REVIEW

The limits of oral therapy in pulmonary arterial hypertension management

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Abstract: Pulmonary arterial hypertension (PAH) is a devastating disease in which remodeling of the small pulmonary arteries leads to a progressive increase in pulmonary vascular resistance and right-sided heart failure. Over the past decade, new treatments for PAH, such as the use of ERAs, PDE-5 inhibitors and prostacyclin analogs, have brought about dramatic improvements in clinical outcomes. Epoprostenol infusion therapy has been shown to improve hemodynamics, functional status, and survival, and it remains the gold standard for treatment of patients with severe PAH. Many agents, approved for PAH are always delivered in pill form. Although oral therapy occupies an important position, it has some drawbacks and limitations in PAH management. For patients in World Health Organization functional class IV and with severe right heart failure, there are few data on the long-term survival of patients treated with oral medications. Further research, exploration, and clinical experience with oral therapy in severe PAH and combination therapy will redefine its position in PAH management.

Keywords: pulmonary arterial hypertension, right heart failure, oral therapy, survival

Introduction

Pulmonary arterial hypertension (PAH) is a series of diseases characterized by elevated pulmonary vascular resistance (PVR) and may lead to right heart failure and death, especially in patients with World Health Organization functional class (WHO-FC) III or IV.[1–4] Progress in medical treatment over the past decade has considerably improved the overall quality of life and outcome of PAH patients.[5–8] The clinical use of epoprostenol improves clinical condition and survival in PAH patients, opening the modern management era.[9–11] Oral therapy for PAH patients, such as bosentan, sildenafil, tadalafil, et al, because of its stability and convenient administration route, occupies an important position in the PAH management. However, when comparing with other routes of administration, oral therapy shows a number of drawbacks and limitations in the PAH management, especially in patients with PAH crisis and severe right heart failure. This review will focus on the advantages and disadvantages of orally administered PAH-specific drugs versus intravenous, subcutaneous, and inhaled drugs. Furthermore, we will discuss the combination therapy strategy and treatment choices.

PAH-specific drugs and administration routes

Therapy with PAH-specific drugs needs to be initiated in PAH patients who are not long-term vasoreactive or are vasoreactive but not responding appropriately to calcium channel blockers. A brief description of PAH-approved drugs, according to the related pharmacological pathway is provided subsequently. Classical compounds include ERAs, PDE-5 inhibitors, sGC stimulators, and prostacyclin analogs. There are

new agents targeting established vasodilatory pathways. Compounds for this new approach include TKIs and selective prostacyclin receptor (IP receptor) agonists. The treatment algorithm includes four different routes of administration (oral, inhaled, subcutaneous, and intravenous).[12] In addition to intravenous, inhaled and subcutaneous prostacyclin analogs and intravenous sildenafil, other compounds which have been approved for PAH therapy are always delivered in pill form.

In the modern treatment era, PAH-specific drugs have brought about more available choices.

The orally administered dual ETA and ETB receptors antagonist bosentan improved exercise capacity and cardiopulmonary hemodynamics in patients with PAH.[13] The selective ETA receptor antagonist ambrisentan, leading to release of vasodilators and antiproliferative substances,[14] has been approved for the treatment of WHO-FC II and III patients, and has been demonstrated to be effective on symptoms, exercise capacity, hemodynamics, and time to clinical worsening (TTCW) of patients with idiopathic PAH and PAH associated with connective tissue disease and HIV infection.[15,16] Macitentan is characterized by sustained receptor binding and enhanced tissue penetration.[17,18] In the SERAPHIN study, macitentan significantly reduced the composite endpoint of morbidity and mortality among patients with PAH and also increased exercise capacity.[19] Sitaxentan, a highly selective ETA receptor antagonist, was withdrawn from the market in 2010 because of an increasing number of deaths attributed to acute liver toxicity.[20]

