

Advances in Prostanoid Therapy: New Studies, New Methods of Delivery



Marius M.
Hoeper, MD

Marius M. Hoeper, MD

Department of Respiratory Medicine
Hanover Medical School
Hanover, Germany

Two decades ago, pulmonary arterial hypertension was considered an untreatable disease. With the introduction of effective therapies this situation has changed. Today, endothelin receptor antagonists together with prostanoids and phosphodiesterase-5 (PDE5) inhibitors are the mainstays of treatment. All these drugs lead to hemodynamic and functional improvement within 3 to 4 months, and there is evidence to suggest that they also delay disease progression. Unfortunately, none of the currently available treatments offers a chance for cure, and many patients eventually experience progressive disease despite active treatment. Since the different classes of drugs act via different intracellular mechanisms, it appears logical and attractive to use combinations for better disease control. Clinical and scientific evidence to support the use of combination therapy for pulmonary arterial hypertension is rapidly cumulating.

Impact of Currently Available Drugs

Pulmonary arterial hypertension is characterized by extensive pulmonary vascular remodeling resulting from proliferation of endothelial cells, vascular smooth muscle cells, and fibroblasts. Excessive matrix deposition, in situ thrombosis, and pulmonary vasoconstriction contribute to the disease process. The etiology is still unclear, making causal treatment impossible. All currently available drugs act as pulmonary vasodilators but they also affect the mechanisms involved in pulmonary vascular remodeling, as suggested by several lines of experimental evidence.

Prostanoids

Prostanoids replace endogenous prostacyclin, production of which is decreased or absent in the pulmonary vessels of patients with pulmonary arterial hypertension, and exert vasodilatory and antiproliferative effects predominantly via the intracellular second messenger cyclic adenosine monophosphate (cAMP) as well as by some other mechanisms. Several prostanoids are approved for pulmonary arterial hypertension. Intravenous epoprostenol (Flolan), intravenous and subcutaneous treprostinil (Remodulin), and inhaled iloprost (Ventavis)

have all been shown to improve hemodynamics and exercise capacity in patients with various forms of the disease.¹⁻⁴ However, robust long-term survival data are available only for intravenous epoprostenol, and to a lesser extent for inhaled iloprost⁵ and subcutaneous treprostinil.⁶ With intravenous epoprostenol treatment, two long-term observational studies yielded survival rates at 1 year of 85% and 88%, respectively, at 2 years of 70% and 76%, and at 3 years of 63% and 63%.^{7,8} When interpreting these results it has to be kept in mind that these studies enrolled very sick patients. Placebo-controlled survival studies have never been performed in pulmonary arterial hypertension (and never will be for ethical reasons), but the reported survival rates compared favorably with historical controls and also with expected survival as calculated from the National Institutes of Health equation that was developed to estimate survival of patients with idiopathic pulmonary arterial hypertension (IPAH) based on their hemodynamic status.⁹

Data on long-term outcome with inhaled iloprost treatment are sparse. A retrospective study from Germany studying 76 patients with IPAH showed that in patients receiving first-line therapy with inhaled iloprost, survival free of transplantation or change in treatment was only 29% after 2 years, and 42% of the patients were eventually transitioned to intravenous prostanoid therapy.¹⁰

Endothelin receptor antagonists

Endothelin-1 is overexpressed in the pulmonary vasculature of patients with pulmonary arterial hypertension and causes deleterious effects such as pulmonary vasoconstriction and vascular smooth muscle cell proliferation; effects that are blocked by the administration of endothelin receptor antagonists. Endothelin-1 acts via two different endothelin receptor isoforms, ET_A and ET_B. Both the nonselective ET_A/ET_B receptor antagonist bosentan (Tracleer) and the selective ET_A receptor antagonists sitaxsentan (Thelin) and ambrisentan have been approved or are currently being studied for treatment of pulmonary arterial hypertension. All three compounds improve hemodynamics and exercise capacity in

patients with the disease.¹¹⁻¹⁵ Again, long-term data are sparse and so far available only for bosentan. In patients with IPAH, first-line treatment with bosentan has been associated with survival rates of 96% at 1 year and 89% at 2 years.¹⁶ When interpreting these results it is important to note that the survival data were not achieved with bosentan therapy alone, since 23% of these patients eventually required other medications, either alone or in combination with bosentan.

