EXPERT REVIEWS

What's new in the treatment of portopulmonary hypertension?

Expert Rev. Gastroenterol. Hepatol. Early online, 1–10 (2015)

Hilary M DuBrock*[1], Richard N Channick[1] and Michael J Krowka[2]

[1]*Massachusetts General Hospital, 55 Fruit St Boston MA 02114, USA*
[2]*Mayo Clinic 200 1st Avenue Southwest, Rochester, MN 55902, USA*
**Author for correspondence:*
Tel.: +1 617 724 3705
Fax: +1 617 643 0791
hdubrock@mgh.harvard.edu

Portopulmonary hypertension (POPH) is a complication of portal hypertension characterized by pulmonary vasoconstriction and vascular remodeling that can lead to right heart failure and death. Differentiation of POPH from other causes of pulmonary hypertension, such as volume overload or a hyperdynamic high flow state, is critical because a diagnosis of POPH has significant implications for liver transplant risk stratification, Model for End Stage Liver Disease exception points, and the use of pulmonary arterial hypertension-(PAH) specific therapy. Currently, there are 12 approved medications for the treatment of PAH in the US, and three of these were approved in 2013. This review will discuss the diagnosis, evaluation and management of POPH and the role of recently approved PAH therapies in the treatment of POPH.

Keywords: macitentan • portopulmonary hypertension • pulmonary arterial hypertension • riociguat • treatment • treprostinil

Pulmonary hypertension

Pulmonary hypertension: diagnosis & mechanisms

Pulmonary hypertension (PH) refers to a heterogeneous group of diseases characterized by an elevated mean pulmonary arterial pressure (mPAP) ≥25 mmHg [1]. PH can develop due to three distinct pathologic mechanisms, all of which can occur in patients with liver disease, as depicted in Figure 1 [2]. These mechanisms include: a hyperdynamic state associated with an elevated cardiac output (CO), pulmonary venous congestion due to volume overload or left-sided cardiac dysfunction, and increased pulmonary vascular resistance (PVR) to flow due to vasoconstriction and vascular proliferation. Right heart catheterization with measurement of mPAP, CO, and pulmonary artery wedge pressure (PAWP) with calculation of PVR using the following equation (PVR = [mPAP- PAWP]/CO) is necessary for the definitive diagnosis of PH as well as determination of the underlying mechanism [1,2]. When PH develops due to increased vascular resistance to flow through the pulmonary arteries, it is referred to as pulmonary *arterial* hypertension (PAH) or precapillary PH [1].

PH: classification

PH is also classified into five distinct groups based on the WHO classification system recently updated at the 5th World Symposium in 2013 [3]. These groups, which are summarized in (Box 1), each have distinct mechanisms and approaches to therapy [3]. Portopulmonary hypertension (POPH), the term for precapillary PH that develops as a consequence of portal hypertension, is a subtype of WHO Group 1 PAH [3]. Both the European Respiratory Society task force on pulmonary vascular complications of liver disease in 2004 [4] and the recent 5th World Symposium on the updated clinical classification of PAH in 2013 [3] endorsed the classification of POPH as a subtype of WHO Group 1 PAH. Group 1 PAH is characterized by pulmonary vasoconstriction and pulmonary vascular remodeling associated with endothelial, fibroblast and smooth muscle cell proliferation, platelet aggregation and *in situ* thrombosis. POPH is classified with idiopathic PAH because it has similar approaches to therapy and potentially similar pathologic mechanisms [4].

Portopulmonary hypertension

POPH: diagnosis & evaluation

POPH is diagnosed in approximately 5–6% of patients evaluated for liver transplant [5–7] and

 10.1586/17474124.2015.1035647 ISSN 1747-4124

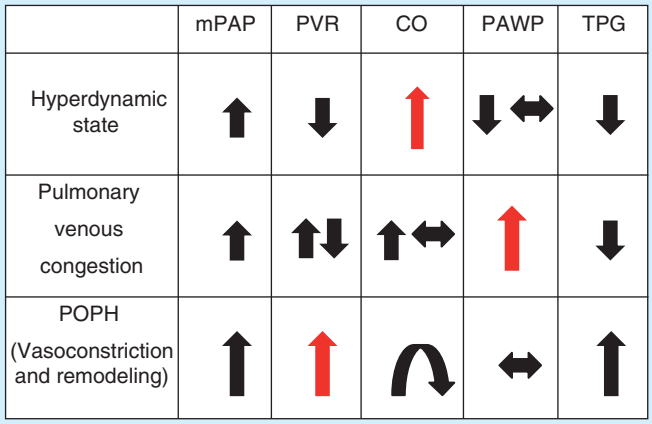

Figure 1. Pulmonary hemodynamic profiles of different pathologic mechanisms of pulmonary hypertension in liver disease.
CO: Cardiac Output; mPAP: Mean pulmonary arterial pressure; PAWP: Pulmonary artery wedge pressure; PVR: Pulmonary vascular resistance; TPG: Transpulmonary gradient (mPAP–PAWP).
Revised and adapted from Krowka MJ [2].

accounts for 5–10% of the overall PAH population [8,9]. Symptoms of POPH and resultant right heart failure include dyspnea, lower extremity edema and abdominal distension. Because these symptoms are non-specific and can frequently overlap with symptoms of liver disease, the diagnosis of POPH can be easily missed. Echocardiography is an effective screening tool for POPH [10]; transthoracic echocardiograms should be performed yearly in patients on the liver transplant list to identify patients that should be referred for right heart catheterization [4]. A recent study identified that an estimated right ventricular systolic pressure (RVSP) cutoff value of 38 mmHg had a sensitivity of 100%, a specificity of 82%, a negative predictive value of 100%, and a positive predictive value of 22% for identification of patients who were subsequently diagnosed with POPH by right heart catheterization [11]. Addition of RV dilation defined as an RV end-diastolic diameter >3.3 cm to the estimated RVSP cutoff value of 38 mmHg improved the specificity to 93% and the positive predictive value to 41%. The authors of this study recommended referral of patients with an estimated RVSP >38 mmHg and right ventricular dilation on echocardiogram for right heart catheterization. According to the most recent guidelines for management of POPH [4], published in 2004, and the Mayo Clinic algorithm for screening (Figure 2) [2,12], patients with an estimated RVSP >40–50 mmHg or right ventricular abnormalities on echocardiogram should be referred for right heart catheterization for further evaluation of POPH.

