CLINICAL INVESTIGATION

Emerging therapies for pulmonary arterial hypertension: a review of recently completed and ongoing clinical trials

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Pulmonary arterial hypertension (PAH) is a rare, progressive disorder that leads to an inexorable rise in pulmonary vascular resistance, ultimately resulting in right ventricular failure and death if left untreated. Currently available pulmonary vasoremodeling therapy has significantly improved morbidity and mortality in PAH. However, 3-year mortality in PAH is still higher than in many other cardiovascular diseases. Recent and ongoing clinical trials in PAH have evaluated five major avenues of clinical investigation: trials of combination therapy using current US FDA-approved agents; trials of new forms or new delivery systems of existing agents; trials of newly developed agents that target novel steps in existing pathways implicated in the pathogenesis of PAH; trials of agents targeting new pathways that may play a role in PAH; and stem-cell and molecular therapy for PAH. This article reviews evidence for emerging therapies for PAH based on recently completed and ongoing clinical trials.

keywords: clinical trials • pulmonary arterial hypertension • pulmonary vasodilators • therapy

Pulmonary arterial hypertension (PAH) encompasses a variety of disorders [1,2] that are thought to share a common pathophysiology characterized by pulmonary vascular smooth muscle-cell proliferation, intimal fibrosis, pulmonary vasoconstriction and *in situ* thrombosis [3,4]. These pathologic changes in the pulmonary vasculature lead to a progressive rise in right ventricular afterload, and ultimately, to right ventricular failure and death.

Prior to the availability of current pulmonary vasodilator therapy, the morbidity and mortality of PAH was high. In the NIH Registry of patients with primary pulmonary hypertension, now termed idiopathic PAH, 1- and 5-year mortality was 68 and 34%, respectively, with a median survival of 2.8 years [5].

As a result of considerable basic and clinical research, our knowledge of the pathophysiology of PAH has increased tremendously. Three molecular pathways have now been identified that contribute to the pathophysiology of PAH: the NO pathway, the endothelin pathway and the prostaglandin pathway [6]. These pathways form the physiologic basis for the 12 current US FDA-approved drugs for the treatment of PAH. As a result of these advances in PAH-specific therapy, contemporary estimates of mortality in two large PAH registries have decreased relative to the original NIH Registry [7,8].

Alhough it is heartening to note the significant improvement in survival afforded by existing PAH-specific therapies, morbidity and mortality from PAH remains higher than in many other cardiovascular disorders. In recent years, ongoing research has continued to advance our knowledge of PAH physiology and the optimal treatment strategies for this disease. Recent clinical trials in PAH have focused on five major avenues of investigation: evaluating combinations

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of existing PAH-specific therapy; evaluating new delivery methods for existing PAH therapy; exploring new drugs that target known PAH-related pathways; exploring new pathways that may contribute to the pathophysiology of PAH; and evaluating stem cell and molecular therapy in PAH. This article will review recently completed and ongoing clinical trials of therapeutic agents in PAH.

Clinical trials of combination therapy in PAH

With the availability of a variety of therapeutic agents that target different pathways implicated in the pathogenesis of PAH, there is now an array of options for the initial treatment of PAH patients. From a physiologic perspective, the concept of combining therapeutic agents that act on different PAH pathways to, in turn, provide synergistic effects is intellectually appealing. In addition, the most appropriate initial therapy for the PAH patient is not well defined.

A variety of clinical trials have recently been completed and a number remain ongoing to try to address the relative benefit of combination therapy and of whether one or other agent should be used in a preferential fashion. Nine clinical trials of add-on combination therapy have been completed (Table 1), with several more studies ongoing (Table 2). Most commonly, these studies have examined the impact of the addition of prostanoids to a PDE-5 inhibitor or ERA. All of the studies completed to date have evaluated surrogate clinical end points such as 6-min walk distance (6MWD), WHO functional class and/or time to clinical worsening (TTCW). Of the completed studies, results have been somewhat inconsistent with regard to the relative benefits of add-on combination therapy in PAH.