In contrast, a retrospective study from France showed that first-line therapy with bosentan resulted in an event-free survival rate of 44% after 2 years, and 45% of the patients required intravenous prostanoid therapy.¹⁷

Phosphodiesterase-5 inhibitors

PDE5 inhibitors augment the action of endogenous nitric oxide and natriuretic peptides by inhibiting degradation of the second messenger cyclic guanosine monophosphate (cGMP), thereby causing pulmonary vasodilatation and inhibition of vascular smooth muscle cell proliferation. The PDE5 inhibitor sildenafil (Revatio) has been studied most extensively in patients with pulmonary hypertension. A large set of case reports, case series, and randomized, controlled studies has demonstrated beneficial effects on exercise capacity and hemodynamics in patients with pulmonary arterial hypertension.¹⁸ Long-term survival with sildenafil treatment remains to be evaluated, especially since no long-term data are available for the dosage of 20 mg tid, the only dosage that has been approved for pulmonary arterial hypertension. Tadalafil (Cialis), another PDE5 inhibitor with a longer duration of action than sildenafil is currently under investigation for pulmonary arterial hypertension.

Rationale for Combination Therapy

There are several reasons to pursue combination therapy for pulmonary arterial hypertension. As discussed above, all available treatments improve exercise capacity within 3 to 4 months. However, average improvements on 6-minute walk testing range between 30 and 50 meters, and in many patients exercise capacity remains markedly limited despite active treatment. In fact, long-term improvement in functional class is usually achieved in less than 50% of patients with any monotherapy. Perhaps more importantly, none of the available treatment options cures pulmonary arterial hypertension and the disease often progresses despite active treatment. In addition, the three classes of substances currently available for treatment—prostanoids, endothelin receptor antagonists, and PDE5 inhibitors—act via different intracellular pathways as described above. Thus, combining these substances is very likely to produce synergistic effects. Scientific evidence to support these considerations is still limited.

Data for Combination Therapy

Endothelin receptor antagonists and prostanoids

Bosentan and intravenous epoprostenol. Only one randomized, controlled trial has been performed so far to assess combination therapy with bosentan and intravenous epoprostenol, the BREATHE-2 study.¹⁹ This was a true com-

bination study in which 33 patients with advanced disease started intravenous epoprostenol treatment and were simultaneously randomized to receive either bosentan or placebo. Combination therapy appeared to be well tolerated and there was a nonsignificant trend toward a greater hemodynamic improvement in patients receiving combination treatment. However, three deaths occurred during or shortly after the study, all in the group receiving epoprostenol and bosentan. All in all, this study was underpowered to allow definite conclusions.

Data addressing the combination of epoprostenol (or other prostanoids) with either ambrisentan or sitaxsentan are not available.

Bosentan and nonparenteral prostanoids (aerosolized iloprost and beraprost). Two open-label studies have provided preliminary evidence that addition of bosentan to either inhaled iloprost or beraprost (no longer available in the United States and Europe) may be well tolerated and may improve exercise capacity, hemodynamics, and right ventricular function.^{20,21}

More recently, two randomized, controlled studies addressed the opposite approach, ie, addition of aerosolized iloprost to bosentan, the STEP-1 study and the COMBI trial. The STEP-1 (for iloprost inhalation solution safety and pilot efficacy trial in combination with bosentan for evaluation in pulmonary arterial hypertension) study was designed as a randomized, double-blind study and included 65 patients with pulmonary arterial hypertension.²² After 12 weeks of treatment, the difference in the 6-minute walk distance between both groups was 26 meters in favour of the bosentan/iloprost group ($P = .051$). When interpreting these results it has to be noted that the 12-week results were obtained almost immediately after inhalation of iloprost or placebo. In contrast, the preinhalation results at week 12 did not differ significantly in both groups (placebo-adjusted difference, 19 meters; $P = .14$). Nevertheless, time to clinical worsening was significantly delayed with combination therapy.

Like STEP-1, the COMBI (for combination therapy of bosentan and aerosolized iloprost in IPAH) trial was designed to assess whether the addition of inhaled iloprost to bosentan improves exercise capacity in patients with pulmonary arterial hypertension. However, the results of this study differed markedly from those of STEP-1.²³ The COMBI trial was terminated early after a futility analysis predicted failure with respect to the predetermined sample size. At that time 40 patients were randomized to receive either bosentan alone (control group) or bosentan plus inhaled iloprost (combination group) for a 12-week period. The primary end point, change in 6-minute walking distance, was not met (mean changes were +1 meter in the control group and -9 meters in the combination group; $P = .490$). However, these results were markedly affected by three outliers, ie, three patients, all randomized to receive inhaled iloprost, who presented with severe clinical worsening. The trend in the other patients was similar to that in the STEP-1 trial. None of the secondary end points, including functional class, peak oxygen uptake, and time to clinical

worsening, differed significantly between groups.

