Pulmonary Arterial Hypertension – Future Directions

a report by

Robert P Frantz

Associate Professor of Medicine, and Director, Pulmonary Hypertension Clinic, Mayo Clinic College of Medicine, Rochester

Pulmonary arterial hypertension (PAH) is a rare but life-threatening condition that has traditionally required treatment with continuous intravenous epoprostenol via an indwelling central catheter.[1–3] Such therapy improves outcome but is fraught with side effects, expense and risk of catheter-related complications. Therapy of PAH has evolved tremendously in recent years, reflecting the development of novel therapeutic agents and modes of delivery that target either vasodilator pathways that are deficient or vasoconstrictor pathways that are activated in PAH patients. These agents include oral endothelin antagonists (bosentan,[4–6] sitaxsentan,[7,8] ambrisentan[9]), phosphodiesterase (PDE)-5 inhibitors (sildenafil,[10] tadalafil) and prostanoids that do not necessarily require intravenous delivery (inhaled iloprost,[11,12] subcutaneous treprostinil[13]).

Treprostinil

Treprostinil is a prostacyclin analogue with a half-life of three hours that, unlike epoprostenol, is stable at room temperature. It is US Food and Drug Administration (FDA)-approved for both intravenous and subcutaneous use. Owing to its stability, longer half-life and equivalent haemodynamic effect when given subcutaneously, it has been clinically applied in this manner. Compared with placebo, subcutaneous treprostinil tends to improve exercise capacity on six-minute walk testing, quality of life and haemodynamics, but the benefits in the randomised trial were quite small, probably reflecting low dosing in the short-term trial. At higher doses and among more symptomatic patients, the beneficial effects are much more pronounced.

Treprostinil exhibits a similar side-effect profile to epoprostenol, but also often produces pain at the infusion site. This may limit the ability to raise subcutaneous doses to a level likely to produce optimal benefit in some patients. However, it can be effective in patients who can tolerate appropriate subcutaneous doses. The expense of treprostinil is greater than that of epoprostenol, since it is less potent on a per milligram basis. The advantages of treprostinil are the potential absence of a central venous catheter if given subcutaneously and smaller infusion pump apparatus. It is also effective for intravenous use, and its longer half-life compared with epoprostenol may be an advantage in the situation of an inadvertent disconnect during therapy of a highly dependent patient. Randomised placebo-controlled trials of inhaled and oral preparations of treprostinil are in progress.

Robert P Frantz has been a Consultant in the Division of Cardiovascular Diseases at the Mayo Clinic since 1990. He is Assistant Professor of Medicine and Director of the Pulmonary Hypertension Clinic and Cardiovascular Studies Unit at the Mayo Clinic College of Medicine, and a member of the Education Committee of the Pulmonary Hypertension Association. Dr Frantz obtained his undergraduate degree in biochemistry at Harvard University and completed his medical degree and internal medicine residency at Mayo Clinic College of Medicine. He trained in cardiology at the University of Rochester Medical Center in Rochester, New York.

E: frantz.robert@mayo.edu

Iloprost

Iloprost is a stable prostacyclin analogue available in Europe for intravenous and aerosolised administration and in the US for aerosolised administration. Inhaled iloprost improves functional class, exercise capacity and pulmonary haemodynamics in open and randomised studies, with side effects of flushing, headache and cough in some patients. The relatively short duration of action of inhaled iloprost means five- to 15-minute inhalations are required six to nine times daily in order to obtain a sustained clinical benefit. It is often used in combination with an oral agent such as bosentan or sildenafil. It does not appear to be as effective as continuous epoprostenol or treprostinil because its half-life is so short that pressures bounce back up between treatments. Patients with progressive symptoms despite inhaled iloprost combined with an oral agent should be converted from iloprost to a continuous prostanoid infusion.[14]

Endothelin Antagonists

Bosentan is a non-selective endothelin receptor antagonist, blocking the action of endothelin-1 (ET-1), a potent vasoconstrictor and smooth-muscle mitogen, at endothelin A and B (ETA and ETB, respectively) receptors. Its therapeutic effect derives from the reduction of vasoconstriction caused by increased plasma levels of ET-1 in patients with PAH. Clinical studies of bosentan have demonstrated improved functional classification, improved pulmonary haemodynamics and an augmented six-minute walk distance compared with placebo, leading to FDA approval of the medication. Side effects associated with bosentan include dose-dependent elevation of transaminases that are reversible with dose reduction or cessation, flushing, fluid retention, and, rarely, hypotension or syncope.