The oral PDE-5 inhibitors approved for PAH include sildenafil and tadalafil.[7] Vardenafil is a PDE-5 inhibitor that was approved for the treatment of erectile dysfunction in 2005 and was not approved in either the United States or Europe for PAH. Favorable effects with vardenafil treatment in patients with PAH have been reported.[21–23] The three PDE-5 inhibitors inhibit PDE-5, an enzyme that metabolizes cGMP, thereby enhancing the cGMP-mediated relaxation and growth inhibition of vascular smooth-muscle cells, including those in the lung. Sildenafil was the first PDE-5 inhibitor approved for the treatment of PAH and its efficacy was demonstrated in the SUPER-1 randomized controlled trial (RCT) which showed that three doses (20 mg, 40 mg, and 80 mg) were associated with similar treatment effects in 6-minute walk distance (6MWD).[24] Tadalafil, an orally administered, once-daily dosing, selective inhibitor of PDE-5, was assessed in the PHIRST-1 RCT for 16 weeks and tadalafil 40 mg was well tolerated and improved exercise capacity and quality of life measures and reduced clinical worsening.[25]

Riociguat stimulates sGC directly, independent of nitric oxide (NO) availability. In an RCT – PATENT-1, 443 PAH patients were treated with riociguat up to 2.5 mg three times daily and has shown favorable results on exercise capacity, hemodynamics, WHO-FC, and TTCW.[26] Based on the benefits from clinical trials for both PAH and chronic thromboembolic pulmonary hypertension, riociguat was approved by Health Canada and the United States Food and Drug Administration as the first medical therapy for patients with chronic thromboembolic pulmonary hypertension who are deemed inoperable or have residual/recurrent pulmonary hypertension after pulmonary endarterectomy, and as a novel treatment option for patients with PAH.[27,28]

Epoprostenol (intravenous), iloprost (inhaled), and treprostinil (subcutaneous or intravenous) are approved prostacyclin analogs for PAH patients with WHO-FC II–IV. Epoprostenol, a synthetic prostacyclin analog administered as a continuous intravenous infusion, was the first targeted PAH therapy to be approved.[10,29–31] Alternatives to epoprostenol include subcutaneously administered treprostinil, which is also available for intravenous and inhaled use in the USA, and inhaled iloprost.[32] Oral treprostinil, a tricyclic benzidine analog of epoprostenol, has been evaluated in two RCTs in PAH patients on background therapy with bosentan and/or sildenafil (FREEDOM C1 and C2) and in both the primary endpoint 6MWD did not reach statistical significance.[33,34] An additional RCT of oral treprostinil in PAH naïve patients showed improvement in 6MWD by 26 m at peak dose.[35] However, all studies thus far with oral prostacyclin analogs, such as beraprost, have failed to show a persistent treatment effect as determined by the primary efficacy end-point.[36,37] Beraprost, an orally active prostanoid, has not been approved in the United States or Europe for PAH due to lack of long-term efficacy but was approved in Japan and South Korea.

Imatinib is an antiproliferative agent developed to target the BCR-ABL tyrosine kinase in patients with chronic myeloid leukemia. The inhibitory effects of imatinib on PDGF receptors α and β and c-KIT make it efficacious in PAH.[38–40] Imatinib improved pulmonary hemodynamics in a subgroup of patients with severe disease (defined as PVR $>1,000$ dyn·s·cm^{-5}),[41] the Phase III IMPRES RCT was subsequently conducted.[42] Imatinib improved exercise capacity and hemodynamics in patients with advanced PAH, but importantly, treatment with imatinib was poorly tolerated and serious adverse events and study drug discontinuations were common, including the occurrence of subdural hematomas. The unfavorable risk-benefit ratio of imatinib has resulted in

its cessation from further therapeutic development in PAH. Imatinib has been withdrawn due to unfavorable safety/efficacy profile for PAH.

Selexipag is a first-in-class orally available selective non-prostanoid IP receptor agonist. Selexipag is rapidly hydrolyzed to an active metabolite, ACT-333679. Both selexipag and its metabolite are highly selective for the IP receptor compared with other prostanoid receptors. This selectivity for the IP receptor offers the potential for improved tolerability with selexipag, as side effects (eg, nausea and vomiting) that might result from activation of the other prostanoid receptors may be minimized. Selexipag showed effects on pharmacodynamic endpoints obtained with right heart catheterization in a Phase II trial in patients with PAH,[43] and is being evaluated in the ongoing Phase III trial (GRIPHON trial, Clinicaltrials.gov NCT01106014).