A definitive diagnosis of POPH requires a right heart catheterization that demonstrates precapillary PAH without an alternative etiology in a patient with portal hypertension [13,14]. Precapillary PAH is defined as mPAP ≥25 mmHg and PVR >3 Woods units (240 dyn·s·cm^{-5}) in the setting of a normal PAWP ≤15–18 mmHg [1]. Although the last consensus guidelines published by the European Respiratory Society task force on pulmonary vascular complications of liver disease in 2004 [4] recommended a PAWP ≤15 mmHg for the diagnostic criteria for POPH, more recent literature [15] suggests that a PAWP ≤18 mmHg may be a more appropriate cutoff because filling pressures can be elevated in the setting of the hyperdynamic state that is often present in liver disease. A diagnosis of POPH is also suggested if mPAP, PVR and PAWP are elevated if the transpulmonary gradient (mPAP–PAWP) is >12 mmHg [2]. Patients with this hemodynamic profile often require diuresis in addition to PAH-specific therapy. Patients with an elevated mPAP, PVR, and PAWP and a TPG ≤12 mmHg often just require diuresis. Additional testing to rule out other causes of PH, such as chronic lung disease and chronic thromboembolic PH, is also an important part of the diagnostic evaluation because treatment of these diseases may be different.

Right heart catheterization enables differentiation of POPH from other causes of PH that are frequently encountered in patients with liver disease, as shown in Figure 1. In a Mayo Clinic study of patients with portal hypertension, 101 patients with an estimated RVSP >50 mmHg on echocardiogram underwent right heart catheterization. Sixty-five percent of patients with a mPAP >25 mmHg were diagnosed with POPH, whereas 35% of patients had an elevated mPAP due to an elevated CO or PAWP [5]. An elevated mPAP due to an elevated CO or PAWP did not have any adverse implications for liver transplant. Differentiation of POPH from other causes of PH with right heart catheterization is critical because a diagnosis of POPH has significant implications for perioperative risk stratification and liver transplant candidacy, Model for End Stage Liver Disease (MELD) exception points, and the use of PAH-specific therapy as discussed below.

POPH: pathophysiology

The pathogenesis of POPH is poorly understood. Neither the severity of liver disease [6,16–19] nor the degree of portal hypertension [6,16] are associated with the presence or severity of POPH. A retrospective case–control study identified a higher prevalence of large spontaneous portosystemic shunts among patients with moderate (mPAP 35–50) to severe (mPAP >50) POPH compared with milder or no POPH [20]. Larger shunts were also associated with poor echocardiographic response to treatment [20]. The findings of this study suggest that vasoactive factors bypassing the liver in the presence of portosystemic shunting may play a role in the pathogenesis of disease, but the identity of these factors is not known. Pathologically, POPH is indistinguishable from idiopathic PAH [21]. It is not known, however, whether the pathophysiological mechanisms of these two diseases are distinct. Similar to patients with idiopathic PAH [22,23], small studies have described increased endothelin-1 levels and decreased pulmonary artery prostacyclin synthase expression in patients with POPH [23–26]. Female sex is also considered a risk factor for both idiopathic PAH and POPH [19,27,28], and a case–control study identified genetic variations in estrogen signaling pathways and higher estradiol levels in patients with POPH compared with

cirrhotic controls, suggesting a role for sex hormones in the pathogenesis of disease [29].

POPH: prognosis & implications for liver transplant

POPH can lead to right heart failure and death [8]. Without treatment or liver transplant, POPH is associated with a 1-year survival of 46% and a 5-year survival of 14% [30]. In the modern PAH treatment era, a large, multicenter prospective Registry to Evaluate Early and Long-term PAH disease management (REVEAL) registry in the US reported worse survival for patients with POPH compared with patients with idiopathic or familial PAH (2-year survival 67 vs 85% and 5-year survival 40 vs 64%) as depicted in Figure 3 [8]. Patients with POPH had a worse survival despite a lower PVR and higher CO, factors typically associated with a better prognosis. The cause of this increased mortality observed in POPH is not known, but is potentially related to the presence of comorbid liver disease. Improved 1- and 5-year survival rates of 88 and 68%, respectively, were reported in a French cohort of POPH patients with less severe liver disease [31]. In these patients, causes of death were distributed approximately equally between liver disease and PAH. Increased mortality in POPH compared with idiopathic PAH could also be due to a decreased likelihood of patients with POPH to be on PAH-specific therapy. The REVEAL registry also identified that patients with POPH were significantly less likely to be treated with PAH-specific therapy compared with patients with idiopathic or familial PAH [8].

POPH can complicate and preclude liver transplantation due to elevated perioperative mortality risk, which can be stratified based on mPAP [32]. A retrospective study by Krowka *et al.* [32] found that untreated patients with POPH and mPAP >50 mmHg had 100% cardiopulmonary mortality with liver transplant, whereas patients with mPAP 35–50 mmHg had a 50% cardiopulmonary mortality and patients with mPAP <35 mmHg had 0% cardiopulmonary mortality. Based on this study, mPAP >50 mmHg is considered an absolute contraindication to liver transplant and mPAP of 35–50 mmHg is considered a relative contraindication due to increased perioperative mortality risk [33]. For this reason, treatment of POPH to decrease mPAP to <35 mmHg is of utmost importance and urgency in patients awaiting liver transplant to minimize perioperative risk.

In addition to hemodynamic assessment of mPAP, the evaluation of right ventricular function is also essential in determining perioperative risk for liver transplant candidates with POPH. Adequate right ventricular function is necessary to handle the acute increase in CO that occurs with liver transplant during reperfusion [34,35]. In patients with right ventricular dysfunction and a fixed PVR, a decreased capacity to handle the increase in CO and pulmonary arterial pressure at the time of reperfusion can lead to right heart failure and death.

Since 2006, patients with treated POPH on the liver transplant list have been eligible to receive waitlist priority upgrades, or MELD exception points to prioritize and expedite liver transplant [36]. According to the current United Network for Organ Sharing (UNOS) MELD exception policy [33], patients with POPH who have an adequate hemodynamic response to PAH-specific therapy (defined as a decrease in mPAP to <35 mmHg and a PVR <400 dyn·s·cm^{-5}) can receive MELD exception points. To remain active on the waitlist and continue to accrue 10% mortality equivalent exception points, patients must undergo right heart catheterizations every 3 months and demonstrate a sustained response to therapy that meets the above hemodynamic criteria. The MELD exception scoring system is used to prioritize liver transplant for patients with POPH, but whether POPH in the absence of significant liver disease should be an indication for liver transplant is not known.

