# Combination Therapies in Pulmonary Arterial Hypertension

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## Introduction

Despite recent advances in the identification of therapeutic targets and the development of novel medications, pulmonary arterial hypertension (PAH) remains a debilitating and progressive condition. Currently available therapies improve functional capacity and quality of life and may improve survival. However, the vast majority of patients are left with severe functional limitations in their daily activities. The pathophysiology of PAH is complex, involving in part imbalances in endogenous mediators that promote vasoconstriction and cell proliferation in the pulmonary vasculature. The mechanisms promoting these pathologic effects involve multiple pathways. In light of this complexity, it is not surprising that many of the therapies employed in PAH do not completely reverse the pathologic changes. Just as systemic hypertension is currently being treated with multiple agents from different classes, patients with PAH may benefit from combination therapy, making this approach appealing in concept.

The goal of combination therapy is aimed at maximizing therapeutic efficacy while limiting toxicity and drug-drug interactions. Endpoints, such as improvement in functional capacity as measured by improvements in New York Heart Association (NYHA) functional class, 6-minute walk test distance, and pulmonary hemodynamics, have been employed to help establish treatment efficacy in monotherapy trials. These same endpoints are being employed in trials of combination therapy. However, there remain many important unanswered questions regarding this approach. For example, what combination of available treatments is most efficacious? Are certain forms of PAH more likely to respond to a particular combination of medications? What are the pharmacologic interactions, safety profiles, and cost-effectiveness of various combinations? Among the physiologic pathways involved in the development and progression of PAH, three currently have targeted therapies and are therefore being pursued in PAH combination therapy trials.

*1) The prostacyclin pathway.* Prostacyclin is a potent pulmonary vasodilator. It stimulates cyclic adenosine monophosphate (cAMP) production, resulting in vascular smooth muscle cell relaxation and inhibition of smooth muscle cell growth. It may prevent pulmonary vascular remodeling.[1] A deficiency of prostacyclin in the lungs of patients with PAH confirmed the relevance of prostacyclin analogues as a treatment.[2] Epoprostenol intravenously, treprostinil via intravenous or subcutaneous infusion, and iloprost as an inhalational agent are the currently available prostanoids in the United States.

*2) The endothelin-1 (ET-1) pathway.* ET-1 is a potent pulmonary vasoconstrictor. Increased levels of ET-1 have been detected in the lung vasculature of patients with PAH. Blocking this pathway using either nonselective or selective ET-1 receptor antagonists (ETRAs) has proved beneficial in the treatment of PAH. Bosentan is a nonselective ETRA blocker and was the first oral therapy approved by the Food and Drug Administration (FDA) for the treatment of PAH.[3] Ambrisentan, a selective ETRA, was more recently approved for this indication.

*3) The nitric oxide pathway.* Nitric oxide enhances the production of cyclic guanosine monophosphate (cGMP), which has actions similar to those of cAMP.[4] cGMP is inactivated by the phosphodiesterase family of enzymes. Phosphodiesterase-5 (PDE5) is abundant in the lung vasculature and PDE5 inhibition by agents such as sildenafil prevents the breakdown of cGMP,[5] resulting in pulmonary vasodilatation.[6] Sildenafil has been approved by the FDA for the treatment of PAH.

Combination therapies can be viewed either as the use of two or more therapies started concomitantly or as add-on therapy, where the second (or third) agent is added to a previously established therapy. The addition of another medication may occur in the setting of patient deterioration or in the scenario of a stable patient who has not had "adequate" improvement with monotherapy. To date, the vast majority of published studies have examined the efficacy of add-on therapies.

*Key Words—Prostanoids; endothelia receptor antagonists; PDE5 inhibitors; goal-directed therapy.*