Other Endothelin Receptor Antagonists

Sitaxsentan and ambrisentan are ETA receptor-selective agents that have completed randomised studies. Initial phase III study results suggest that both agents improve exercise capacity, functional class and pulmonary haemodynamics at 12-week follow-up. Ambrisentan received FDA approval in 2007; sitaxsentan did not, but it is approved for use in some other countries. Sitaxsentan has a serious interaction with warfarin that necessitates careful downward adjustment of warfarin dosing. Liver function test abnormalities may be less common with sitaxsentan and ambrisentan, but can still occur.

Phosphodiesterase-5 Inhibitors

Nitric oxide (NO) is an endogenous vasodilator produced from L-arginine by endothelial cells. It vasodilates by producing cyclic guanosine monophosphate (cGMP), which in turn is degraded by PDE. Agents that inhibit the predominant PDE in the pulmonary vasculature (PDE5) augment the pulmonary vascular response to endogenous NO. Sildenafil is a potent and highly specific PDE5 inhibitor that is effective at improving six-minute walk distance, functional class and haemodynamics in PAH. It is approved for treatment of PAH at a dose of 20mg three times a day. Randomised trials of the once-daily PDE5 inhibitor tadalafil are in progress.

This plethora of therapeutic alternatives is a welcome advance, but brings with it a host of critical issues that must be addressed in the next decade. These issues fall into three broad categories: defining the role of combination therapy; establishing the appropriate strategy and goals of therapy in order to optimise long-term outcome; and defining the role of antiproliferative therapy and understanding which agents are most effective in this regard.

Role of Combination Therapy

In order to understand this issue it is helpful to draw an analogy with the development of effective therapy for congestive heart failure (CHF). New therapeutic agents have usually been studied in addition to, not instead of, previously proven therapy. The randomised trials that demonstrated the efficacy of beta-blockers in CHF, for example, studied patients who were already being treated with angiotensin-converting enzyme (ACE) inhibitors. With the results of these trials the therapeutic strategy became clear: add a beta-blocker to a regimen that includes an ACE inhibitor. Therapy for PAH has largely developed in silos (e.g. the randomised trials of sildenafil excluded patients on bosentan), thereby leaving the question of additive therapy unaddressed. This deficiency is now being addressed by randomised trials of combination therapy. However, conducting the necessary trials of combination therapy in PAH is more difficult than it was for CHF because of the much smaller cohort of PAH patients, complicating trial recruitment efforts.

Given the large number of possible therapeutic combinations and the need for larger trials to prove the efficacy of combination therapy, successful completion of these trials requires the careful attention of the PAH community. Fortunately, patients with PAH have traditionally been extremely supportive of research involvement and have been cared for at academic centres cognisant of the critical nature of PAH research. However, the deceptive simplicity of oral therapy poses some risk to this critical endeavour, if referral of PAH patients to centres engaged in research were to trail off as practitioners consider initiation of therapy in the non-academic practice setting. For this reason, and because monitoring therapy and prognosis in PAH remains highly complex, referral of patients to a tertiary PAH centre is strongly encouraged. It is reasonable to hypothesise that 'triple therapy' with an endothelin antagonist, a PDE5 inhibitor and a sustained-acting prostanoid will provide superior outcomes to less intensive therapy, but it will require the concerted efforts of the PAH community to test this important hypothesis.