Outcomes of POPH with liver transplant are variable and unpredictable. Several case series have described improved hemodynamics and de-escalation of POPH therapy in select patients after liver transplant [37–40]. Hollatz *et al.* [37] described 11 patients treated predominantly with oral sildenafil and subcutaneous

Box 1. Updated clinical classification of pulmonary hypertension according to the Fifth World Symposium.

1. PAH
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
   - 1.3 Drug and toxin induced
   - 1.4 Associated with:
     - 1.4.1 Connective tissue disease
     - 1.4.2 HIV infection
     - 1.4.3 Portal hypertension
     - 1.4.4 Congenital Heart Disease
     - 1.4.5 Schistosomiasis

   1' Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

   1'' Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease
   - 2.1 Left ventricular systolic dysfunction
   - 2.2 Left ventricular diastolic dysfunction
   - 2.3 Valvular Disease
   - 2.4 Left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. Pulmonary hypertension due to lung diseases and/or hypoxia
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
   - 5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   - 5.2 Systemic disorders: Sarcoidosis, etc.
   - 5.3 Metabolic disorders: Glycogen storage disease, thyroid disorders, etc.
   - 5.4 Others

PAH: Pulmonary arterial hypertension.
Abbreviated and reproduced with permission from [3].

doi: 10.1586/17474124.2015.1035647

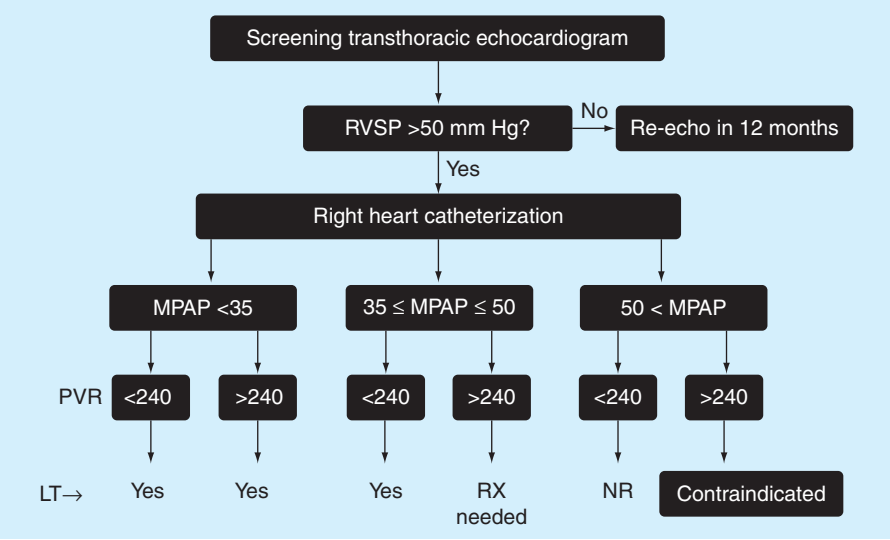

Figure 2. Mayo Clinic Screening algorithm for portopulmonary hypertension.
LT: Liver transplant; MPAP: Mean pulmonary arterial pressure; NR: Never reported; PVR: Pulmonary vascular resistance; RVSP: Right ventricular systolic pressure.
Reprinted with permission from [12].

treprostinil, who successfully underwent liver transplant with 0% mortality after 7–60 months of follow-up. Sixty-four percent of patients were off all pulmonary vasodilators post-transplant. Sussman *et al.* [38] also described four patients with moderate-to-severe POPH, who underwent liver transplant after treatment with epoprostenol to decrease mPAP to <35 mmHg, and Ashfaq *et al.* [39] described 11 patients with moderate-to-severe POPH, who underwent liver transplantation after treatment with PAH-specific therapy to decrease mPAP to <35 mmHg. In these patients, 1-year survival was 91% and 5-year survival was 67%. In addition, nine out of 11 patients were off PAH therapy after a median 9.2 months post-transplant. Although reporting bias is possible given the retrospective nature of these reports, most case series suggest that liver transplant may be important in the therapeutic management of POPH.

Worsening of POPH post-transplant has been described as well [41,42]. Some case reports have also described the development or worsening of POPH after liver transplant in patients with antecedent hepatopulmonary syndrome [42,43]. A recent analysis of the Scientific Registry of Transplant Recipients data also demonstrated that patients who received a MELD exception score for POPH between 2002 and 2010 (n = 78) had a higher risk of death and graft failure 1 year post-transplant [44]. An additional analysis of the Organ Procurement and Transplantation Network data from 2006 to 2012 demonstrated that only 47.1% of patients receiving a MELD exception met the formal hemodynamic criteria for POPH [45]. These studies demonstrate that prospective studies to determine which patients will benefit the most from liver transplant and to evaluate the post-transplant outcomes in patients with POPH are warranted.

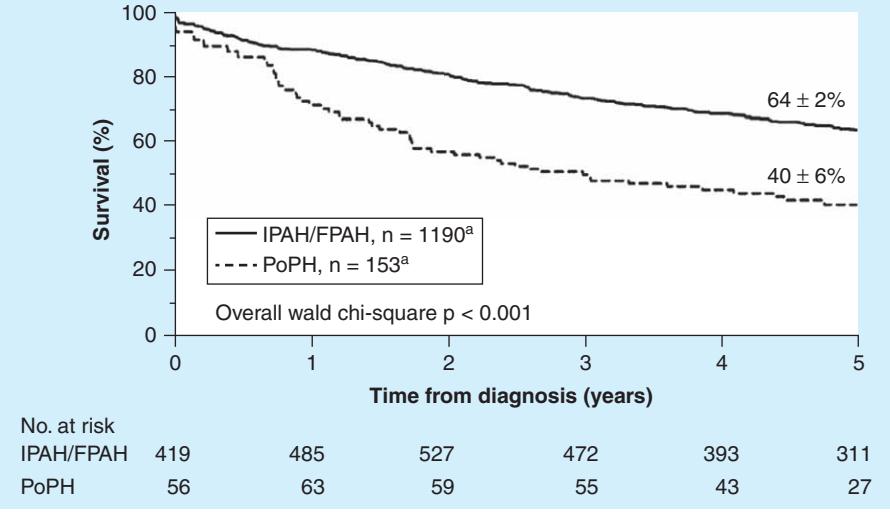

Figure 3. Kaplan–Meier curves from REVEAL study demonstrating 5-year survival for patients with idiopathic/familial PAH (IPAH/FPAH) (solid line) versus POPH (dashed line) (64 vs. 40%, p <0.001).
Reproduced with permission from the American College of Chest Physicians [8].
IPAH: Idiopathic PAH.