The BREATHE-2 study was a randomized, controlled trial that evaluated the effect of adding bosentan versus placebo to intravenous (iv.) epoprostenol therapy in 33 patients with PAH and WHO functional class III or IV symptoms. After 16 weeks of therapy, there was a trend towards improvement in clinical and hemodynamic parameters, specifically total pulmonary resistance, and there was no statistically significant difference between treatment groups [9]. The FREEDOM-C trial evaluated the addition of oral form of treprostinil versus placebo to background therapy of sildenafil and/or bosentan in 354 PAH patients. After 16 weeks of therapy, there was no significant change in placebo-corrected function capacity (6MWD increase of 11 vs 5 m in placebo; $p = 0.07$) [10]. The COMBI trial was a German, multicenter, open-label study that evaluated the addition of inhaled iloprost to bosentan in WHO functional class III patients with PAH. The study did not show a benefit from combination therapy on 6MWD at 12 weeks, although the results were impacted by small sample size (19 patients on combination therapy) and the overall results were potentially skewed by three combination-therapy patients presenting with severe clinical worsening [11].

In contrast to these negative findings, the other completed add-on combination-therapy studies have all shown a significant benefit to the added therapy. The STEP-1 trial also evaluated the addition of inhaled iloprost to stable WHO functional class III PAH patients treated with bosentan, but with differing results to the smaller COMBI trial. The 67 enrolled patients had WHO functional class III or IV symptoms at baseline and after 12 weeks of therapy, the combination did show a significant

Table 1. Completed add-on combination therapy trials.

Trial	Baseline therapy	Added therapy	Patients	Follow-up	End point	Result	Ref.
BREATHE-2	iv. epoprostenol	Bosentan	33	16 weeks	Hemodynamics 6MWD	Negative	[9]
COMBI	Bosentan	Inhaled iloprost	40	12 weeks	6MWD	Negative	[11]
STEP-1	Bosentan	Inhaled iloprost	67	12 weeks	6MWD	Positive	[12]
PACES-1	iv. epoprostenol	Sildenafil	267	16 weeks	6MWD	Positive	[15]
TRIUMPH-1	Sildenafil and bosentan	Inhaled treprostinil	235	12 weeks	6MWD	Positive	[13]
FREEDOM-C	Sildenafil and/or bosentan	Oral treprostinil	354	16 weeks	6MWD	Negative	[10]
PHIRST-1	Bosentan	Tadalafil	405	16 weeks	6MWD	Positive	[16,17]
ARIES-3	Sildenafil	Ambrisentan	224	24 months	6MWD	Positive	[18]
COMPASS-3	Bosentan	Sildenafil	100	28 weeks	6MWD	Positive	[19]

6MWD: 6-min walk distance; iv.: Intravenous.

Table 2. Ongoing add-on combination therapy clinical trials.

Trial	Baseline therapy	Added therapy	Patients	Follow-up	End point	Ref.
PFIZER†	Sitaxsentan	Sildenafil	106	12 weeks	6MWD	[119]
COMPASS-2	Sildenafil	Bosentan	180	Event driven	Morbidity/mortality	[101]
ATHENA-1	Sildenafil	Ambrisentan	80	16 weeks	6MWD	[102]

†Study terminated due to toxicity concerns regarding sitaxsentan.
6MWD: 6-min walk distance.

improvement in 6MWD (30 m; p = 0.001), WHO functional class improvement by 1 or more (34 vs 6%; p = 0.002) and delayed TTCW (p = 0.02) [12]. These data were replicated with inhaled treprostinil in the TRIUMPH-1 study. TRIUMPH enrolled 235 PAH patients with predominantly WHO functional class III symptoms despite therapy with sildenafil and bosentan. At 12 weeks, there was a significant increase in 6MWD (20 m; p = 0.0066) after the addition of inhaled treprostinil to sildenafil or bosentan [13]. In a long-term, open-label extension including 206 patients completing the TRIUMPH-1 study, the improvement noted in 6MWD continued through 24 months of therapy [14].

However, adding a PDE-5 inhibitor to a prostanoid/ERA or *vice versa* has also been shown to be beneficial. The PACES-1 trial evaluated the addition of sildenafil (titrated to a maximum of 80 mg three-times daily) versus placebo to long-term iv. epoprostenol therapy in 267 PAH patients over 16 weeks [15]. The addition of sildenafil led to a significant increase in 6MWD (29 m; p < 0.001), improvement in mean PA pressure (-3.8 mmHg), increase in cardiac output (0.9 l/min) and delayed TTCW at 16 weeks.