Establishing the Appropriate Strategy and Goals of Therapy in Order to Optimise Long-term Outcome

Randomised placebo-controlled trials of PAH therapy have usually been short (12–16 weeks), and have had primary end-points of improvement in exercise tolerance (six-minute walk distance). Such an approach has been effective in bringing new therapeutic alternatives to market, but leaves important questions unanswered. Is tiered therapy (starting with an oral agent and adding a second agent, or switching to a different agent only when deterioration has occurred) an effective strategy, or is early aggressive therapy with a continuous prostanoid or combination therapy superior? What are the appropriate end-points in deciding when to alter therapy? For a patient who is currently being treated with oral monotherapy, which of the following end-points should be reached prior to a recommendation for additional therapy?

- failure to achieve or maintain a six-minute walk distance >380m;[15]
- failure to achieve or maintain World Health Organization (WHO) functional class II status;[15]
- failure to achieve or maintain a right atrial pressure of 12mmHg or less;[15]
- failure to achieve or maintain brain natriuretic peptide level <180pg/ml;[16]
- failure to achieve or maintain right-ventricular end-diastolic volume <84ml/meter^2;[17] or
- none of the above – optimal outcome will be achieved by aggressive therapy earlier in the course of the disease, not by waiting until deterioration occurs.

Intermediate-term (two-year) observational studies of oral monotherapy with bosentan, reserving addition of other therapy for patients who deteriorate, suggest reasonable outcome, but the length of follow-up is too short for long-term outcomes of such a strategy to be certain, and addition of other therapies is often needed.[18–20] An observational study of subcutaneous treprostinil found 70% four-year survival with monotherapy.[21] Generating the necessary data to answer questions such as these should be a top priority of the PAH community in the coming decade. The six-minute walk distance is widely utilised in clinical practice and as an end-point in PAH trials, so there are ample data relating outcome to walk distance, demonstrating that PAH patients with a walk distance <380m despite at least three months of epoprostenol therapy had worse outcomes than patients with greater walk distances.[11]

Limitations of walk distance as a prognostic marker include failure to account for age, level of fitness, weight and orthopaedic conditions. Young patients who are otherwise fit can sometimes maintain six-minute walk distances of 400–550m even in the presence of severe progressive PAH as exhibited by progressive right-ventricular dilation, worsening tricuspid regurgitation and need for escalating diuretic dosing and elevated and/or rising B-type natriuretic peptide (BNP) levels. They appear to be at risk of rather abrupt clinical deterioration. For such patients, it is intuitively appealing to believe that increasingly aggressive therapy implemented prior to deterioration of six-minute walk distance should improve long-term outcomes, but such a strategy has never been extensively tested.

Goal-orientated therapy based on six-minute walk distance >380m, peak oxygen consumption >10.4ml/kg/min and systolic blood pressure

Table 1: Therapeutic Agents for Pulmonary Arterial Hypertension

Medications Used in the US for Treatment of PAH Based on FDA Approval or Reported Experience	Agents Under Investigation or Consideration, or Available Outside the US	Possible Future Treatment Concepts that May Warrant Clinical Investigation	Adjunctive Treatment Modalities[m]
Epoprostenol[a]	Sitaxsentan[h]	Aspirin, clopidogrel	Oxygen
Treprostinil[b]	Tadalafil[i]	Oral antithrombin agents	Warfarin
Ambrisentan[h]	Beraprost[j]	Statins	Digoxin
Bosentan[c]	Fasudil[k]	Serotonin transport inhibitors	Diuretics
Sildenafil[d]	Imatinib[l]	ACE inhibitors	
Iloprost[e]	Vasoactive intestinal peptide	Sirolimus	
Calcium channel blockers[f]	L-arginine	Potassium channel openers	
Nitric oxide[g]		Elastase inhibitors	