Treatment of PAH

Therapeutic pathways in PAH

Therapy for WHO Group 1 PAH targets three distinct pathways involved in the pathogenesis of pulmonary vasoconstriction and vascular remodeling: the prostacyclin, nitric oxide, and endothelin pathways [46]. There are currently four classes of therapeutics that target these pathways. These include prostacyclin analogs, phosphodiesterase 5 inhibitor (PDE5I), endothelin receptor antagonists (ERAs) and soluble guanylate cyclase (sGC) stimulators. Drugs available in each class are listed in Table 1 along with their trade names and route of administration. Prostacyclin analogs, such as epoprostenol and treprostinil, are cytoprotective and antiproliferative therapies that cause vasodilation and inhibit platelet aggregation [46]. PDE5I, such as sildenafil and tadalafil, prevent the metabolism of cGMP, which mediates the vasodilatory effects of nitric oxide. These medications have been shown to improve exercise capacity and pulmonary hemodynamics [46]. ERAs, which include

bosentan, ambrisentan, and now macitentan, antagonize the effect of endothelin-1, resulting in both vasodilation and decreased cellular proliferation. They have been shown in clinical trials to improve exercise capacity and hemodynamics [46]. Riociguat, a sGC stimulator discussed in more detail below, increases the production of cGMP independent of nitric oxide, resulting in vasodilation [47]. Sildenafil, tadalafil, riociguat, and ERAs are available in oral formulations, whereas prostacyclin analogs are now available in oral (PO), inhaled (IH), subcutaneous (SC), and intravenous (IV) formulations.

Table 1. Currently approved therapies for the treatment of World Health Organization Group 1 pulmonary arterial hypertension in the United States.

Therapeutic class	Drug	Brand name	Route
Prostacyclin analogs	Epoprostenol Treprostinil Iloprost	Flolan Remodulin/Tyvaso/Orenitram Ventavis	IV IV and SC/INH/PO INH
Endothelin receptor antagonists	Bosentan Ambrisentan Macitentan	Tracleer Letairis Opsumit	PO PO PO
Phosphodiesterase-5 Inhibitors	Sildenafil Tadalafil	Revatio Adcirca	PO PO
Soluble guanylate cyclase stimulators	Riociguat	Adempas	PO

INH: Inhaled; IV: Intravenous; PO: Oral; SC: Subcutaneous.

New treatments for PAH

In 2013, three new oral therapies were approved for the treatment of PAH. These included macitentan, a dual ERA with enhanced tissue penetration, oral treprostinil, the first approved oral prostacyclin analog, and riociguat, a first-in-class sGC stimulator. With the approval of these medications, there are now 12 PAH-specific therapies available in the USA. Further details about these recently approved medications and the clinical trials that evaluated their efficacy are detailed below.

Macitentan (Opsumit, Actelion Pharmaceuticals)

Macitentan is a novel dual ERA with improved tissue penetration compared with other ERAs [48]. The pivotal study that led to its approval, Study with an ERA in Pulmonary arterial Hypertension to Improve cliNical outcomes (SERAPHIN) [49], was the largest, longest and first event-driven trial published in PAH to date. Seven hundred and forty-two patients with symptomatic PAH were randomized 1:1:1 to receive placebo (n = 250), macitentan 3 mg (n = 250), or macitentan 10 mg (n = 242) and were followed for a median duration of 115 weeks. Macitentan was associated with a decreased time to a primary composite endpoint of morbidity or mortality events. Worsening of PAH was the most frequent component of the composite endpoint, and there was no significant difference in mortality alone. Macitentan was also well tolerated. The most common side effects were peripheral edema (18.2%), upper respiratory tract infection (15.3%), nasopharyngitis (14.0%), headache (13.6%), and anemia (13.2%), and the number of adverse events reported was similar in all groups. Unlike bosentan, which was associated with a 10.1% annual rate of aminotransferase elevation in post-marketing surveillance [50], macitentan does not require monthly monitoring of liver function tests. In SERPAHIN [49], ALT and AST elevation >3×, the upper limit of normal occurred in 3.4% of patients on macitentan 10 mg compared with 4.5% of patients in the placebo arm. Additional studies have also demonstrated that dose adjustment in patients with hepatic or renal impairment is not necessary [51].

Oral treprostinil (Orenitram, United Therapeutics)

Oral treprostinil is an oral prostacyclin analog developed by United Therapeutics. Oral treprostinil has been evaluated in several clinical trials to date. The trial that led to the US FDA approval was FREEDOM-M [52], which evaluated the effect of oral treprostinil as monotherapy on exercise capacity in patients with WHO Group 1 PAH. Three hundred and forty-nine patients were randomized to treprostinil (n = 233) or placebo (n = 116). In a modified intention-to-treat analysis, they found that oral treprostinil improved exercise capacity as assessed by 6-min walk distance by 23 m in the treatment group compared with placebo over 12 weeks of treatment. Most common side effects were similar to side effects with other prostacyclin therapies and included headache (69%), nausea (39%), diarrhea (37%), jaw pain (25%), and vomiting (24%). Ten percent of patients on the study drug discontinued the therapy due to adverse effects. Notably, the FREEDOM-C and FREEDOM-C2 studies [53,54], which evaluated the effect of oral treprostinil in combination with other background PAH therapy, did not demonstrate a significant improvement in exercise capacity.

Riociguat (Adempas, Bayer Healthcare)

Riociguat is a sGC stimulator that acts on the nitric oxide pathway, similar to PDE5I, but directly increases cGMP production, leading to vasodilation [47]. Riociguat was approved for the treatment of PAH following completion of PATENT-1 [47], a Phase III, randomized, controlled, double-blinded study, in which 443 patients with symptomatic PAH received placebo (n = 126), riociguat in doses up to 2.5 mg three times daily (n = 254), or riociguat in doses up to 1.5 mg three times daily as an exploratory arm (n = 63). By week 12, riociguat improved exercise capacity, pulmonary hemodynamics, WHO functional class (FC), and time to clinical worsening. The most common adverse effects in patients receiving riociguat included headache (27%), dyspepsia (19%), edema (17%), nausea (16%), dizziness (16%) and diarrhea (14%). Three percent of patients in the treatment arm discontinued the study drug due

doi: 10.1586/17474124.2015.1035647

to adverse effects. Compared with placebo, hypotension was also significantly more common (10%) in patients receiving riociguat.