Similarly, adding tadalafil to background therapy with bosentan may increase functional capacity in PAH. The PHIRST-1 study evaluated the effect of adding 16 weeks of tadalafil therapy at doses up to 40 mg in 405 PAH patients who were either treatment-naive or on background ERA therapy. In the subgroup of bosentan-treated patients, tadalafil increased 6MWD by 23 m, which was borderline statistically significant (p = 0.09), but also improved TTCW (68% risk reduction; p = 0.038) and quality-of-life measures [16,17]. The addition of an ERA to existing therapy with a PDE-5 inhibitor may also have additive value. In ARIES-3, an open-label study of ambrisentan 5 mg in 224 patients with PAH of varied etiologies, followed for 24 months, ambrisentan improved 6MWD in the subgroup already receiving sildenafil [18].

The COMPASS-3 study evaluated the efficacy and safety of a stepwise approach of adding sildenafil to bosentan monotherapy in PAH patients who failed to meet a target 6MWD of 380 m at 16 weeks of monotherapy with bosentan. The trial enrolled 100 patients with a baseline 6MWD of 273 m and at 28 weeks the study revealed a significant increase in 6MWD with the combined therapy [19].

Currently ongoing clinical trials of add-on combination therapy for PAH all examine the addition of either an ERA to a PDE-5 inhibitor or the reverse combination with the addition of a PDE-5 inhibitor to an ERA (Table 2). Particularly notable among these trials is the COMPASS-2 study, which is a large randomized clinical trial of bosentan added to sildenafil monotherapy in PAH that, in addition to 6MWD, will also examine the concrete end point of long-term morbidity and mortality [101]. The ATHENA-1 study is an open-label, multicenter study evaluating the effect of ambrisentan in patients with PAH and a suboptimal response to monotherapy with a PDE-5 inhibitor. The primary end point will examine reductions in pulmonary vascular resistance (PVR) at 24 weeks, with change in functional capacity as a secondary end point. ATHENA-1 has recently completed enrollment. Together, these studies should help to answer the question of whether it is preferable to use a PDE-5 or an ERA as initial therapy in terms of their relative impact on functional capacity [102].

As useful as add-on combination therapy may be, there is an emerging paradigm in the treatment of PAH to consider using early, 'up-front' multidrug combination therapy to achieve stabilization of the disease in a manner similar to that employed in other disease states such as rheumatoid arthritis [20,21]. One large, ongoing, randomized clinical trial, AMBITION, is designed to address whether up-front combination therapy with ambrisentan and tadalafil is superior to monotherapy with either of these agents in terms of the primary end point of TTCW and secondary end points of 6MWD and WHO functional class [103].

In Europe and the USA, there is a trend towards relative underutilization of parenteral prostanoids given the current availability of oral and inhaled agents, which are more convenient and do not expose patients to the infectious risk of continuous iv. access. However, up-front prostanoid therapy may still be the optimal therapy in selected patients with PAH and

severe symptoms. The French PAH center conducted a small, single-center study of up-front combination therapy with iv. epoprostenol and bosentan in 23 patients with WHO functional class III and IV symptoms. After 4 months of combination therapy there was a significant increase in 6MWD and PVR with sustained improvements over 30-month follow-up. Compared with matched controls on iv. epoprostenol alone, there was a trend towards improved survival with combination therapy (p = 0.07) [22].

Clinical trials of novel delivery systems for existing therapies

Several clinical trials have recently been completed that focused on evaluating novel delivery systems for existing PAH therapies. The FREEDOM-C and -C2 studies evaluated an oral version of treprostinil versus placebo in combination with bosentan and/or sildenafil background therapy. The concept of the FREEDOM studies was that patients and providers would ultimately be more willing to consider therapy with a prostacyclin if this did not come with the associated inconvenience of inhalational agents (multiple inhalations four- to six-times per day) or the risks associated with iv. agents such as catheter-related infections and venous thrombosis. Unfortunately, both studies of add-on therapy with oral treprostinil have not shown substantial benefit. As discussed in the previous section, the FREEDOM-C study of oral treprostinil versus placebo in 354 PAH patients showed no significant difference in 6MWD, WHO functional class or delay in TTCW versus placebo at 16 weeks of therapy [10]. One major problem in FREEDOM-C was the inability to achieve target doses of oral treprostinil and study drug discontinuation (14%) due to severe gastrointestinal side effects. This was partially ameliorated later in the trial with the introduction of smaller tablets that were better tolerated. In those that achieved a dose of 3.5 mg twice daily or greater, the improvement in 6MWD was 34 m [10].