Advantages and disadvantages of orally administered drugs versus intravenous, subcutaneous, and inhaled drugs
The side effects and damages of major PAH-specific drugs

Prostacyclin analogs (intravenous, subcutaneous or inhaled) improved symptoms, exercise capacity, and clinical outcome in patients with PAH, but are limited by either parenteral or inhaled delivery systems, the need for laboratory monitoring, or frequent dosing schedules. Orally administered ERAs, PDE-5 inhibitors, and prostacyclin analogs have also demonstrated clinical and hemodynamic improvement.[24,35,44,45] However, orally administered drugs, despite their chemical stability, steady-state plasma concentration, and convenient administration route, are inevitably associated with significant side effects. For PAH-specific oral administration, the most common adverse effects include headaches, flushing, liver enzyme abnormalities, dyspepsia, and diarrhea. The side effects and damages of major PAH-specific therapies were shown in Table 1.

Liver enzyme abnormalities are the most outstanding side effects of oral ERA. Increases in hepatic aminotransferases occurred in approximately 10% of the subjects who take bosentan but were found to be dose-dependent and reversible after dose reduction or discontinuation.[46,47] Sitaxentan was withdrawn from the market because of association with acute liver toxicity.[20] The irreversible liver failure caused by sitaxentan and its withdrawal from global markets emphasized the importance of hepatic monitoring in patients treated with ERAs.[48] In the event-driven macitentan SERAPHIN study,[19]

no liver toxicity was shown. Ambrisentan has been approved for the treatment of WHO-FC II and III patients and the incidence of abnormal liver function tests range from 0.8% to 3%. An increased incidence of peripheral edema has been reported with ambrisentan use.[49]

Most side effects of PDE-5 inhibitor (sildenafil, tadalafil, and vardenafil) are mild to moderate and mainly related to vasodilation (headaches, flushing or epistaxis).[21,24,25,35,50] Considering the potential hypotension, the concurrent use of PDE-5 inhibitors with riociguat is not recommended.

Sildenafil is not used in the United States for pediatric PAH, but approved in the European Union. The double-blind, placebo-controlled STARTS-1 study assessed sildenafil in pediatric patients with PAH; improved hemodynamics and exercise capacity occurred in medium- and high-dose groups.[51] STARTS-2 was the extension study.[52] In STARTS-2, sildenafil-treated patients continued STARTS-1 dosing; placebo-treated patients were randomized to one of the three sildenafil dose groups. As of August 2011, all children received ≥3 years of treatment (unless discontinued) from STARTS-1 baseline. Although children randomized to higher comparing with lower sildenafil doses had an unexplained increased mortality, all sildenafil dose groups displayed favorable survival for children with PAH. Survival in all dose groups was favorable compared with other reports in children using PAH-specific drugs that were only approved for adult PAH.[53–59] Most patients reported adverse events during STARTS-1 and -2. The most frequently reported adverse events were upper respiratory tract infection, headaches, and vomiting. The majority of adverse events were of mild or moderate intensity. The most common treatment-related adverse events were headaches (15%) and vomiting (6%). Five patients had serious adverse events that were assessed as treatment related (low-dose group: enterocolitis, n=1; medium-dose group: convulsion, n=1; high-dose group: hypersensitivity and stridor, n=1; hypoxia, n=1; ventricular arrhythmia, n=1).