Unlike the SERAPHIN and FREEDOM-M studies evaluating the safety and efficacy of macitentan and oral treprostinil, respectively, PATENT-1, the Phase III study that led to approval of riociguat for the treatment of WHO Group I PAH, included 13 patients with POPH. Eleven patients with POPH were included in the treatment arm and two patients were included in the placebo arm. There was no published subgroup analysis; however, preliminary analysis suggested a significant improvement in PVR and 6-min walk distance with riociguat versus placebo [MJ Krowka, Pers. Comm.].

Treatment of POPH

Goals of therapy & approach to treatment

In WHO Group 1 PAH, the main goal of therapy is to improve symptoms and FC. Improvements in exercise capacity, right ventricular function, and survival are additional goals of therapy [55]. The current guidelines recommend initiation and titration of therapy based on FC and symptoms, rather than specific hemodynamic parameters, such as mPAP [46,56]. These guidelines recommend an ERA, PDE5I or riociguat for initial therapy in patients with FC II symptoms (PH resulting in a slight limitation in physical activity); an ERA, PDE5I, riociguat, inhaled, IV or SC prostacyclin, or initial combination therapy in patients with FC III symptoms (PH resulting in marked limitation of physical activity); and IV epoprostenol for patients with FC IV symptoms (PH resulting in inability to perform any physical activity without symptoms, symptoms at rest or syncope). IV epoprostenol is recommended for patients with FC IV symptoms as it is the only PAH therapy that has been shown to improve survival in patients with PAH [57]. With the exception of IV epoprostenol for patients with FC IV symptoms, the current guidelines do not recommend a particular therapeutic agent or pathway for the treatment of PAH.

In patients with POPH being considered for liver transplant, the goals of therapy are similar, but an additional goal is to decrease mPAP to <35 mmHg to facilitate safe liver transplantation. Targeting this hemodynamic parameter can often drive treatment decisions in POPH. The approach to choosing a therapeutic agent in POPH is similar to other subtypes of WHO Group 1 PAH, and there is no evidence to suggest that use of one therapeutic class or agent over another is preferred in patients with FC II–III symptoms. As a subtype of WHO group 1 PAH, IV epoprostenol is also recommended for POPH patients with FC IV symptoms. In addition, beta blockers, frequently prescribed for prophylaxis in patients with esophageal varices, have been associated with decreased exercise capacity and worsening pulmonary hemodynamics in POPH [58] and they should be discontinued or used with caution in these patients.

Patients receiving a MELD exception for POPH also must undergo serial catheterizations every 3 months to ensure pulmonary hemodynamics are acceptable for liver transplant and to accrue MELD exception points. Serial catheterization is not typically performed on a routine basis in patients with other subtypes of PAH unless clinically indicated. Although right heart catheterization is a generally safe and well-tolerated procedure, the risk of repeated catheterizations in patients with liver disease who often have concomitant thrombocytopenia and coagulopathy is not insignificant.

The use of PAH therapies in POPH

Although there has been an increase in the number of available therapies for the treatment of WHO Group 1 PAH, there remains little data to guide the medical management of patients with POPH. There have been no prospective randomized controlled trials to determine the safety and efficacy of therapy in this subgroup of patients, and most studies in PAH have typically excluded patients with POPH, including two out of three of the recent studies described above. Consequently, the safety, tolerability and efficacy of PAH-specific therapy in patients with POPH is not known but inferred from published case series, observational studies and provider experience.

Numerous case reports have described improved hemodynamics with the use of IV epoprostenol in POPH [17,38,39,59–61], although improvements in survival have not been described with epoprostenol in POPH [31,38]. In one recent single center case series [62], Khaderi *et al.* described the use of continuous IV epoprostenol to successfully reduce the mPAP to <35 mmHg in six of seven patients with POPH to facilitate liver transplant. There are also challenges with the use of IV prostacyclin therapy in patients with liver disease, however. Continuous IV prostacyclin therapy requires placement of a central venous catheter, which can be associated with an increased risk of bloodstream infections and other complications. Adverse effects, such as progressive splenomegaly and thrombocytopenia, have also been reported in patients with POPH [63,64]. In addition to IV epoprostenol favorable hemodynamic effects have been described with the use of other prostacyclin analogs as well, including IV and SC treprostinil [37,65] and inhaled iloprost [18,66].

Small studies have described the use of PDE5I and ERAs in POPH as well. Retrospective series have reported that sildenafil improved functional capacity and decreased PVR and mPAP in POPH [67–69], and the successful use of sildenafil in combination with SC treprostinil to facilitate liver transplant has also been reported [37]. Additional studies have described improved pulmonary hemodynamics with bosentan and ambrisentan in patients with POPH [70,71]. Seven patients (annual rate of 5.5%) in the bosentan study developed elevations in liver transaminases >3 × the upper limit of normal, which resolved with dose reduction or discontinuation, and no patients in the ambrisentan study (n = 13) had significant changes in liver function parameters. The use of oral combination therapy with PDE5I and ERAs as a bridge to liver transplant has also been reported in a case series of seven patients with POPH [72].

Limited experience has documented that highly selected, treated POPH patients normalize pulmonary hemodynamics

after liver transplant and subsequently, pulmonary vasoactive medications can be safely weaned and discontinued [30,37–39,62,69,72]. In addition, a recent systematic review and meta-analysis reported that the use of PAH-specific therapy in POPH was associated with improved pulmonary hemodynamics as well as exercise capacity. In a review of 12 publications, PAH therapy was associated with an improvement in mPAP by 7.54 mmHg, CO by 1.77 l/min and PVR by 253 dyn·s·cm^{-5}. PAH therapy also increased 6-min walk distance by 61.8 m [73]. The safety and efficacy of macitentan, oral treprostinil and riociguat in patients with POPH, however, has yet to be described in the literature.

Expert commentary

POPH is a serious yet treatable disease of pulmonary vasoconstriction and vascular remodeling associated with portal hypertension. Unfortunately, there is little data to guide management of POPH. The safe and effective use of prostacyclin analogs, ERAs, and PDE5 inhibitors has been described in case series and case reports, but patients with POPH have been excluded from most randomized clinical trials in PAH. Although the armamentarium for the treatment of PAH has been expanding at a rapid pace, we do not yet have a method for predicting clinical or hemodynamic response to a particular agent or therapeutic class.