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## Table 1. Prostanoids Plus Endothelin Receptor Antagonist Combination Trials

| Combination | Study Design | Number of Patients | Dosing | Results | *P* value |
|---|---|---|---|---|---|
| **Bosentan + iloprost/beraprost**[30] | OL | 20 | Bosentan 125 mg bid + Prostanoid, maximal tolerated dose | 6MWD + 45 m<br>Exercise testing parameters | < .05<br>< .05 |
| **Bosentan + epoprostenol (BREATHE-2)**[31] | RCT | 33 | Bosentan 125 mg bid + Epoprostenol 12-16 ng/kg/min | PVR<br>-36% vs -23%<br>6MWD<br>NYHA FC | NS<br><br>NS<br>NS |
| **Bosentan + iloprost (COMBI)**[11] | RCT | 40 | Bosentan 125 mg bid + Iloprost 5 mcg 6 times daily | 6MWD<br>TCW<br>Functional Class | NS<br>NS<br>NS |
| **Bosentan + iloprost (STEP)**[10] | RCT | 67 | Bosentan 125 mg bid + Iloprost 5 mcg up to 6 times daily | 6MWD + 26 m<br>Delayed TCW | .051<br>.022 |
| **Bosentan + prostanoids**[12] | OL | 16 | Bosentan 125 mg bid + Iloprost intravenous or inhaled; or Beraprost | 6MWD<br>+ 42 ± 66 m<br>Tei index improved | < .001<br><br><.001 |

NYHA FC = New York Heart Association functional class; OL = open label; PVR = pulmonary vascular resistance; RCT = randomized controlled trial; 6MWD = 6-minute walk test distance; Tei index = echocardiographic index of right ventricular function; TCW = time to clinical worsening.

## Current Studies of Combination Therapy

### Prostanoids and ET-1 Receptor Antagonists

Results from early animal studies suggest that this combination is effective in the treatment of PAH.[7] Early observational and unblinded clinical studies examining this combination were also encouraging (**Table 1**). The addition of bosentan in an open-label fashion was studied in 20 PAH patients stable on either inhaled iloprost or oral beraprost (maximum tolerated dose).[8] This regimen was well tolerated and resulted in significant improvement in 6-minute walk test distance (6MWD), as well as in parameters of exercise testing (maximal oxygen consumption, anaerobic threshold, oxygen pulse, ventilatory efficiency, and peak systolic blood pressure during exercise). However, the first placebo-controlled trial of this combination of medications raised questions about their efficacy together. BREATHE-2 was a 16-week, double-blinded, randomized, placebo-controlled prospective trial examining the efficacy of adding oral bosentan at the initiation of intravenous epoprostenol therapy.[9] Intravenous epoprostenol therapy was started in 33 PAH patients (idiopathic PAH or connective tissue disease-related PAH). Two days later they were randomized to receive either oral bosentan or placebo. The target dosage of epoprostenol at week 16 was 12 to 16 ng/kg/min and the target dosage of bosentan was 125 mg bid. In patients receiving the combination, hemodynamic improvement was not significant in comparison with placebo and epoprostenol; nor was there significant improvement in functional class or exercise capacity. Leg edema was encountered more frequently in the group receiving bosentan (27% vs 9% with placebo). In addition, three deaths occurred during the course of the study; all were in the combination arm. This study, however, was not powered to detect differences in survival, and the survival difference was of concern but not statistically significant.

**The goal of combination therapy is aimed at maximizing therapeutic efficacy while limiting toxicity and drug-drug interactions. Endpoints, such as improvement in functional capacity as measured by improvements in New York Heart Association (NYHA) functional class, 6-minute walk test distance, and pulmonary hemodynamics, have been employed to help establish treatment efficacy in monotherapy trials. These same endpoints are being employed in trials of combination therapy.**

In the recent multicenter, placebo-controlled STEP trial, iloprost or placebo was added to treatment in 67 PAH patients in New York Heart Association (NYHA) functional class III or IV whose condition was clinically stable with bosentan.[10] The primary endpoint of this study was the postinhalation 6MWD. The 6MWD significantly improved by 26 m (placebo-adjusted) at week 12 in patients receiving combination therapy. NYHA functional class, time to clinical worsening, and postinhalation hemodynamics also were significantly improved. The combination of inhaled iloprost and bosentan appeared to be safe and well tolerated. These data were sufficient for the FDA to approve iloprost as an add-on therapy in patients receiving bosentan. In the COMBI multicenter trial, Hoeper et al studied patients with idiopathic PAH stable on bosentan to whose regimen iloprost or placebo was added.[11] The investigators planned to enroll 72 patients, but the study was terminated early because the interim analysis of 40