This ultimately prompted the design of the FREEDOM-C2 trial, which sought to evaluate lower initial doses of oral treprostinil, with dose titration using smaller (0.25 mg) tablets. In FREEDOM-C2, 310 PAH patients who were treated with an ERA, PDE-5 or both were randomized to oral treprostinil or placebo with a primary end point of change in 6MWD at 16 weeks, with inclusion criteria similar to the original FREEDOM-C trial. Unfortunately, placebo-corrected 6MWD only improved by 10 m (p = 0.089). Of the patients receiving study drug, 11% discontinued due to adverse events [104].

The conclusion from FREEDOM-C and -C2 is that oral treprostinil is not of significant benefit when added to existing therapy with bosentan and sildenafil at doses that can be orally tolerated by most patients. However, in treatment-naive patients, preliminary results suggest that oral treprostinil may be beneficial. FREEDOM-M evaluated oral treprostinil versus placebo in 349 treatment-naive PAH patients with WHO functional class II and III symptoms. The primary analysis centered on the 228 patients who had access to the smaller, better tolerated 0.25 mg tablet. At 12 weeks of treatment, placebo-corrected increase in 6MWD was 23 m for oral treprostinil (p = 0.0125) [105].

An alternative means of reducing prostacyclin catheter-related complications is a completely implantable infusion catheter and infusion system. This has the appeal of avoiding an external component to the infusion system and could, therefore, possibly reduce infection rates. A completely implantable infusion system for iv. treprostinil has been developed by Medtronic (Model 10642 Implantable Intravascular Catheter; MN, USA) and is currently being evaluated in the DellVery for PAH clinical trial. The study is a nonrandomized, open-label study to evaluate the safety of the Dellvery Pivot system with an estimated enrollment of 70 patients and a primary outcome measure of rate of catheter-related complications per 1000 patient-days with 6-month follow-up [106].

Two studies are currently being initiated to examine the feasibility of using a portable NO system to treat PAH. NO inhalation has, to date, been limited to short-term therapy in the hospital setting due to the cost of inhaled NO, short half-life and the size of the equipment required to store and deliver a stable quantity of inhaled NO. However, two studies are examining the feasibility and efficacy of more portable NO systems.

The PHIANO trial is an open-label, dose-escalation study set to evaluate the acute efficacy of an inhaled-NO system versus placebo using a standard sized portable tank and proprietary system to generate inhaled NO. This study will evaluate the acute hemodynamic effects in terms of change in PVR of the inhaled-NO system in patients with WHO group I PAH and those with interstitial lung disease at 45 and 120 min of study-drug inhalation [107].

An alternative system developed by INO Therapeutics (Kent, UK) uses a small, portable ambulatory device to generate inhaled NO. This system will be evaluated in a Phase II, randomized, placebo-controlled trial in symptomatic patients with PAH on background therapy. The primary end point will be change in PVR at 16 weeks, with secondary end points of 6MWD, TTCW and WHO functional class [108].

Clinical trials of new therapies targeting existing pathways implicated in PAH

To date, three distinct pathways have been implicated in the pathophysiology of PAH:

- Relative deficiency in endothelial NO, a potent endogenous vasodilator;
- Relative excess of endothelin-1, a vasoconstrictor and promoter of fibrosis and vascular smooth-muscle cell proliferation;
- Relative deficiency of prostaglandins, an endogenous systemic and pulmonary vasodilator [6].

All of the current FDA-approved PAH therapies target one of these existing pathways, but a variety of new drugs have been developed that act on different steps in these pathways.

The SERAPHIN trial, initiated in 2007, is a large Phase III randomized trial of two doses of the tissue-targeted endothelin receptor antagonist macitentan versus placebo in PAH. Macitentan is a potent, tissue-specific endothelin receptor antagonist targeted towards blocking the adverse effects of tissue endothelin on the cardiovascular system [23]. The SERAPHIN trial is a large, long-term, event-driven trial with a primary end point of time to first morbidity or mortality event, with results expected in 2012 [109].

Two novel agents, cicletanine and riociguat, have been developed that target different steps in the NO pathway. Riociguat, and to a lesser extent cicletanine, have a potential advantage over PDE-5 inhibitors, which also target this pathway, in that they theoretically do not rely upon the presence of endogenous NO for their efficacy.

Cicletanine is an activator of vascular NO activity through endothelial NO synthase coupling. Cicletanine has been shown to reduce mean PA pressure in a small study of patients with pulmonary hypertension secondary to chronic obstructive pulmonary disease (WHO group III) and in a case of severe idiopathic PAH (WHO group I) [24,25]. A Phase II study of cicletanine versus placebo in patients with PAH on background therapy with an ERA, PDE-5 inhibitor and/or parenteral prostanoid, with a primary end point of change from baseline 6MWD at 12 weeks, was recently terminated due to lack of clinical efficacy [110].