Taken together, further studies and long-term data are needed to define the efficacy of adding inhaled iloprost to bosentan.

Prostanoids and PDE5 inhibitors

Epoprostenol and sildenafil. The combination of epoprostenol and sildenafil has been studied in a large, multicenter, 12-week, randomized, controlled trial, the PACES study. The full study has not been completely published but the main results have been presented at international congresses. PACES enrolled 267 patients receiving stable dosing of epoprostenol and randomly added sildenafil or placebo. Apparently, improvement in 6-minute walk distance was significantly better with the combination than with epoprostenol alone, but the final results have yet to be presented. It needs to be noted that in this trial sildenafil was started at a dosage of 20 mg tid and titrated up to 80 mg tid, which is substantially higher than the currently FDA-approved sildenafil dosage of 20 mg tid.

Subcutaneous treprostinil and sildenafil. Only a small observational study addressing the combination of subcutaneous treprostinil and sildenafil has been published.²⁴ Sildenafil was used as add-on treatment in 9 patients with pulmonary arterial hypertension receiving treprostinil. This combination was well tolerated and resulted in improved exercise capacity in all patients.

Aerosolized iloprost and sildenafil. So far, the evidence for safety and efficacy of combining aerosolized iloprost and sildenafil is limited to acute hemodynamic intervention studies and one case series. The two hemodynamic studies have provided convincing evidence that the addition of sildenafil to aerosolized iloprost and vice versa has synergistic effects on pulmonary arterial pressure, cardiac output, and pulmonary vascular resistance.^{25,26} However, it remains to be shown how these acute hemodynamic effects translate into long-term clinical outcome. Currently, only a single case series has provided some preliminary information about the combination of inhaled iloprost with sildenafil. Ghofrani et al. studied the effects of sildenafil as add-on medication in 14 patients whose condition deteriorated despite treatment with aerosolized iloprost. The patients had been receiving iloprost treatment for a mean period of 18 months. Addition of sildenafil was well tolerated by all patients and resulted in a mean increase in 6-minute walk distance of 88 meters after 3 months accompanied by hemodynamic improvement. The effects on exercise capacity were maintained throughout the observation period of up to 12 months.²⁷

Endothelin receptor antagonists and PDE5 inhibitors

Bosentan and sildenafil. Only a few case series have been published addressing safety and efficacy of combining bosentan and sildenafil in patients with pulmonary arterial hypertension.²⁸ The first study included 9 patients with severe idiopathic disease. Therapy for these patients was started with bosentan and sildenafil was added when clinical deterioration occurred, after a mean interval of 11

months of bosentan therapy. Three months after addition of sildenafil, the 6-minute walk distance had increased by 115 meters, accompanied by a significant improvement in maximum oxygen uptake as measured by cardiopulmonary exercise testing. The improvement in exercise capacity was maintained throughout the observation period, which lasted between 6 and 12 months. Combination therapy with bosentan and sildenafil was tolerated without adverse events. The second, yet unpublished, series included 18 patients with pulmonary arterial hypertension who either had sildenafil added to bosentan ($n = 13$) or vice versa ($n = 5$). Six-minute walk distance improved by 44 meters. Six patients had also been treated with intravenous epoprostenol, and four of them were able to wean off of it. These were highly selected patients who had already experienced marked improvement in hemodynamics and walk distance with epoprostenol, and results should not be generalized to less well compensated patients.

In contrast to the other combination regimens described above, coadministration of bosentan and sildenafil may be associated with relevant pharmacokinetic interactions.²⁹ Sildenafil has inhibitory effects on CYP3A4 activity, which may lead to increased plasma concentrations of bosentan. Bosentan, like other endothelin receptor antagonists, may exert hepatotoxic effects and there is concern about a higher risk of liver damage with combined administration of bosentan and sildenafil. None of the patients in the case series described above experienced elevations in hepatic aminotransferases when sildenafil was added to bosentan, but the small number of patients precludes any meaningful safety analysis. On the other hand, induction of CYP3A4 activity by bosentan may accelerate metabolism of sildenafil, which may decrease the plasma concentrations of sildenafil by as much as 60%. This interaction may be important since sildenafil has been approved for treatment of pulmonary arterial hypertension only at a dosage of 20 mg tid. It is unknown whether lower dosages or lower plasma concentrations are still efficacious. To date, those are theoretical considerations and the clinical relevance of these interactions has not been studied.