The role of new medications, such as macitentan, oral treprostinil and riociguat in the treatment of POPH remains to be determined. Macitentan, the first oral PAH therapy to demonstrate an improvement in a composite endpoint of morbidity and mortality, is a potentially promising treatment for POPH given the description of increased endothelin levels in POPH and the absence of significant aminotransferase elevation compared with placebo in SERAPHIN. It is important to note, however, that macitentan was not studied in patients with POPH and there have been no head-to-head trials with ambrisentan or other classes of PAH therapeutics. Anemia, which was more frequent in patients taking macitentan compared with placebo, may also limit its use in patients with preexisting anemia or risk factors for bleeding. Given issues with continuous IV administration of prostacyclin analogs, particularly in patients with POPH, oral treprostinil is also an appealing new agent. The frequency of adverse effects and lack of significant improvement in exercise capacity with background PAH therapy, however, may limit its use compared with other PAH therapies. The randomized controlled trial, PATENT-1, that studied the safety and efficacy of riociguat, included patients with POPH, but the results in this subgroup have not been reported in peer-reviewed literature. In addition, because this is a new class of PAH medications, there have been no published case reports yet that have described the outcomes of sGC stimulators in POPH. The main concern with the use of riociguat in POPH is an increased risk of hypotension and the need to closely monitor blood pressure with dose titration. Consequently, the use of riociguat in patients with liver disease may be restricted to patients with higher baseline blood pressures.

Despite an increasing number of medications available for the treatment of PAH, there is still a great deal to learn about the use of both older and newer PAH therapies and the optimal management of patients with POPH. First, it is unknown if patients with POPH have distinct pathophysiologic mechanisms of disease that could have therapeutic implications. Patients with hepatic autoimmune disorders, such as primary biliary cirrhosis with CREST syndrome, or who have had splenectomy may have different responses to PAH-targeted therapy. We also do not know if patients with POPH would benefit more from targeting a particular therapeutic pathway, such as endothelin, or an alternative pathway that is not currently a target of approved PAH drugs, such as estradiol.

Second, the role of liver transplant in the management of POPH needs prospective study. There are no known prognostic factors that predict the pulmonary hemodynamic response to transplant, but POPH can resolve, at least hemodynamically, following liver transplant in highly selected patients. Given the unpredictable outcomes of POPH with transplant and lack of long-term POPH treatment data without transplant, it is questionable that treated POPH should be an indication for liver transplant in patients with *mild* liver disease. In addition, treatment may dramatically reduce PVR and increase CO, yet the resultant mPAP may be elevated due to a high flow state as opposed to obstruction to flow. Hence, the reliance on mPAP alone as determining priority for liver transplant needs reconsideration. The treatment effect on right ventricular size and function are also underemphasized, important parameters that should be included in the evaluation of transplant candidates with POPH.

Third, the use of serial right heart catheterizations every 3 months to target a specific mPAP is associated with increased risk and discomfort for patients with POPH, particularly those with concomitant coagulopathy. Although right heart catheterization is a valuable diagnostic tool, there is a pressing need to develop non-invasive surrogate biomarkers to follow the progression of this disease so patients are not subjected to the risk of repeated procedures.

In summary, the field of PAH therapeutics has been evolving at a rapid pace over the past few years with the approval of three new drugs in 2013 and a paradigm shift toward developing long-term studies with clinical endpoints. As in the past, we expect to learn more about the use of these new therapies through the publication of case reports and case series that will describe provider experience with macitentan, oral treprostinil and riociguat in patients with POPH. Prospective studies of PAH therapeutics to better understand their safety and efficacy in patients with POPH, however, is warranted.

Five-year view

In 5 years, we anticipate that we will have a better understanding of the pathogenesis of POPH, which may have significant implications for the use of targeted therapeutics in this group of patients. We also hope that we will have an improved understanding of the role of liver transplant in the management of

doi: 10.1586/17474124.2015.1035647

this disease and will be able to identify prognostic factors that are predictive of post-transplant outcomes in POPH. Ideally, this information could then be incorporated into the MELD exception scoring system so livers can be allocated to patients who are most likely to benefit from transplant. Although a challenging patient population to study given the presence of comorbid liver disease, we hope that patients with POPH will be included as a subgroup in future studies so we can learn more about the safety and efficacy of PAH therapeutics in POPH.

Financial & competing interests disclosure

MJ Krowka is a member of the steering committee for Portico, a multicenter study for the use of macitenan in portopulmonary hypertension, sponsored by Actelion. RN Channick is a consultant for Actelion pharmaceuticals, Bayer, United Therapeutics, Respira and ZappRx. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Key issues

- PAH, diagnosed with right heart catheterization, is characterized by an elevated mean pulmonary arterial pressure and pulmonary vascular resistance in the setting of a normal pulmonary artery wedge pressure.
- POPH is a subtype of WHO Group 1 PAH that develops in patients with portal hypertension and can preclude liver transplantation due to elevated perioperative risk.
- Compared with patients with idiopathic PAH, patients with POPH have a significantly higher mortality and are less likely to be on PAH-specific therapy.
- There are currently 12 US FDA-approved medications for the treatment of PAH that target the nitric oxide, endothelin, and prostacyclin pathways; although not specifically evaluated in prospective clinical trials, these drugs are also used for the treatment of POPH.
- Three new therapies for the treatment of PAH (macitentan, riociguat, and oral treprostinil) were approved in 2013 and represent significant advances in the field of PAH, although patients with POPH were only included in one out of three of these studies.
- We anticipate that future studies in WHO Group 1 PAH will include patients with POPH and will also determine if patients with POPH have unique pathophysiology that would affect clinical and hemodynamic response to therapy.
- POPH is a serious but treatable disease with important implications for liver transplant candidacy, MELD exception points, the use of PAH-specific therapy, and overall prognosis.

References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

1. Hoeper MM, Bogaard HJ, Condliffe R, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol 2013;62(25 Suppl):D42-50
2. Krowka MJ. Portopulmonary hypertension. Semin Respir Crit Care Med 2012;33(1): 17-25
3. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013;62(25 Suppl):D34-41
4. Rodriguez-Roisin R, Krowka MJ, Herve P, et al. Pulmonary-Hepatic vascular Disorders (PHD). The Eur Respir J 2004;24(5): 861-80

•• **European Respiratory Society guidelines on the diagnosis and management of pulmonary vascular complications of liver disease.**

5. Krowka MJ, Swanson KL, Frantz RP, et al. Portopulmonary hypertension: Results from a 10-year screening algorithm. Hepatology 2006;44(6):1502-10

•• **Prospective study describing the prevalence of portopulmonary hypertension in patients evaluated for liver transplant, the use of an echocardiography screening algorithm, and the results of right heart catheterization.**