Riociguat is a novel molecule that stimulates soluble guanylyl cyclase, ultimately leading to higher levels of cyclic GMP in vascular smooth-muscle cells, which is the final common step in the NO pathway resulting in vasodilatation. A Phase II uncontrolled, open-label study examined the effect of riociguat in WHO functional class II and III patients with PAH or chronic thromboembolic pulmonary hypertension (CTEPH) who were either treatment-naive or on bosentan monotherapy [26]. Riociguat led to an increase in 6WMD of 55 m in CTEPH patients and 57 m in PAH patients, $p < 0.0001$. Two large, Phase III, international, randomized clinical trials of riociguat have recently completed enrollment. The CHEST-1 study randomized patients with CTEPH (WHO group IV) who were either inoperable or who had recurrent disease after surgery, to riociguat versus placebo with a primary outcome measure of 6MWD at 16 weeks of therapy [111]. Similarly, the PATENT-1 trial evaluated the effect of riociguat versus placebo in patients who had treatment-naive PAH or those on monotherapy with an ERA or inhaled prostanoid, with a primary end point of change in 6MWD at 12 weeks [112].

Two oral agents have been developed that modulate the prostacyclin pathway. The biologic efficacy of parenteral prostacyclin therapy has previously been established, but drawbacks of parenteral therapy include infusion-site pain, complexity of operating an infusion pump and potential for life-threatening infections related to central venous catheters. Previous studies using oral forms of prostacyclin, such as oral treprostinil, have been limited by severe gastrointestinal side effects that limit the target dose achieved. Newer formulations of oral prostacyclin analogs and receptor agonists have focused on mitigating these side effects and achieving a more effective target dose.

Beraprost is an oral, long-acting prostacyclin analog. The original immediate release formulation of beraprost was previously evaluated in two large, Phase II, randomized clinical trials in 2002 and 2003. These suggested that beraprost therapy resulted in a short-term improvement in 6MWD at 3 months, but that this effect was not seen at longer term follow-up after 12 months of therapy [27,28]. Beraprost was never FDA-approved for use in the USA, but is available for the treatment of PAH in Japan. A new sustained release formulation of beraprost containing only the most pharmacologically active isomer (beraprost-MR) has also been developed. This showed promise in an open-labeled, 12-week clinical trial in 46 PAH patients in Japan, with significant increases in 6MWD and decrease in mean PA pressure at 12 weeks [29]. Beraprost-MR is presently being evaluated in a Phase II clinical trial, with three dosing regimens in PAH patients on background therapy with an ERA, PDE-5 inhibitor or both. The primary end point will be change in hemodynamics at 12 weeks, with change in functional capacity as a secondary end point [113].

Selexipag is a newly developed oral prostacyclin IP receptor agonist. In contrast to currently available prostanoids, it does not target other prostanoid

receptors and, therefore, has the appeal of minimizing many of the commonly encountered prostacyclin side effects [30]. In a 43-patient, Phase II, randomized clinical trial in patients with PAH on background therapy with an ERA or PDE-5 inhibitor, selexipag lowered PVR by 30% after 17 weeks of therapy (p = 0.0045) [31]. GRIPHON, a very large, long-term international Phase III randomized trial of selexipag in PAH patients on current background therapy is currently ongoing, with primary end point of time to first clinical event of morbidity or mortality [114].

Clinical trials of agents targeting new pathways implicated in the pathogenesis of PAH

A variety of drugs are being evaluated that target new pathways that may play an important role in the pathogenesis of PAH. Most of these drugs are existing compounds developed for alternative applications such as leukemia, ischemic heart disease and left ventricular systolic dysfunction.

Receptor tyrosine kinase inhibitors such as imatinib and nilotinib were originally developed for the treatment of chronic myelogenous leukemia and as such block cellular proliferation [32]. However, in PAH several receptor tyrosine kinases have been implicated in pulmonary vascular smooth muscle cell proliferation, specifically PDGF, EGF, FGF and VEGF [6]. Therefore, receptor tyrosine kinase inhibitors are potentially attractive as agents to treat PAH [33–35]. These drugs have the appeal of potential syngery with other currently available PAH-specific therapies, such as PDE-5 inhibitors and prostacyclins, given their predominantly antiproliferative mechanism of action versus the predominantly vasodilating properties of PDE-5 inhibitors and prostacyclin.