a. Intravenous (IV) prostacyclin analogue; b. Subcutaneous or IV prostacyclin analogue, oral and inhaled formulations are undergoing randomised trials; c. Non-selective endothelin receptor antagonist; d. Phosphodiesterase (PDE)-5 inhibitor; e. Inhaled prostacyclin analogue; f. Not US Food and Drug Administration (FDA)-approved for this purpose; g. Primarily used in a hospital setting and as a vasoreactivity testing agent; h. Endothelin A (ETA) receptor selective antagonist, randomised studies completed; i. PDE5 inhibitor; randomised studies in progress; j. Oral prostacyclin analogue, available outside the US, FDA approval not sought after randomised study results; k. Rho-kinase inhibitor; l. Tyrosine kinase inhibitor, feasibility studies under way in Europe; m. Commonly used and felt to be efficacious in reducing symptoms or consequences, but no rigorous study data.
Adapted from McGoon.
PAH = pulmonary arterial hypertension; FDA = US Food and Drug Administration; ACE = angiotensin-converting enzyme.

>120mmHg during exercise has been proposed as a strategy for guiding therapy.[22] Future studies will increasingly examine the role of prognostic markers such as six-minute walk distance, neurohormones (BNP, N-terminal BNP), right ventricular volume/function by magnetic resonance imaging (MRI) or computed tomography (CT) and haemodynamics (obtained via implantable haemodynamic monitors[23] or serial catheterisation) in guiding therapy and optimising outcome.

Distinguishing Disease-modifying Therapy from Symptomatic Relief

Treatment of inflammatory arthritides such as rheumatoid arthritis took a quantum step forward with the recognition of the role of therapies that not only relieve symptoms but also modify the course of the disease. This includes agents such as methotrexate and the tumour necrosis factor alpha antagonists (e.g. infliximab). The understanding of which, if any, of the currently available vasodilator therapies for PAH are disease-modifying is in its infancy, due in large part to the short duration of randomised trials and the lack of readily available biomarkers of pulmonary vascular pathological progression. It is understood that the currently available agents appear to improve outcome compared with historical controls. This may reflect the antiproliferative effects of these agents, as demonstrated in animal models of PAH, but this remains to be proved in humans. Future studies will focus on the role of both novel vasodilator agents that may also possess antiproliferative effects such as Rho-kinase inhibitors (e.g. fasudil[24–26]), vasoactive intestinal peptide[27] and specific antiproliferative agents such as platelet-derived growth factor receptor inhibitors (e.g. imatinib[28,29]) and serine elastase inhibitors.[30,31] ■