## Table 2. Ongoing Clinical Trials of Combination Add-on Therapies

| | Initial Therapy | Added Therapy | Number of Patients | Study Duration | Primary Endpoint |
|---|---|---|---|---|---|
| **FREEDOM-C** | Bosentan and/or sildenafil | Treprostinil | 300 | 16 weeks | 6 MWD |
| **TRIUMPH-1** | Bosentan | Treprostinil | 150 | 12 weeks | 6 MWD |
| **PACES (extension)** | Epoprostenol | Sildenafil | 264 | Long-term | 6 MWD |
| **VISION** | Sildenafil | Iloprost | 180 | 16 weeks | 6 MWD |
| **PHIRST** | Naïve or bosentan | Tadalafil | 400 | 16 weeks | 6 MWD |
| **Pfizer** | Bosentan | Sildenafil | 106 | 12 weeks | 6 MWD |
| **COMPASS-2** | Sildenafil | Bosentan | 180 | Event driven | 6 MWD<br>Morbidity/mortality events |
| **COMPASS-3** | Bosentan | Sildenafil | 100 | 12 weeks | 6 MWD |

6MWD = 6-minute walk test distance.

patients did not demonstrate efficacy. Interestingly, as in the STEP trial, the 3 patients whose condition showed significant deterioration in all objective outcomes were in the combination arm. Lastly, in an open-label trial, the addition of bosentan was studied in 16 PAH patients stable on inhaled iloprost or intravenous iloprost or oral beraprost.[12] The combination significantly improved the average 6MWD as well as echocardiographic indices of right ventricular function. Nine patients had an improvement in functional class. Effects were sustained at over 6 months.

Two multicenter trials are currently being conducted to analyze the combination of an ETRA with a prostacyclin analogue (**Table 2**). TRIUMPH-1 is a 12-week placebo-controlled trial that is enrolling PAH patients stable on bosentan in whom placebo or inhaled treprostinil qid is added. In the second trial, FREEDOM-C, PAH patients who are receiving bosentan and/or sildenafil will have oral treprostinil added in escalating doses. Although both of these studies have as their main goal the establishment of efficacy for inhaled or oral treprostinil in the combination treatment of PAH, the results of these trials will also shed light on the safety of combining these therapies with ETRAs.

**There is experimental evidence of a costimulatory cross-talk between the cAMP and cGMP pathways, including certain animal models of PAH. The combination of sildenafil and beraprost in monocrotaline-induced pulmonary hypertension in rats attenuated the development of pulmonary hypertension and pulmonary vascular remodeling to a greater degree than did either drug alone.**

### Prostanoids and PDE5 Inhibitors

There is experimental evidence of a costimulatory cross-talk between the cAMP and cGMP pathways, including certain animal models of PAH. The combination of sildenafil and beraprost in monocrotaline-induced pulmonary hypertension in rats attenuated the development of pulmonary hypertension and pulmonary vascular remodeling to a greater degree than did either drug alone.[13] Animal survival improved and increases in plasma cAMP and cGMP levels were noted. Acute clinical hemodynamic studies and short-term trials in patients have demonstrated potentiation of the vasodilator actions of prostacyclins by sildenafil, thus holding promise for this combination (**Table 3**).

Ghofrani et al[14] administered inhaled iloprost and sildenafil to 30 patients with severe PAH or chronic thromboembolic pulmonary hypertension. The combination was more potent than either agent alone. Sildenafil extended the duration of iloprost effects beyond 3 hours, suggesting that less frequent dosing of iloprost might be possible. In an open-label study Kuhn et al administered 50 mg of sildenafil (one dose) to 8 patients with PAH receiving long-term epoprostenol therapy.[15] They observed improvements in mean pulmonary artery pressure (mPAP), cardiac output, and pulmonary vascular resistance (PVR), suggesting that sildenafil remains a potent acute pulmonary vasodilator in patients receiving chronic epoprostenol therapy.