Prostacyclin analogs also have drawbacks with respect to frequent dosing (iloprost), injection site pain (subcutaneous treprostinil), recurrent infections of the intravenous catheter (intravenous epoprostenol), and typical prostanoid-associated side-effects such as headaches, flushing, diarrhea, and jaw pain.[32,60]

Pharmacokinetic characteristics

Compared with subcutaneous, intravenous, and inhaled prostacyclin analogs, orally administered compounds have a much longer plasma half-life, Table 2. Weakness associated with the longer plasma half-life is that, when adverse

Table 1 The side effects and damage of major PAH-specific therapies

Major targeted pathways	Compounds	PAH-specific drugs	Administration routes	The side effects and damages		
				Related to the administration routes	Related to the pharmacological action	
					More frequent	Others
Endothelin pathway	ERAs	Bosentan	Oral	–	Liver transaminase elevation	Flushing, headaches dizziness, peripheral edema, palpitations, chest pain, nasopharyngitis, anemia
		Ambrisentan	Oral	–	Peripheral edema	Nasal congestion, upper respiratory tract infection, nausea, sinusitis, nasopharyngitis, flushing, headaches, liver transaminase elevation, abdominal pain, constipation, palpitations, dyspnea
		Macitentan	Oral	–	Headaches, nasopharyngitis, anemia	Peripheral edema, anemia, upper respiratory tract infection, dizziness, bronchitis, dyspnea, cough, liver transaminase elevation
		Sitaxentan*	Oral	–	Acute liver toxicity	Nasal congestion, flushing
Nitric oxide-cGMP pathway	PDE-5 inhibitors	Sildenafil	Oral	–	Headaches, flushing, epistaxis	Left ventricular dysfunction, postural hypotension, dyspepsia, back pain, diarrhea, extremity pain, myalgia, cough, pyrexia, insomnia, influenza, visual disturbance, grand mal seizure, drug hypersensitivity, urticaria, angioedema, gastroesophageal reflux disease, posterior subcapsular cataract, neck stiffness, abdominal pain
			Intravenous	–	Flushing	Flatulence, hypotension, syncope
		Tadalafil	Oral	–	Headaches, myalgia, flushing	Diarrhea, nausea, back pain, dyspepsia, dyspnea, extremity pain, muscle spasms, upper respiratory tract infection, epistaxis, palpitations, arthralgia, chest pain, vomiting, fatigue, nasal congestion, edema, bronchitis, insomnia, urinary tract infection, blurred vision
	sGC stimulators	Riociguat	Oral	–	Headaches, flushing, hypotension	Dyspepsia, peripheral edema, nausea, syncope, bleeding (including hemoptysis), dizziness, diarrhea, vomiting, nasopharyngitis, anemia, palpitations, chest pain, dyspnea, gastroesophageal reflux disease, cough, nasal congestion, pyrexia, fatigue, chest discomfort, gastritis
Prostacyclin pathway	Prostacyclin analogs	Epoprostenol	Continuous intravenous infusion	Catheter-related infections, sepsis, thromboembolic event, irritation, bleeding, drug-delivery system malfunction	Jaw pain, diarrhea, flushing	Headaches, nausea, vomiting
		Iloprost	Inhaled	Increased cough	Flushing, jaw pain, headaches	Hypotension, influenza-like syndrome, peripheral edema, nausea, diarrhea, dizziness
		Treprostinil	Oral	–	Headaches, flushing, nausea	Diarrhea, jaw pain, vomiting, extremity pain
			Continuous subcutaneous infusion	Severe infusion site pain, reaction, bleeding and bruising	Diarrhea, jaw pain, flushing	Peripheral edema, nausea, rash, dizziness, vomiting, headaches, vasodilatation

Table 2 Half-life of PAH-specific drugs

Drugs	Half-life
Bosentan[61]	5.4 h
Ambrisentan[62]	9–15 h
Macitentan[17,18]	Macitentan, ACT-064992 (2 h)[17] active metabolite, ACT-132577 (8.4 h)
Epoprostenol[63,64]	2–3 min
Iloprost[64]	30 min
Treprostinil[64,65]	4.5 h
Beraprost*,[64]	35–40 min
Sildenafil (for PAH)[66]	3.7 h
Tadalafil (for PAH)[67]	18 h
Riociguat[68]	5–10 h

Note: *Beraprost has been approved in Japan and South Korea, but not in the US or Europe for PAH.
Abbreviations: PAH, pulmonary arterial hypertension; h, hours; min, minutes.

reactions occur, such as hypotension and pulmonary edema, it is difficult to reverse in a short time.