1. Badesch DB, Tapson VF, McGoon MD, et al., Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease, *Ann Intern Med*, 2000;132:425–34.
2. 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;334:296–301.
3. McLaughlin VV, Shillington A, Rich S, Survival in primary pulmonary hypertension: the impact of epoprostenol therapy, *Circulation*, 2002;106:1477–82.
4. Rubin LJ, Badesch DB, Barst RJ, et al., Bosentan therapy for pulmonary arterial hypertension, *N Engl J Med*, 2002;346: 896–903.
5. Rosenzweig EB, Ivy DD, Widlitz A, et al., Effects of long-term bosentan in children with pulmonary arterial hypertension, *J Am Coll Cardiol*, 2005;46:697–704.
6. Galie N, Beghetti M, Gatzoulis MA, et al., Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study, *Circulation*, 2006;114:48–54.
7. Barst RJ, Langleben D, Frost A, et al., Sitaxsentan therapy for pulmonary arterial hypertension, *Am J Respir Crit Care Med*, 2004;169:441–7.
8. Barst RJ, Langleben D, Badesch D, et al., Treatment of pulmonary arterial hypertension with the selective endothelin-A receptor antagonist sitaxsentan, *J Am Coll Cardiol*, 2006;47:2049–56.
9. Galie N, Badesch D, Oudiz R, et al., Ambrisentan therapy for pulmonary arterial hypertension, *J Am Coll Cardiol*, 2005;46: 529–35.
10. Galie N, Ghofrani HA, Torbicki A, et al., Sildenafil citrate therapy for pulmonary arterial hypertension, *N Engl J Med*, 2005;353:2148–57.
11. Ghofrani HA, Weidemann R, Rose F, et al., Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension, *Ann Intern Med*, 2002;136:515–22.
12. Olschewski H, Simonneau G, Galie N, et al., Inhaled iloprost for severe pulmonary hypertension, *N Engl J Med*, 2002;347:322–9.
13. McLaughlin VV, Gaine SP, Barst RJ, et al., Efficacy and safety of treprostinil: an epoprostenol analog for primary pulmonary hypertension, *J Cardiovasc Pharmacol*, 2003;41:293–9.
14. Opitz CF, Wensel R, Winkler J, et al., Clinical efficacy and survival with first-line inhaled iloprost therapy in patients with idiopathic pulmonary arterial hypertension, *Eur Heart J*, 2005;26(18):1895–1902.
15. Sitbon O, Humbert M, Nunes H, et al., Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival, *J Am Coll Cardiol*, 2002;40: 780–88.
16. Nagaya N, Nishikimi T, Uematsu M, et al., Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension, *Circulation*, 2000;102:865–70.
17. Van Wolferen SA, Marcus JT, Boonstra A, et al., Prognostic value of right ventricular mass, volume, and function in idiopathic pulmonary arterial hypertension, *Eur Heart J*, 2007; Epub ahead of print.
18. Provencher S, Sitbon O, Humbert M, et al., Long-term outcome with first-line bosentan therapy in idiopathic pulmonary arterial hypertension, *Eur Heart J*, 2006;27(5):589–95.
19. McLaughlin VV, Sitbon O, Badesch DB, et al., Survival with first-line bosentan in patients with primary pulmonary hypertension, *Eur Respir J*, 2005;25:244–9.
20. Sitbon O, McLaughlin VV, Badesch DB, et al., Survival in patients with class III idiopathic pulmonary arterial hypertension treated with first line oral bosentan compared with an historical cohort of patients started on intravenous epoprostenol, *Thorax*, 2005;60:1025–30.
21. Barst RJ, Galie N, Naeije R, et al., Long-term outcome in pulmonary arterial hypertension patients treated with subcutaneous treprostinil, *Eur Respir J*, 2006;28:1195–203.
22. Hoeper MM, Markevych I, Spiekerkoetter E, et al., Goal-oriented treatment and combination therapy for pulmonary arterial hypertension, *Eur Respir J*, 2005;26(5):858–63.
23. Frantz RP, Benza RL, Kjellstrom B, et al., Continuous hemodynamic monitoring in pulmonary arterial hypertension patients using an implantable ambulatory hemodynamic monitor, manuscript submitted, *Circulation*, 2007.
24. Fukumoto Y, Matoba T, Ito A, et al., Acute vasodilator effects of a Rho-kinase inhibitor, fasudil, in patients with severe pulmonary hypertension. [Letter, Research Support, Non-US Government], *Heart*, 2005;91(3):391–2.
25. Petkov V, Mosgoeller W, Ziesche R, et al., Vasoactive intestinal peptide as a new drug for treatment of primary pulmonary hypertension. [Journal Article. Research Support, Non-US Government], *J Clin Invest*, 2003;111(9):1339–46.
26. Barst RJ, PDGF signaling in pulmonary arterial hypertension, *J Clin Invest*, 2005;115(10):2691–4.
27. Xing XQ, Gan Y, Wu SJ, et al., Rho-kinase as a potential therapeutic target for the treatment of pulmonary hypertension, *Drug News Perspect*, 2006;19(9):517–22.
28. Ghofrani HA, Seeger W, Grimminger F, Imatinib for the treatment of pulmonary arterial hypertension, *N Engl J Med*, 2005;353:1412–13.
29. Souza R, Sitbon O, Parent F, et al., Long term imatinib treatment in pulmonary arterial hypertension, Letter, *Thorax*, 2006;61(8):736.
30. Cowan KN, Jones PL, Rabinovitch M, Elastase and matrix metalloproteinase inhibitors induce regression, and tenascin-C antisense prevents progression of vascular disease, *J Clin Invest*, 2000;105:21–34.
31. Cowan KN, et al., Complete reversal of fatal pulmonary hypertension in rats by a serine elastase inhibitor, *Nat Med*, 2000;6:698–702.