In an acute vasodilation study in 5 patients with PAH, the combination of oral sildenafil with inhaled iloprost was superior to iloprost alone.[16] Similarly, addition of sildenafil to oral beraprost in 6 patients with moderate to severe PAH produced improvements in mPAP and PVR when compared with beraprost alone.[17] In 14 PAH patients showing clinical deterioration with inhaled iloprost, add-on therapy with sildenafil reversed the deterioration, significantly increasing the 6MWD and functional class; these improvements were sustained after 9 to 12 months of combination therapy.[18]

## Table 3. Prostanoids Plus PDE5 Inhibitor Combination Trials

| Combination | Study Design | Number of Patients | Dosing | Results | *P* value |
|---|---|---|---|---|---|
| **Iloprost + sildenafil vs inhaled NO** [14] | Acute, OL | 30 | Iloprost 2.8 mcg, then sildenafil 12.5 mg or 50 mg after 1 hour, or inhaled NO | PVR -44.2% vs 14.1% with inhaled NO | |
| **Iloprost + sildenafil**[16] | Acute, OL | 5 | Iloprost 8.5-10.5 mcg, then sildenafil 25 mg after 30 min | mPAP -13.8 mmHg vs 8.4 mmHg | .009 |
| **Beraprost + sildenafil**[17] | Short-term, OL | 6 | Beraprost 40 mcg –day 1; beraprost 40 mcg + sildenafil 25 mg, days 2-6 | 2.2 x reduction in mPAP<br>1.6 x reduction in PVR | < .05 |
| **Epoprostenol + sildenafil** [32] | Acute OL | 8 | Epoprostenol average 25.7 ng/kg/min + sildenafil 50 mg once | mPAP -10%<br>PVR -13% | .05<br>NS |
| **Iloprost + sildenafil**[18] | Long-term, OL | 14 | Iloprost up to 9x/day + sildenafil 25-50 mg tid | 6MWD + 90 m at 3 months | .002 |
| **Treprostinil sq + sildenafil**[19] | Long-term, OL | | Treprostinil 35-90 ng/kg/min + sildenafil 50 mg tid | Treadmill time + 42% | .049 |
| **Prostanoids + sildenafil**[20] | Long-term, OL | 20 | | 6MWD<br>+79 m (1 year)<br>+ 105 m (2 years)<br>NYHA FC improved | <.05 |
| **Epoprostenol + sildenafil PACES**[21] | 16 weeks, RCT | 267 | Epoprostenol + sildenafil 80 mg tid | 6MWD +26 m<br>TCW delay | .0088<br>.012 |

mPAP = mean pulmonary artery pressure; NO = nitric oxide; NYHA FC = New York Heart Association functional class; OL = open label; PDE5 = phosphodiesterase 5; PVR = pulmonary vascular resistance; RCT = randomized controlled trial; 6MWD = 6-minute walk test distance; TCW = time to clinical worsening.

More recently, Gomberg-Maitland et al[19] reported on an open-label study in which 9 stable PAH patients in NYHA functional class II-IV on stable doses of subcutaneous treprostinil had sildenafil added to their regimen. After 12 weeks, patients had significant improvement in their treadmill exercise capacity. Lastly, in a retrospective study, 20 patients with severe PAH who showed clinical deterioration on prostanoid therapy (8 subcutaneous, 7 intravenous, and 5 inhaled) had sildenafil added to their regimen.[20] The 6MWD, functional class, and echocardiographic parameters of right ventricular function improved significantly, and the beneficial effects lasted more than 24 months.

These combination studies, albeit reporting on a limited number of patients in mostly open-label studies, suggested that PDE5 inhibitors improve pulmonary hemodynamics and symptoms in PAH patients receiving prostanoid therapy. A large multicenter, double-blind, randomized trial (PACES) of this combination awaits publication. This trial enrolled patients stable on epoprostenol and randomized them to the addition of placebo or sildenafil titrated to tolerance up to 80 mg three times daily. Preliminary results reported in an abstract at the American Thoracic Society meeting in May 2007 demonstrated an average of 26 meters improvement in 6MWD at week 16 in the combination therapy arm as well as a delay in time to clinical worsening.[21]

### ETRAs and PDE5 Inhibitors

The combination of oral therapies is an attractive option to both clinicians and patients as it avoids the disadvantages of infusion therapies (**Table 4**). A few reports have addressed the significant pharmacologic interactions between sildenafil and bosentan. In a recent study, 51 healthy volunteers completed a randomized, double-blind, placebo-controlled, parallel group study with three arms (sildenafil 80 mg three times daily, bosentan 125 mg twice daily, and sildenafil plus bosentan) for 18 days.[22] On day 16, bosentan decreased maximum plasma concentration of sildenafil by 55%, while sildenafil increased bosentan concentration by 42%. Despite this pharmacokinetic interaction, the combination of sildenafil and bosentan was well tolerated.