Absorption refers to the transport of orally administered drugs across membranes of the epithelial cells in the gastrointestinal tract. In severe right heart failure patients, gastrointestinal congestion may affect the drug absorption.

The lack of pulmonary selectivity results in systemic side effects, and drug tolerance leads to progressive increases in dose. Systemic side effects and drug tolerance are the most common problems of oral therapy. Inhaled therapy for pulmonary hypertension may provide selectivity of the hemodynamic effects to the lung vasculature, thus decreasing systemic side effects. As an alternative, inhaled nitric oxide possesses pulmonary selectivity, but it is less potent than prostacyclin in the pulmonary vasculature.[69,70]

Iloprost is a stable analog of prostacyclin with a longer duration of vasodilatation. When administered during a short aerosolization maneuver to patients with pulmonary hypertension, its pulmonary vasodilatory potency was similar to that of prostacyclin, but its effects lasted for 30 to 90 minutes, as compared with 15 minutes.[71–73] Inhaled iloprost therapy has a proven clinical efficacy in PAH, and this therapy necessitates six to nine inhalation sessions per day.[74] In contrast to epoprostenol, treprostinil is chemically stable at room temperature and neutral pH and has a longer half-life (about 4 hours) permitting continuous subcutaneous infusion rather than continuous intravenous infusion, avoiding the risks of severe infection and thrombosis.[75] Inhaled treprostinil exerts sustained pulmonary vasodilation with excellent tolerability at relatively low doses and may be inhaled in a few breaths.[32,74,76]

Voswinckel et al conducted randomized controlled pilot studies comparing the hemodynamic and systemic side effects of inhaled treprostinil with inhaled iloprost.[74] Inhaled treprostinil had maximal effects occurring later than

Route			
Continuous intravenous infusion	Catheter-related blood stream infection, thromboembolic event, irritation, bleeding, drug-delivery system malfunction	Extremity pain, headaches, diarrhea	Jaw pain, nausea, fatigue, loose stools, vomiting, dizziness, dyspnea, flushing, palpitations, peripheral edema
Inhaled	Cough, throat irritation, pharyngolaryngeal pain	Headaches, nausea, dizziness	Flushing, diarrhea, anemia, abdominal pain, diabetes mellitus, gastric ulcer
Oral	–	Headaches, flushing, jaw pain	Diarrhea, extremity pain, nausea, pharyngitis, asthenia, palpitations, vasodilatation
Beraprost		–	

Note: *Sitaxentan was withdrawn from the market in 2010 because of an increasing number of deaths attributed to acute liver toxicity. –, not applicable.
Abbreviation: PAH, pulmonary arterial hypertension.

iloprost (18 ± 2 minutes versus 8 ± 1 minutes, $P<0.001$), and the effects lasted longer ($P<0.0001$): while the hemodynamic effects of iloprost had vanished within 1 hour, they persisted for >2 hours after treprostinil inhalation. A transient drop in systemic arterial pressure occurred after iloprost inhalation but not with treprostinil.[64,74]

Inhaled iloprost and treprostinil, combining the beneficial effects of prostacyclin with those of an inhalational application, is associated with a longer duration of vasodilatation than intravenous epoprostenol and higher pulmonary vascular selectivity. The advantages of intermittent inhaled therapy over intravenous and oral therapy, coupled with the improvement in a number of clinically meaningful variables, suggest that inhaled therapy may be a suitable alternative to continuous intravenous prostacyclin, especially in patients who do not derive a clear survival benefit with oral therapy.[77,78]

The relevant studies with PAH-specific drugs regarding disease severity and treatment choices

According to the guideline (National Institute for Health and Care Excellence, 2013), WHO-FC, as assessed through the symptoms, may be considered as the most important treatment indicator.[79] Similarly, physical exercise capability, biochemical markers, and other hemodynamic parameters are also important indicators.