Clinical studies addressing the combination of other endothelin receptor antagonists, ie, ambrisentan or sitaxsentan with sildenafil or tadalafil, have not been published. On the basis of pharmacologic data, it is unlikely that drug-drug interactions will play a relevant role when any of these substances are combined. However, clinical studies have to be awaited to show whether this assumption holds true.

Future Concepts and Long-Term Outcome with Combination Therapy

All current treatment guidelines for pulmonary arterial hypertension include the option of combination therapy and place it somewhere near the end of the cascade, ie, for patients with advanced illness not responding sufficiently well to monotherapy. Perhaps, in the future, combination therapy will be introduced right after the diagnosis is made (following the “hit-hard-and-early” concept). However, as long as no data are available to show that such a concept truly improves treatment results, a step-wise approach is a

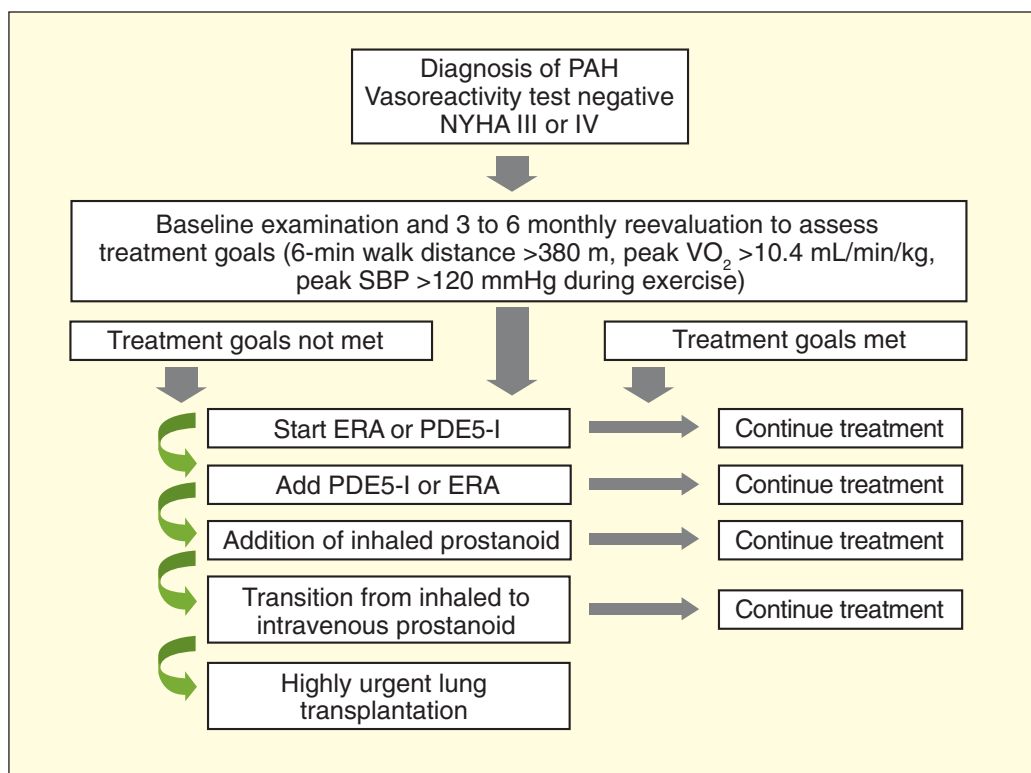


Figure 1. Goal-oriented treatment strategy for pulmonary arterial hypertension (PAH).³⁰ Peak VO₂ = peak oxygen uptake; peak SBP = peak systolic blood pressure; ERA = endothelin receptor antagonist; PDE5-I = phosphodiesterase-5 inhibitor.