Another pharmacologic study assessed the combination of bosentan with sildenafil in 10 patients with PAH.[23]

## Table 4. Endothelin Receptor Antagonists Plus PDE5 Inhibitor Trials

| Combination | Study Design | Number of Patients | Dosing | Results | *P* value |
|---|---|---|---|---|---|
| **Bosentan + sildenafil[25]** | OL | 25 | Bosentan 125 mg bid + sildenafil 20-100 mg tid | 6MWD + 46 m in idiopathic PAH<br>NYHA FC improved in 5/13 with idiopathic PAH | .05<br>NS |
| **Bosentan + sildenafil[24]** | OL | 9 | Bosentan 125 mg bid + sildenafil 25-50 mg tid | 6MWD + 115 m<br>VO2 max + 3.4 mL/min/kg | < .007<br>.006 |
| **Bosentan + sildenafil[27]** | Post-marketing surveillance | 4,996 | Bosentan alone vs bosentan + sildenafil | Safety reports similar | |

OL = open-label; 6MWD = 6-minute walk test distance; NYHA FC = New York Heart Association functional class.

Bosentan was given at a dosage of 62.5 mg twice daily for 1 month, then at 125 mg twice daily for the second month. Sildenafil 100 mg was given before the first bosentan dose and at the end of each month of bosentan treatment. Treatment with bosentan 62.5 mg twice daily was associated with a twofold increase in sildenafil clearance. Increasing the dose of bosentan to 125 mg twice daily led to a further increase in sildenafil clearance, demonstrating that bosentan decreases the plasma concentration of sildenafil in PAH patients.

Although these short-term pharmacologic studies proved safe, there is a theoretical concern of increased liver toxicity from elevated bosentan levels in patients taking a combination of these medications. We know from the BREATHE-1 study that bosentan at 250 mg twice daily is associated with a higher risk of liver toxicity than is the currently approved dose (125 mg twice daily).[3] Therefore, patients taking the combination of bosentan and sildenafil should be carefully monitored for evidence of liver toxicity.

**There is debate among PAH specialists as to whether combination therapy should be reserved for patients whose condition deteriorates (add-on therapy) or should be started up front. This paradigm resembles the "induction" therapy used in cancer treatment, followed by maintenance therapy with one or more agents once patients have improved.**

In a small study of idiopathic PAH patients, bosentan was employed as add-on therapy in those whose condition was clinically deteriorating with sildenafil monotherapy.[24] The combination was well tolerated, 6MWD improved significantly, and patients remained stable throughout the median follow-up of 9 months. A retrospective study analyzed 25 patients with idiopathic PAH or PAH related to scleroderma who were receiving bosentan but who required addition of sildenafil because of clinical deterioration.[25] In this small cohort, only idiopathic PAH patients showed an improvement in average 6MWD with the addition of sildenafil, with 5 of the 13 idiopathic PAH patients showing improvement in NYHA functional class, while scleroderma patients did not have significant improvement with combination therapy. This result emphasizes the difficulties of treating patients with scleroderma-associated PAH. Preliminary results from the EARLY trial[26] were reported for 29 patients with mild PAH (functional class II) receiving sildenafil in whom bosentan was added. Addition of bosentan improved PVR by 20% and delayed time to clinical worsening, although there was no significant improvement in the 6MWD. In a prospective, Internet-based, postmarketing surveillance study required by the European regulatory authorities for assessing the safety of bosentan in PAH patients, of almost 5000 PAH patients who were captured over 30 months, 218 patients received sildenafil in addition to bosentan.[27] Combination therapy appeared to be well tolerated in this subgroup; their safety data were similar to those for bosentan alone.

There are three ongoing clinical trials looking at the sildenafil and bosentan combination from which data are not yet available (**Table 2**).

