PVR: pulmonary vascular resistance

IV: intravenous

Inh: inhaled

Table 2:

Pharmacokinetics, gastrointestinal side effects and dosing of PAH-specific medications in liver disease

Medication	Metabolism	Excretion^	GI side effects > 1%	Dosing of PHA medications by degree of liver impairment
Sildenafil PO	Hepatic via CYP3A4 (major) and CYP2C9 (minor route).	**Feces:** 80% **Urine:** 13%	Dyspepsia, diarrhea, gastritis, nausea, increased liver enzymes	**C-P A, B:** No adjustment **C-P C:** Not studied
Tadalafil PO	Hepatic, via CYP3A4	**Feces:** 61% **Urine:** 36%	Dyspepsia, nausea, GERD, abdominal pain, diarrhea, gastroenteritis, dysphagia, abnormal liver function tests.	**C-P A, B:** Use with caution; consider initial dose of 20 mg once daily **C-P C:** Not studied
Riociguat PO	Hepatic via CYP1A1, CYP3A, CYP2C8 and CYP2J2.	**Feces:** 53% **Urine**: 40%	Dyspepsia, nausea, diarrhea, vomiting, gastritis, constipation, GERD	**C-P A, B:** No adjustments **CP C:** Not studied
Bosentan PO	Hepatic via CYP2C9 and CYP3A4 to three primary metabolites.	**Feces:** mainly **Urine:** <3%	Increased in AST and ALT	**C-P A:** No adjustment **C-P B,C:** Avoid use
Ambrisentan PO	Hepatic via CYP3A4, CYP2C19, and UGT 1A9S, 2B7S, and 1A3S	**Feces:** mainly	Dyspepsia	**C-P A:** No adjustment **C-P B, C:** Use not recommended.
Macitentan PO	Hepatic via CYP3A4 (major) and CYP2C19	**Feces:** 24% **Urine:** 50%	Increased liver enzymes.	No dosage adjustments provided.
Epoprostenol IV	Rapidly hydrolyzed	**Feces:** 4% **Urine:** 84%	Nausea, vomiting, anorexia, diarrhea.	No dosage adjustments provided.
Treprostinil SQ / IV	Hepatic via CYP2C8	**Feces:** 13% **Urine:** 79%	Diarrhea, nausea.	**C-P A, B:** Use with caution and titrate slowly. **CP C:** No dosage adjustments provided. Use with caution and titrate slowly.
Treprostinil inh	Hepatic via CYP2C8	**Feces:** 13% **Urine:** 79%	Diarrhea, nausea.	No dosage adjustments provided. Use with caution and titrate slowly.
Treprostinil PO	Hepatic via CYP2C8	**Feces:** 13% **Urine:** 79%	Diarrhea, nausea.	**C-P A:** Use with caution and titrate slowly. **C-P B:** Avoid use. **C-P C:** Use is contraindicated.
Selexipag PO	Hepatic via CYP3A4, CYP2C8, UGT1A3 and UGT2B7.	**Feces:** 93% **Urine:** -	Diarrhea, nausea, vomiting, decreased appetite	**C-P A:** No dosage adjustment necessary. **C-P B:** Once daily. **C-P C:** Avoid use
Iloprost inh	Hepatic via beta oxidation of the carboxyl side chain	**Feces:** 12% **Urine:** 68%	Nausea, vomiting, glossalgia	**CP A:** No dosage adjustment necessary. **C-P B, C:** Consider increasing dosing interval

* Data was obtained from Lexicomp Online (http://online.lexi.com/lco/action/home), Wolters Kluwer, accessed in October 2017.

^ Excretion percentages are approximate.

Abbreviations: ALT: alanine aminotransferase, AST: aspartate aminotransferase, C-P: Child-Pugh, CYP: cytochrome P, IV: intravenous, PO: orally, SQ: subcutaneous, UGT: uridine 5'-diphosphate glucuronosyltransferases.

Table 3:

Barriers to treat PoPH patients with PAH-specific medications.

1. Accurate diagnosis
a. Need to rule out volume overload and high flow state as reasons for high mPAP
b. Measure portal venous gradient or adequately establish the presence of portal hypertension
2. Limited evidence-based information
a. Scarce information supporting efficacy of PAH-specific therapies
b. Lack of clinical trials “proof” in PoPH
c. Unclear whether combination or triple PAH-specific therapy results in better outcomes in patients with PoPH.
d. Lack of a national PoPH registry
3. Advanced liver disease and its complications have an impact on drug metabolism and treatment adherence
a. Overlap of liver signs/symptoms with medications side effects
b. Thrombocytopenia related to PAH, prostacyclin use and liver disease
c. Impact of hepatic encephalopathy on PAH treatment (e.g. parenteral administration, compliance with twice or thrice daily dosing, etc)
4. Liver transplantation
a. Variable criteria to offer / deny liver transplantation among liver transplant teams and regional review boards
b. Restrictive criteria to obtain Model for End-stage Liver Disease.(MELD) exception points based on PoPH (95)
c. Not appreciating / recognizing the positive treatment effect on PVR, CO, and RV function when minimal changes in mPAP occur (23).
d. Limited studies documenting dose reduction/ discontinuation of PAH-specific therapies post-liver transplant