reasonable alternative. One open question is when to initiate combination therapy. The group at Hanover Medical School in Germany has introduced the concept of goal-oriented therapy, which may provide a possible approach to this question.³⁰ This concept is based on the definition of treatment goals, a concept that is fundamentally different from the approach of most clinical trials in pulmonary arterial hypertension. The majority of trials have examined whether any given treatment improves 6-minute walk distance by a certain amount. However, we have learned that improvement in 6-minute walk distance is important but may not translate into improved long-term outcome. In fact it has become clear that certain thresholds have to be reached. For instance, it has been shown that patients who reach a 6-minute walk distance of more than 380 meters with medical therapy have a substantially better outcome than patients who are not able to cover this distance (although individual factors such as height, weight, age, and physical conditions may affect the interpretability of 6-minute walk test results).⁷ We have also learned that the peak oxygen consumption or the peak blood pressure during exercise can help to predict the prognosis.³¹ On the basis of these data, the Hanover researchers decided to define treatment goals for their patients, including a 6-minute walk distance greater than 380 meters, a peak oxygen consumption greater than 10 mL/min/kg, and a peak systolic blood pressure during exercise greater than 120 mmHg. Whenever these treatment goals were not reached on two consecutive visits, initiation of combination therapy was considered. This approach was combined with a predefined therapeutic strategy depicted in **Figure 1**. This concept resulted in 3-year

survival rates of approximately 80%, significantly better than the survival in a historical control group as well as the expected survival estimated from the NIH registry formula (**Figure 2**). In comparison with the historical control group, the use of combination treatment also improved the combined end point of death, lung transplantation, and need for intravenous iloprost treatment.

This concept will probably be modified in the future, but the overall strategy to follow predefined therapeutic goals (with individual modification) may prove to be useful. Other end points may be added or may replace some of those used previously; for instance plasma levels of brain natriuretic peptide (BNP) or its N-terminal fragment (NT-proBNP) might make a useful addition.³² The choice of medications may vary depending on availability and the given clinical situation.

The Hanover researchers started their study when bosentan was the only drug approved for pulmonary arterial hypertension in Germany, but today sildenafil would appear to be an equally suited choice as first-line treatment (as well as other endothelin receptor antagonists, PDE5 inhibitors, or novel substances in the future).

A Call to Support Clinical Trials

There is no doubt that combination therapy is going to play a major role in the treatment of pulmonary arterial hyper-

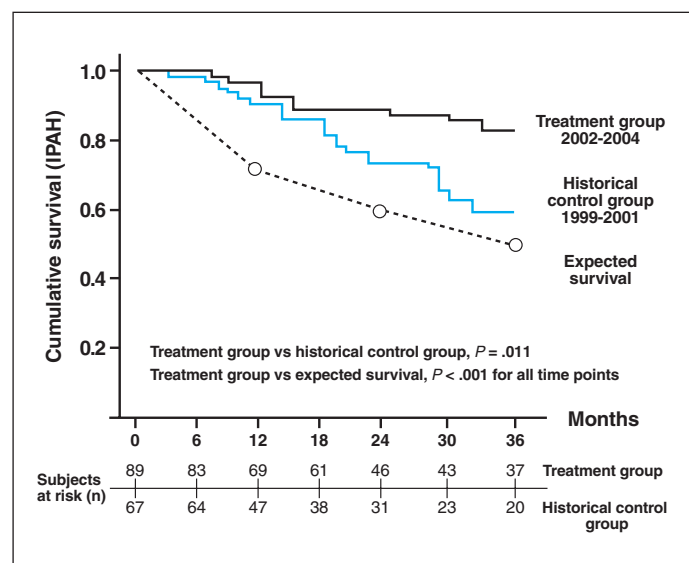


Figure 2. Survival of patients with idiopathic pulmonary arterial hypertension (IPAH) with a goal-oriented treatment strategy compared to a historical control group and the expected survival.³⁰

tension. In fact, it already does so. The introduction of several new active treatments has been a blessing for affected patients, many of whom are already benefiting from the use of combination therapy. The problem is that we still do not know the most effective combinations, which patients benefit the most from combination therapy, and the best time to initiate combination therapy. We also need to make sure that combining several treatments is not associated with increased toxicity. Finally, given the current costs of treatments, identifying the value of combination therapy will have socioeconomic implications.

Several clinical trials are under way to study the effects of combination therapy, including VISION (sildenafil and inhaled iloprost), TRIUMPH (bosentan or sildenafil and inhaled treprostinil), COMPASS 1/2 (sildenafil and bosentan), and PHIRST (bosentan and tadalafil). Among these trials, COMPASS-2 stands out as the first study to compare long-term outcome of a combination regimen (bosentan plus sildenafil) versus a monotherapy (sildenafil) in a large group of patients. All these trials are expected to provide important new information, helping to optimize the treatment of patients with pulmonary arterial hypertension. Thus, eligible patients should consider participating in these trials whenever possible, for their own sake as well as for the benefit of the many other patients affected by the disease now or in the future. Physicians treating patients with pulmonary arterial hypertension should be aware of these trials and should not hesitate to inform patients about ongoing studies in which they may be able to participate. ■

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