6. Colle IO, Moreau R, Godinho E, et al. Diagnosis of portopulmonary hypertension in candidates for liver transplantation: a prospective study. Hepatology 2003;37(2): 401-9
7. Torregrosa M, Genesca J, Gonzalez A, et al. Role of Doppler echocardiography in the assessment of portopulmonary hypertension in liver transplantation candidates. Transplantation 2001;71(4):572-4
8. Krowka MJ, Miller DP, Barst RJ, et al. Portopulmonary hypertension: a report from the US-based REVEAL Registry. Chest 2012;141(4):906-15

•• **Manuscript describing survival and all-cause hospitalization rates in 174 patients with portopulmonary hypertension enrolled in the REVEAL registry.**

9. Humbert M, Sitbon O, Chaouat A, et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med 2006;173(9):1023-30
10. Kim WR, Krowka MJ, Plevak DJ, et al. Accuracy of Doppler echocardiography in the assessment of pulmonary hypertension in liver transplant candidates. Liver Transpl 2000;6(4):453-8
11. Raevens S, Colle I, Reyntjens K, et al. Echocardiography for the detection of portopulmonary hypertension in liver transplant candidates: an analysis of cutoff values. Liver Transpl 2013;19(6):602-10
12. Cartin-Ceba R, Krowka MJ. Preoperative Assessment and Management of Liver Transplant Candidates with Portopulmonary Hypertension. Adv Pul Hypert 2013;12(2): 60-7
13. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the american college of cardiology foundation task force on expert consensus documents and the american heart association developed in collaboration with

the american college of chest physicians; american thoracic society, Inc.; and the pulmonary hypertension association. J Am Coll Cardiol 2009;53(17):1573-619

14. Galie N, Hoeper M, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2009;30(20):2493-537
15. McGoon MD, Miller DP. REVEAL: a contemporary US pulmonary arterial hypertension registry. Eur Respir Rev 2012; 21(123):8-18
16. Hadengue A, Benhayoun MK, Lebrec D, Benhamou JP. Pulmonary hypertension complicating portal hypertension: prevalence and relation to splanchnic hemodynamics. Gastroenterology 1991;100(2):520-8
17. Fix OK, Bass NM, De Marco T, et al. Long-term follow-up of portopulmonary hypertension: effect of treatment with epoprostenol. Liver Transpl 2007;13(6): 875-85
18. Hoeper MM, Seyfarth HJ, Hoeffken G, et al. Experience with inhaled iloprost and bosentan in portopulmonary hypertension. Eur Respir J 2007;30(6):1096-102
19. Kawut SM, Krowka MJ, Trotter JF, et al. Clinical risk factors for portopulmonary hypertension. Hepatology 2008;48(1): 196-203
20. Talwalkar JA, Swanson KL, Krowka MJ, et al. Prevalence of spontaneous portosystemic shunts in patients with portopulmonary hypertension and effect on treatment. Gastroenterology 2011;141(5): 1673-9
21. Krowka MJ, Edwards WD. A spectrum of pulmonary vascular pathology in portopulmonary hypertension. Liver Transpl 2000;6(2):241-2
22. Giaid A, Yanagisawa M, Langleben D, et al. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. N Engl J Med 1993;328(24):1732-9
23. Tuder RM, Cool CD, Geraci MW, 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
24. Benjaminov FS, Prentice M, Sniderman KW, et al. Portopulmonary hypertension in decompensated cirrhosis with refractory ascites. Gut 2003;52(9): 1355-62
25. Pellicelli AM, Barbaro G, Puoti C, et al. Plasma cytokines and portopulmonary hypertension in patients with cirrhosis waiting for orthotopic liver transplantation. Angiology 2010;61(8):802-6
26. Tsiakalos A, Hatzis G, Moyssakis I, et al. Portopulmonary hypertension and serum endothelin levels in hospitalized patients with cirrhosis. Hepatobiliary Pancreat Dis Int 2011;10(4):393-8
27. Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension. A national prospective study. Ann Intern Med 1987;107(2):216-23
28. Badesch DB, Raskob GE, Elliott CG, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. Chest 2010;137(2):376-87
29. Roberts KE, Fallon MB, Krowka MJ, et al. Genetic risk factors for portopulmonary hypertension in patients with advanced liver disease. Am J Respir Crit Care Med 2009; 179(9):835-42

•• **Multi-center case–control study describing genetic risk factors for portopulmonary hypertension.**

30. Swanson KL, Wiesner RH, Nyberg SL, et al. Survival in portopulmonary hypertension: Mayo Clinic experience categorized by treatment subgroups. Am J Transplant 2008;8(11):2445-53
31. Le Pavec J, Souza R, Herve P, et al. Portopulmonary hypertension: survival and prognostic factors. Am J Respir Crit Care Med 2008;178(6):637-43
32. Krowka MJ, Plevak DJ, Findlay JY, et al. Pulmonary hemodynamics and perioperative cardiopulmonary-related mortality in patients with portopulmonary hypertension undergoing liver transplantation. Liver Transpl 2000;6(4):443-50
33. Krowka MJ, Wiesner RH, Heimbach JK. Pulmonary contraindications, indications and MELD exceptions for liver transplantation: a contemporary view and look forward. J Hepatol 2013;59(2):367-74

•• **Recent review describing the current pulmonary contraindications, indications and MELD exceptions for liver transplantation.**

34. Safdar Z, Bartolome S, Sussman N. Portopulmonary hypertension: an update. Liver Transpl 2012;18(8):881-91
35. Ramsay M. Portopulmonary hypertension and right heart failure in patients with cirrhosis. Curr Opin Anaesthesiol 2010; 23(2):145-50
36. Krowka MJ, Fallon MB, Mulligan DC, et al. Model for end-stage liver disease (MELD) exception for portopulmonary hypertension. Liver Transpl 2006; 12(12 Suppl 3):S114-16
37. Hollatz TJ, Musat A, Westphal S, et al. Treatment with sildenafil and treprostinil allows successful liver transplantation of patients with moderate to severe portopulmonary hypertension. Liver Transpl 2012;18(6):686-95
38. Sussman N, Kaza V, Barshes N, et al. Successful liver transplantation following medical management of portopulmonary hypertension: a single-center series. Am J Transpl 2006;6(9):2177-82
39. Ashfaq M, Chinnakotla S, Rogers L, et al. The impact of treatment of portopulmonary hypertension on survival following liver transplantation. Am J Transpl 2007;7(5): 1258-64
40. Mancuso L, Scordato F, Pieri M, et al. Management of portopulmonary hypertension: new perspectives. World J Gastroenterol 2013;19(45):8252-7
41. Koch DG, Caplan M, Reuben A. Pulmonary hypertension after liver transplantation: case presentation and review of the literature. Liver Transpl 2009;15(4): 407-12
42. Martinez-Palli G, Barbera JA, Taura P, et al. Severe portopulmonary hypertension after liver transplantation in a patient with preexisting hepatopulmonary syndrome. J Hepatol 1999;31(6):1075-9
43. Aucejo F, Miller C, Vogt D, et al. Pulmonary hypertension after liver transplantation in patients with antecedent hepatopulmonary syndrome: a report of 2 cases and review of the literature. Liver Transpl 2006;12(8):1278-82
44. Salgia RJ, Goodrich NP, Simpson H, et al. Outcomes of liver transplantation for porto-pulmonary hypertension in model for end-stage liver disease era. Dig Dis Sci 2014;59(8):1976-82
45. Goldberg DS, Batra S, Sahay S, et al. MELD Exceptions for Portopulmonary Hypertension: Current Policy and Future Implementation. Am J Transpl 2014;14(9): 2081-7
46. Galie N, Corris PA, Frost A, et al. Updated treatment algorithm of pulmonary arterial hypertension. J Am Coll Cardiol 2013; 62(25 Suppl):D60-72
47. Ghofrani HA, Galie N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med 2013;369(4):330-40