For patients with WHO-FC II, ambrisentan, bosentan, macitentan, riociguat, sildenafil, and tadalafil was recommended at Grade I and level of Evidence of A or B. For patients with WHO-FC III, intravenous epoprostenol, inhaled iloprost, subcutaneous and inhaled treprostinil were added. For patients with WHO-FC IV, intravenous epoprostenol was the only specific drug which was recommended at Grade I and level of Evidence of A or B.[7]

WHO-FC status of patients and primary endpoints in studies with PAH-specific drugs were shown in Table 3. In studies on macitentan and epoprostenol, morbidity and mortality are the primary endpoints.[19,31] The traditional primary endpoint of the studies about oral therapy performed in PAH has always been the 6MWD to assess the exercise capacity, but unable to assess the long-term survival. The effect on survival of most of the oral PAH-specific compounds has not been appropriately assessed in individual trials because of small sample size and short duration.[80] Oral therapy has almost been shown to improve exercise capacity, hemodynamics, and

Table 3 WHO-FC of patients and primary endpoints in studies with PAH-specific drugs

Drugs (study)	WHO-FC I no (%)	WHO-FC II no (%)	WHO-FC III no (%)	WHO-FC IV no (%)	Primary endpoint no (%)	Year
Bosentan[46] (BREATHE-1)	0	0	195 (92)	18 (8)	6MWD	2002
Ambrisentan[15] (ARIES-1)	5 (2)	65 (32)	117 (58)	14 (7)	6MWD	2008
Ambrisentan[15] (ARIES-2)	3 (1)	86 (45)	99 (52)	4 (2)	6MWD	2008
Macitentan[19] (SERAPHIN)	1 (1)	387 (52)	337 (45)	14 (2)	TTCW	2013
Epoprostenol[31]	0	0	120 (67)	58 (33)	6MWD	2002
Iloprost[81] (inhaled)	0	0	119 (59)	84 (41)	6MWD and WHO-FC	2002
Treprostinil[75] (subcutaneous)	0	53 (12)	382 (81)	34 (7)	6MWD	2002
Beraprost*,[36]	0	61 (53)	55 (47)	0	6MWD	2003
Sildenafil[82] (SUPER-1 study)	1 (1)	107 (38)	160 (58)	9 (3)	6MWD	2005
Sildenafil[83] (SUPER-2 study)	1 (1)	100 (38)	150 (58)	7 (3)	WHO-FC and 6MWD	2011
Tadalafil[25] (PHIRST)	4 (1)	130 (32)	264 (65)	7 (2)	6MWD	2009
Vardenafil**,[21] (EVALUATION)	0	30 (47)	34 (53)	0	6MWD	2011
Riociguat[26] (PATENT-1)	14 (3)	187 (42)	237 (53)	4 (1)	6MWD	2013

Notes: *Beraprost has been approved in Japan and South Korea, but not in the US or Europe for PAH; **vardenafil is currently not approved for PAH patients.
Abbreviations: PAH, pulmonary arterial hypertension; WHO-FC, World Health Organization functional class; 6MWD, 6-minute walk distance; TTCW, time to clinical worsening.

quality of life in most patients with severe PAH. There are few data on the long-term survival of patients with PAH treated with oral medicines, especially in WHO-FC IV.

However, Sitbon et al described significantly improved survival in an analysis of 178 patients with PAH in WHO-FC III or IV treated with intravenous epoprostenol infusion over a 10-year period.[31] For comparison, survival data are also shown for a historical control group of 135 patients with PAH matched for WHO-FC and who never received intravenous epoprostenol therapy. In the group of patients treated with epoprostenol, the overall survival rates at 1, 2, 3, and 5 years were 85%, 70%, 63%, and 55%, respectively, as compared with 58%, 43%, 33%, and 28% in the historical control group ($P<0.0001$ by the Cox–Mantel log-rank test). The efficacy of continuous intravenous administration of epoprostenol on survival has been proven in another two studies in patients with idiopathic PAH.[9,10]

Two retrospective, multicenter, uncontrolled trials have investigated the long-term outcomes of treprostinil. Overall, both trials demonstrated long-term benefits of subcutaneous treprostinil on exercise capacity, functional class, and survival.[83,84] Both trials enrolled subjects with WHO-FC II-IV, with the majority being class III, and allowed open-label treprostinil management titrated at the discretion of the physician based on symptoms.