A Phase II randomized trial of imatinib versus placebo in 59 patients with PAH and an inadequate response to established PAH therapy (WHO functional class II–IV) showed no significant increase in 6MWD at 24 weeks, but did show a significant decrease in PVR and increase in cardiac output [33]. Following on from these preliminary results, the IMPRES trial evaluated 24 weeks of treatment with imatinib versus placebo in 202 patients with PAH and PVR >800 dynes/s/cm^{-5}, despite receiving at least two background PAH-specific therapies. Placebo-corrected treatment effects at week 24 versus baseline included improved 6MWD (32 m; p = 0.002), PVR (-379 dynes/s/cm^{-5}; p <0.001), cardiac output (0.88 l/min; p <0.001) and NT-pro-BNP values (-45.10 pmol/l, p = 0.04). There was no significant difference in TTCW with imatinib and the rate of adverse events was higher with imatinib.

Nilotinib, a newer, more potent receptor tyrosine kinase inhibitor, is currently being evaluated in an ongoing Phase II randomized clinical trial in patients with PAH and inadequate response to at least one PAH-specific therapy. The primary end point is change in PVR at 24 weeks with secondary end point of change in 6MWD relative to baseline [115].

Another chemotherapeutic agent, rituximab, is presently being evaluated in the RESTORE study, a National Institutes of Allergy and Infectious Disease sponsored multicenter study of PAH associated with scleroderma [116]. Rituximab is a monoclonal antibody targeting CD-20 that is found on the surface of B-cells. As a result, rituximab has been used for the treatment of a wide variety of hematologic malignancies, including B-cell lymphomas such as non-Hodgkin's lymphoma and post-transplant lymphoproliferative disorders [36]. However, rituximab is a powerful immune system modulator and has also been used to treat autoimmune disorders such as rheumatoid arthritis, hemolytic anemia and post-transplant antibody mediated rejection [37]. Immunotherapy has shown promise in the treatment of scleroderma-associated lung disease [38]. RESTORE is an ongoing Phase II multicenter randomized, placebo-controlled trial, which will evaluate rituximab versus placebo in scleroderma-associated PAH patients currently being treated with one or more PAH-specific therapy for 48 weeks. The primary efficacy end point will be PVR as measured via right heart catheterization, with 6MWD and TTCW as secondary end points [116].

VIP is a 28 amino acid neuropeptide typically secreted in the GI tract, which has potent vasodilatory properties and also inhibits platelet aggregation and vascular smooth muscle cell proliferation [39,40]. Endogenous VIP is concentrated in the lung and previous studies revealed that serum levels of VIP are significantly lower in PAH than in normal controls [39]. Aviptadil is a synthetic version of VIP that can be delivered by inhalation. A small pilot study of aviptadil in 20 patients with varied etiologies of pulmonary hypertension showed a small but significant acute decrease in PVR [41]. Aviptadil was then evaluated in a multicenter, randomized, Phase II clinical trial in patients with PAH, WHO functional class II or III symptoms and therapy with an ERA, PDE-5 inhibitor or both. The primary end point was change in PVR at 180 min postinhalation. Secondary end points included change in PVR, 6MWD, WHO functional class and NT-ProBNP at 12 weeks. Unfortunately, results of the study revealed that although aviptadil appeared safe, there was no significant change in PVR either at 180 min in the acute phase or at 12 weeks with aviptadil therapy. Similarly, there was no significant difference versus placebo in 6MWD, WHO functional class or NT-ProBNP, suggesting that inhaled aviptadil may not be effective

for the treatment of PAH despite plausible physiologic rationale [42].