• **Manuscript describing the results of the Phase III randomized controlled trial evaluating the safety and efficacy of riociguat in pulmonary arterial hypertension.**

doi: 10.1586/17474124.2015.1035647

48. Iglarz M, Binkert C, Morrison K, et al. Pharmacology of macitentan, an orally active tissue-targeting dual endothelin receptor antagonist. J Pharmacol Exp Ther 2008;327(3):736-45

49. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med 2013;369(9):809-18

- **Manuscript describing the results of the Phase III randomized controlled trial evaluating the safety and efficacy of macitentan in pulmonary arterial hypertension.**

50. Humbert M, Segal ES, Kiely DG, et al. Results of European post-marketing surveillance of bosentan in pulmonary hypertension. Eur Respir J 2007;30(2): 338-44

51. Sidharta PN, Lindegger N, Ulc I, et al. Pharmacokinetics of the novel dual endothelin receptor antagonist macitentan in subjects with hepatic or renal impairment. J Clin Pharmacol 2013;54(3):291-300

52. Jing ZC, Parikh K, Pulido T, et al. Efficacy and safety of oral treprostinil monotherapy for the treatment of pulmonary arterial hypertension: a randomized, controlled trial. Circulation 2013;127(5):624-33

- **Manuscript describing the results of the Phase III randomized controlled trial evaluating the safety and efficacy of oral treprostinil as monotherapy in pulmonary arterial hypertension.**

53. Tapson VF, Torres F, Kermeen F, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients on background endothelin receptor antagonist and/or phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C study): a randomized controlled trial. Chest 2012;142(6):1383-90

54. Tapson VF, Jing ZC, Xu KF, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients receiving background endothelin receptor antagonist and phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C2 study): a randomized controlled trial. Chest 2013; 144(3):952-8

55. McLaughlin VV, Gaine SP, Howard LS, et al. Treatment goals of pulmonary hypertension. J Am Coll Cardiol 2013; 62(25 Suppl):D73-81

56. Taichman DB, Ornelas J, Chung L, et al. Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST guideline and expert panel report. Chest 2014;146(2):449-75

57. Barst RJ, Rubin LJ, Long WA, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med 1996;334(5): 296-301

58. Provencher S, Herve P, Jais X, et al. Deleterious effects of beta-blockers on exercise capacity and hemodynamics in patients with portopulmonary hypertension. Gastroenterology 2006;130(1):120-6

59. Kuo PC, Johnson LB, Plotkin JS, et al. Continuous intravenous infusion of epoprostenol for the treatment of portopulmonary hypertension. Transplantation 1997;63(4):604-6

60. Plotkin JS, Kuo PC, Rubin LJ, et al. Successful use of chronic epoprostenol as a bridge to liver transplantation in severe portopulmonary hypertension. Transplantation 1998;65(4):457-9

61. Krowka MJ, Frantz RP, McGoon MD, et al. Improvement in pulmonary hemodynamics during intravenous epoprostenol (prostacyclin): A study of 15 patients with moderate to severe portopulmonary hypertension. Hepatology 1999;30(3):641-8

62. Khaderi S, Khan R, Safdar Z, et al. Long-term follow-up of portopulmonary hypertension patients after liver transplantation. Liver Transpl 2014;20(6): 724-7

63. Findlay JY, Plevak DJ, Krowka MJ, et al. Progressive splenomegaly after epoprostenol therapy in portopulmonary hypertension. Liver Transpl Sur 1999;5(5):362-5

64. Touma W, Nayak RP, Hussain Z, et al. Epoprostenol-induced hypersplenism in portopulmonary hypertension. Am J Med Sci 2012;344(5):345-9

65. Sakai T, Planinsic RM, Mathier MA, et al. Initial experience using continuous intravenous treprostinil to manage pulmonary arterial hypertension in patients with end-stage liver disease. Transpl Int 2009;22(5):554-61

66. Melgosa MT, Ricci GL, Garcia-Pagan JC, et al. Acute and long-term effects of inhaled iloprost in portopulmonary hypertension. Liver Transpl 2010;16(3):348-56

67. Reichenberger F, Voswinckel R, Steveling E, et al. Sildenafil treatment for portopulmonary hypertension. Eur Respir J 2006;28(3):563-7

68. Gough MS, White RJ. Sildenafil therapy is associated with improved hemodynamics in liver transplantation candidates with pulmonary arterial hypertension. Liver Transpl 2009;15(1):30-6

69. Hemnes AR, Robbins IM. Sildenafil monotherapy in portopulmonary hypertension can facilitate liver transplantation. Liver Transpl 2009;15(1): 15-19

70. Savale L, Magnier R, Le Pavec J, et al. Efficacy, safety, and pharmacokinetics of bosentan in portopulmonary hypertension. Eur Respir J 2013;41(1):96-103

71. Cartin-Ceba R, Swanson K, Iyer V, et al. Safety and efficacy of ambrisentan for the treatment of portopulmonary hypertension. Chest 2011;139(1):109-14

72. Raevens S, De Pauw M, Reyntjens K, et al. Oral vasodilator therapy in patients with moderate to severe portopulmonary hypertension as a bridge to liver transplantation. Eur J Gastroenterol Hepatol 2013;25(4):495-502

73. Faisal M, Siddiqi F, Alkaddour A, et al. Effect of PAH specific therapy on pulmonary hemodynamics and six-minute walk distance in portopulmonary hypertension: a systematic review and meta-analysis. Pulm Med 2014;2014:528783