In randomized, double-blind, placebo-controlled trials for oral therapy in PAH, almost all enrolled patients were in WHO-FC II or III, and few trials included patients in WHO-FC IV. The traditional primary endpoint of the RCTs performed in PAH has been the 6MWD that assesses the exercise capacity, and secondary endpoints have included hemodynamics and TTCW, a composite endpoint including death, hospitalization, and disease progression.[85] The effect on survival of these oral compounds has not been appropriately assessed in PAH individual trials.

The role of oral administration in PAH-specific combination therapy strategy

After initial therapy, the next steps are based on the clinical response.[7] If the clinical response is considered not adequate, combination therapy is considered. Intravenous or subcutaneous therapies are more appropriate than oral therapies for advanced patients, but, in fact, most patients with severe PAH are usually not on monotherapy throughout. Combination therapy strategy that includes multiple classes of PAH-specific drugs is an attractive option for the management of end-stage PAH. The specific combination therapies include

three separate signaling pathways involved in the disease: the endothelin pathway, the NO pathway, and the prostacyclin pathway. The ways of combination include sequential combination therapy and upfront combination therapy.[86]

The use of combination therapy to achieve predefined treatment goals has emerged as a major theme to improve long-term outcomes in PAH. Main aspects and characteristics of studies with patients exposed to combination therapy of approved PAH drugs were shown in Table 4.

Almost all combination therapies included oral administration drugs, and the primary endpoint was 6MWD. Additional oral therapy may reduce the need to up-titrate the intravenous and inhaled prostacyclin analogs or other oral drugs' dose and, therefore, potentially decrease the dose-related side-effects. However, the primary endpoint of combination therapy studies has not consistently been met in the STEP,[87] COMBI,[88] FREEDOM-C,[33] FREEDOM-C2,[34] and BREATHE-2[89] studies.

In TRIUMPH-1 study,[90] the efficacy and safety of inhaled treprostinil or placebo in PAH patients receiving therapy with either bosentan or sildenafil were assessed. The primary endpoint was peak 6MWD at 12 weeks and it has met the defined statistical significance.

The 16-week, double-blind, placebo-controlled, parallel group study, the addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial (PACES Study).[91] Trial demonstrated that the addition of sildenafil to background intravenous epoprostenol therapy improved 6MWD and delayed TTCW, but this treatment sequence does not often correspond to clinical practice because oral therapy is usually initiated first.

The two completed RCTs of macitentan (SERAPHIN trial)[19] and riociguat (PATENT-1 trial)[26] have substantially contributed to the evidence base of combination therapy. About 63% of enrolled subjects in SERAPHIN trial and 50% in PATENT-1 trial, were on background therapy with predominantly oral PAH agents. In both of these RCTs, the primary endpoint of the studies has been met.

The experience of BREATHE-2 study[89] with initial combination therapy failed to demonstrate any significant difference between patients treated initially with the combination epoprostenol and bosentan as compared with epoprostenol alone. In a recent study, 23 treatment naïve PAH patients were treated with the initial combination of epoprostenol and bosentan and compared with a matched historical control group treated with epoprostenol.[92] The study showed a statistically significantly greater decrease in PVR in the

Table 4 Characteristics of studies with patients exposed to combination therapy of approved PAH drugs

Combination drugs	No of subjects	Major WHO-FC status of subjects	Follow-up time	Primary endpoint	Primary endpoint meets the defined significance	Type of combination
Bosentan + inhaled iloprost (STEP)[87]	67	III (94%)	12 weeks	6MWD	No	Sequential combination
Bosentan + inhaled iloprost (COMBI)[88]	40	III (100%)	12 weeks	6MWD	No	Sequential combination
Bosentan or sildenafil + inhaled treprostinil (TRIUMPH-1)[90]	235	III (98%)	12 weeks	6MWD	Yes	Sequential combination
ERA or PDE-5 inhibitors or both + oral treprostinil (FREEDOM-C)[33]	350	II (21%), III (76%)	16 weeks	6MWD	No	Sequential combination
ERA or PDE-5 inhibitors or both + oral treprostinil (FREEDOM-C2)[34]	310	II (26%), III (73%)	16 weeks	6MWD	No	Sequential combination
Epoprostenol + sildenafil (PACES)[91]	267	II (25%), III (66%), IV (6%)	16 weeks	6MWD	Yes	Sequential combination
Epoprostenol + bosentan (BREATHE-2)[89]	33	III (76%), IV (24%)	16 weeks	Hemodynamic evaluation	No	Upfront combination
Epoprostenol + bosentan + sildenafil[93]	19	III (42%), IV (58%)	Median exposure 39.2 months	6MWD and PVR	Yes	Upfront combination