### Goal Directed Therapy

There is debate among PAH specialists as to whether combination therapy should be reserved for patients whose condition deteriorates (add-on therapy) or should be started up front. This paradigm resembles the "induction" therapy used in cancer treatment, followed by maintenance therapy with one or more agents once patients have improved. Both approaches have theoretical advantages and disadvantages. In the add-on therapy approach, physicians must follow their patients very closely to avoid a delay in initiating more aggressive therapy should patients not improve or worsen. A lack of improvement in functional class with treatment and development of class IV symptoms are both associated with a very poor prognosis. However, employing an up-front combination regimen may expose patients to unnecessary drug-drug interactions, toxicity, and higher costs.

An interesting study conducted in Europe adopted a rigorous algorithm employing the approach of add-on therapy. In this "goal directed" trial, Hoeper et al enrolled 123 con-

secutive PAH patients.[28] Goals of therapy included improvement in 6MWD to more than 380 meters, peak systolic blood pressure greater than 120 mmHg during exercise testing, and a peak $VO_2$ greater than 10.4 $mL \times min^{-1} \times kg^{-1}$. Patients were evaluated every 2 to 6 months. If the goals of therapy were not met, another therapy was added and the patient was reassessed. Therapies were instituted in the following order: bosentan, sildenafil, inhaled iloprost, and transition to intravenous iloprost, then referral for urgent lung transplantation as a last resort. At entry to the study 98 patients were in functional class III and 25 patients were in class IV. Using this algorithm, reported survival was 93%, 83%, and 79.9% at 1, 2, and 3 years, respectively. This was an improvement in survival compared to pre-2000 era historical PAH controls at the same center. It is important to note that monotherapy failed in 43% of patients in this study, 16% required three-drug combination therapy, and 5% were treated with intravenous prostanoids after triple therapy failed.

**Because PAH is a rare disease, it is difficult to adequately power therapeutic trials to evaluate significant morbidity or mortality differences between various drug therapies. At this point, it is premature to either dismiss or strongly favor any one combination of therapies over another. Careful design of future trials testing these comparisons is vital.**

## Where Are We Now?

The studies discussed above all have made important contributions toward our understanding of the treatment of patients with PAH. As a whole they suggest that combination therapy is well tolerated and may be beneficial in certain groups of patients. Randomized controlled trials have demonstrated the efficacy of an intravenous prostacyclin analog combined with a PDE5 inhibitor (PACES) and an inhaled prostanoid combined with an ETRA (STEP) as add-on therapies. However, a combination of an intravenous prostanoid and an ETRA started concomitantly (BREATHE 2) did not demonstrate efficacy. While the data on combination therapies are still in their infancy, PAH physicians are faced with the practical dilemma of how to treat patients who do not improve significantly or who deteriorate with monotherapy. Preliminary results from the REVEAL registry, presented at the American College of Chest Physicians meeting in October 2007 provided a glimpse of current clinical practice in the United States.[29] Among the first 1226 PAH patients enrolled, only 47% were being treated with monotherapy (bosentan 13%; sildenafil 13%; intravenous epoprostenol 8%; sitaxsentan 2%; and calcium channel blockers 4%). A significant percentage (36%) are receiving two-drug combination therapy (intravenous epoprostenol plus sildenafil 8%; bosentan plus sildenafil 8%; bosentan plus epoprostenol 3%; bosentan plus inhaled iloprost 3%; and sildenafil plus inhaled iloprost 2%), and 9% receive three or more PAH-specific medications. Therefore, in the absence of rigorous evidence supporting multidrug therapy, a diverse array of combination strategies has emerged into clinical practice.

It is clear that there remain significant shortcomings in our understanding of the use of combination therapy in PAH. Most of the available trials to date have included only small numbers of patients. Many of these trials were open label and not randomized. The potential for publication bias exists, as negative studies are less likely to be published. A number of questions remain unanswered as we strive to improve outcomes with PAH treatment.

## The Future of Combination Therapy

Because PAH is a rare disease, it is difficult to adequately power therapeutic trials to evaluate significant morbidity or mortality differences between various drug therapies. At this point, it is premature to either dismiss or strongly favor any one combination of therapies over another. Careful design of future trials testing these comparisons is vital. We hope that the future will provide the answers as to which combinations are most effective, the appropriate timing of combination therapy, the identification of subgroups of patients who may respond to particular combinations, as well as establishing the cost-effectiveness of various combination therapies. ■

*Acknowledgments.* We thank Dr. Joel Wirth for assisting with the tables.

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