Agents that have previously been used for the treatment of ischemic heart disease have recently been investigated in PAH. Aspirin, the postubiquitous antiplatelet agent, irreversibly inhibits cyclooxygenase, thus preventing platelet aggregation. HMG-CoA reductase inhibitors ('statins') have transformed the medical therapy of ischemic heart disease in large part through reduction of LDL cholesterol [43–46]. However, statins are known to have a multitude of effects independent of LDL reduction, their so-called 'pleotropic effects', such as improving endothelial function and reducing oxidative stress and, thus, many have hypothesized that they may be beneficial in PAH [47]. In the large JUPITER trial of rosuvastatin versus placebo in patients with normal cholesterol but elevated C-reactive protein, rosuvastatin therapy resulted in a lower incidence of venous thromboembolism [48]. Based on these potential beneficial physiologic effects, the concept that aspirin and statin therapy would be beneficial in PAH patients was appealing. These drugs were recently evaluated in the ASA-STAT study, which was a multicenter, NIH-sponsored randomized clinical trial of aspirin 81 mg and simvastatin 40 mg versus placebo in PAH patients with a 2 × 2 factorial design. The primary study end point was change in 6MWD at 6 months. The study was terminated early due to futility in terms of simvastatin reaching the primary end point. There was no significant difference in 6MWD with ASA versus placebo or with simvastatin versus placebo, and no significant difference in any of the secondary end points. Indeed, there was a trend towards worsening 6MWD with simvastatin [49].

Activation of the neurohormonal axis is known to be deleterious in patients with left ventricular systolic dysfunction with chronically elevated levels of circulating catecholeamines, leading to adverse cardiac remodeling. β-adrenergic blockers attenuate this effect and β-blockers such as carvedilol, bisoprolol and metoprolol succinate have all been shown to improve morbidity and mortality in chronic left ventricular systolic heart failure [50–52]. β-blockers have not been well studied in patients with right ventricular dysfunction and right ventricular failure. An ongoing Phase II clinical trial is examining the effect of carvedilol versus placebo on cardiac output and right ventricular mass assessed by MRI in patients with PAH and RV failure [117].

Stem cell therapy for treatment of PAH

There has been growing interest in the use of stem cells for the treatment for a wide variety of cardiovascular disorders including PAH. Autologous, rather than embryonic, endothelial progenitor cells can now be harvested and result in neovascularization when transplanted to ischemic limbs in mice [53]. In idiopathic pulmonary arterial hypertension, a recent 12-week, randomized, placebo-controlled pilot study of autologous endothelial progenitor cells infusion in 31 Chinese patients treated with standard PAH background therapy revealed a significant 42 m improvement in 6MWD versus placebo and improved hemodynamic parameters [54]. In addition, autologous EPCs can be genetically modified to produce specific molecules that may have favorable effects in PAH. For example, in north America, a Phase I clinical trial of injected EPCs engineered to produce NO synthase in patients with PAH is currently ongoing [118]. Stem cell and molecular therapy, although presently in its infancy, may ultimately prove to be a major avenue for therapeutic advances in PAH.

Limitations of current therapeutic & research strategies

The wealth of ongoing clinical research in PAH provides promise for future therapeutic advances in this field. However, the spectrum of current research underscores the fact that we still have a relatively limited understanding of the interplay of the various molecular pathways implicated in PAH. From a scientific perspective, the most appropriate initial therapy, or combination of PAH-specific therapies, is not certain based on currently available clinical trial data. It also remains uncertain whether new drugs targeting existing PAH pathways will have significant additive benefits beyond those drugs already available acting upon the same pathway – that is, whether there is a limit to the benefit accrued from action on a single pathway. Therefore, from the perspective of future research agenda, it remains questionable where precious research resources should be allocated towards novel agents targeting existing pathways or towards developing agents that act upon novel pathways that may be implicated in PAH.

Future perspective

The availability of the current array of pulmonary vasodilators has transformed therapy for pulmonary arterial hypertension and has led to improvement in important clinical end points in patients with PAH. The optimum means of combining existing therapies is currently being investigated in clinical trials such as AMBITION and, pending results of this and other trials, it is likely that there will be a paradigm shift from one of stepwise add-on therapy following

Executive summary

Introduction

- Pulmonary arterial hypertension (PAH) encompasses a variety of disorders that are thought to share a common pathophysiology characterized by pulmonary vascular smooth muscle cell proliferation, intimal fibrosis, pulmonary vasoconstriction and *in situ* thrombosis. Prior to the availability of current pulmonary vasodilator therapy, the morbidity and mortality of PAH was high with 1- and 5-year mortality of 68 and 34%, respectively. These have decreased registry as a result of advances in PAH-specific therapy.

Clinical trials of combination therapy in PAH

- From a physiologic perspective, combining therapeutic agents that act on different PAH pathways to provide synergistic effects is intellectually appealing.
- Of the completed studies, results have been inconsistent with regards to the relative benefits of add-on combination therapy, although overall there is signal towards benefit.
- Ongoing studies will evaluate the efficacy of up-front combination therapy versus monotherapy with an ERA or PDE-5.