Abbreviations: PVR, pulmonary vascular resistance; PAH, pulmonary arterial hypertension; WHO-FC, World Health Organization functional class; 6MWD, 6-minute walk distance.

initial combination therapy group but this hemodynamic benefit did not translate into a statistically significant difference in survival, or in transplant-free survival. In a pilot study, the efficacy and safety of a triple upfront combination therapy regimen with epoprostenol, bosentan, and sildenafil in patients with severe PAH who present in WHO-FC III/IV together with severe hemodynamic impairment was investigated.[93] At a median follow-up of 39.2 months, 18 of 19 patients had sustained clinical improvement and remained in WHO-FC I/II. 6MWD increased dramatically from 227 to 514 m ($P<0.01$) and PVR declined from 1,718 to 492 dyn·s·cm^{-5} ($P<0.01$). This pilot study provides preliminary evidence of the long-term benefits of upfront triple combination therapy in patients with severe PAH.

From Table 4, we can see that the majority of patients in combination studies, except for the triple combination study, were WHO-FC III. For WHO-FC IV PAH patients in case of non-availability of intravenous prostanoids, initial combination therapy has been allocated a grade of recommendation IIb and level of Evidence C.[7]

Insufficient initial therapy and transposition to interventional or surgical procedures

In the modern treatment era, exercise capacity, hemodynamics, quality of life, and survival of patients with PAH have improved. However, some patients do not benefit from the medication treatment, especially oral therapy, and must be considered for balloon atrial septostomy or lung transplantation.[94]

Novel strategies, including atrial septostomy or the pumpless Novalung® lung assist device with conduits, from the pulmonary artery to the left atrium, can be considered as a bridge to transplant for patients with rapid clinical decline, despite maximal medical therapy.[95]

Lung transplantation should continue to be an important option for those who fail on medication treatment programs and remain in WHO-FC III or IV.[30,31,96] It is reasonable to consider eligibility for lung transplantation after an inadequate clinical response to the initial monotherapy and to refer the patient soon after the inadequate clinical response is confirmed on maximal combination therapy.[97] Most of the end-stage PAH patients, who underwent lung transplantation, had been ever treated with epoprostenol.[30,31] In this regard, oral therapy is not as crucial as epoprostenol in the perioperative management of severe PAH and right heart failure before lung transplantation. In the pharmacological management of perioperative PAH patients, intravenous

epoprostenol or inhaled iloprost play an important role in pulmonary vessel diastole.

Conclusion

Orally administered ERAs, PDE-5 inhibitors, sGC stimulator, and prostacyclin analogs have demonstrated clinical and hemodynamic improvement in patients with PAH. However, there are limits in the efficacy and safety profile of oral therapy. Especially for PAH patients with WHO-FC IV and with severe right heart failure, there are few data on the long-term survival of patients treated with oral medications. Intravenous epoprostenol is still considered the gold standard therapy in severe PAH and has reduced the need for lung transplantation in patients with advanced disease. Medicinal chemistry programs must be embarked upon aiming at the identification of novel compounds for PAH with high oral efficacy. Further research, exploration, and clinical experience with oral therapy in severe PAH and combination therapy will redefine its position in PAH management.

Disclosure

Z-C Jing serves as a consultant and scientific advisor to Actelion, Bayer Schering, AstraZeneca, Pfizer and United Therapeutics, in addition to being an investigator in trials sponsored by these companies. Q-Q Liu declares no conflict of interest.

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