Clinical trials of novel delivery systems for existing therapies

- Oral forms of treprostinil have the appeal of avoiding the inconvenience and catheter-related infections of inhaled or intravenous treprostinil.
- However, both trials of add-on combination therapy with oral treprostinil, FREEDOM-C and C2 failed to meet the primary end point and were plagued by patient intolerance.
- Oral treprostinil in treatment-naive patients did show benefit in terms of change in 6-min-walk distance (6MWD).
- Clinical trials are ongoing with a completely implantable intravenous infusion catheter system for treprostinil and for portable inhaled NO.

Clinical trials of new therapies targeting existing pathways implicated in PAH

- Three pathways are known to play a role in the physiology of PAH: the NO pathway, endothelin pathway and prostacyclin pathway.
- Macitentan is a new potent tissue-specific nonselective endothelin antagonist that has shown promise in Phase II clinical trials and is currently being evaluated in the SERAPHIN trial.
- Cicletanine is a novel activator of endothelial NO activity. A Phase II clinical trial of cicletanine in PAH was recently terminated due to lack of clinical efficacy.
- Riociguat is a new soluble guanylylcyclase stimulator that has shown promise in Phase II studies in PAH and chronic thromboembolic pulmonary hypertension. It is currently being evaluated in studies in PAH (PATENT-1) and chronic thromboembolic pulmonary hypertension (CHEST-1), which are nearing completion.
- A novel formulation of the long acting oral prostacyclin Beraprost (Beraprost-MR) is presently being evaluated.
- Selixipag, a novel stimulator of the prostacyclin IP receptor is currently being evaluated in a large, international Phase III trial with a morbidity- and mortality-driven primary end point.

Clinical trials of agents targeting new pathways implicated in the pathogenesis of PAH

- Receptor tyrosine kinases have been implicated in pulmonary vascular smooth-muscle-cell proliferation. Therefore, receptor tyrosine kinase inhibitors such as imatinib and nilotinib are potentially attractive as agents to treat PAH.
- The IMPRES trial showed that imatinib lowered PVR, improved 6MWD, cardiac output and NT-pro-BNP values.
- Nilotinib, a newer, more potent receptor tyrosine kinase inhibitor is currently being evaluated in an ongoing 24-week Phase II randomized clinical trial in patients with PAH and inadequate response to at least one PAH specific therapy.
- Another chemotherapeutic agent, rituximab, is presently being evaluated in the RESTORE study, a multicenter study of PAH associated with scleroderma.
- VIP is a 28 amino acid neuropeptide typically secreted in the GI tract that has potent vasodilatory properties and also inhibits platelet aggregation and vascular smooth-muscle-cell proliferation.
- Aviptadil is a synthetic analog of VIP that can be delivered by inhalation.
- Aviptadil was evaluated in a multicenter, randomized, Phase II clinical trial in patients with PAH, on background therapy with an ERA, PDE-5 inhibitor or both. Unfortunately, the study revealed that there was no significant change in PVR with aviptadil therapy. Similarly, there was no significant difference versus placebo in 6MWD, WHO functional class or NT-ProBNP.
- Aspirin and simvastatin were recently evaluated in the ASA-STAT study, which was a trial of aspirin 81 mg and simvastatin 40 mg versus placebo. The study was terminated early due to futility in terms of simvastatin reaching the primary end point.
- β-blockers have not been well studied in patients with right ventricular dysfunction and right ventricular failure. An ongoing Phase II clinical trial is examining the effect of carvedilol versus placebo on cardiac output and right ventricular mass assessed by MRI.

Stem cell & molecular therapy for PAH

- Genetically modified endothelial progenitor cells have shown promise in a Chinese study of patients with PAH on background therapy and are presently being evaluated in a Phase I clinical trial in the USA.

clinical deterioration to one of up-front combination therapy to stabilize the disease, particularly in patients with WHO functional class III or IV symptoms, low cardiac index or other high-risk features. In the future, our therapeutic options are likely to expand dramatically with the development of therapies targeting new pathways that may be associated with the pathogenesis of PAH, such as immunomodulatory therapies. Lastly, the future holds promise for molecular and cellular therapies for the treatment of PAH. Technology already exists to generate genetically engineered endothelial progenitor cells targeted to the pulmonary vasculature, producing endothelial NO and prostacyclins. Ultimately, targeted molecular and cellular therapies may revolutionize the field of PAH therapy.

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