

# The Current State and Future Promise of Prostacyclin Therapy for Pulmonary Arterial Hypertension

a report by

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Pulmonary circulation plays a pivotal role in the cardiopulmonary functions of gas exchange and oxygen transport, but is vulnerable to injury from developmental or acquired disorders affecting the heart and/or lungs. One of the most serious and potentially devastating chronic disorders of the pulmonary circulation is pulmonary hypertension (PH). This hemodynamic abnormality has diverse etiologies, challenging physicians both diagnostically and therapeutically. Most specialists in this field still accept the definition of PH as outlined by the National Institutes of Health (NIH) Registry on Primary Pulmonary Hypertension (now termed idiopathic pulmonary arterial hypertension, IPAH), as a mean pulmonary artery pressure (mPAP) >25mmHg with a pulmonary capillary wedge or left atrial pressure <15mmHg as measured by cardiac catheterization.<sup>1</sup> The classification of PH was most recently revised in 2003, based on the 2003 World Health Organization (WHO) meeting in Venice, Italy. Appropriate classification, combined with determination of severity, aids in directing therapy.

Irrespective of its etiology, PH is a serious and often progressive disorder that can result in right ventricular dysfunction, impairment of exercise tolerance, and death. The pathogenesis is complex, still incompletely understood, and thought to be affected by genetic and environmental factors that alter vascular structure and function. Dramatic advances in the treatment of PAH have occurred over the past 15 years based on improved understanding of its pathogenesis in the research laboratory and extensive PAH clinical trials. These efforts have led to US Food and Drug Administration (FDA) approval of three prostanoids (epoprostenol, treprostinil, and iloprost), two endothelin receptor antagonists (bosentan and ambrisentan), and a phosphodiesterase-5 inhibitor (sildenafil). Not all countries, however, have access to all of them. Calcium channel blockers have proven effective, but only in the minority of patients who are 'vasodilator responders' at right-heart catheterization. Our focus will primarily be Group I patients—i.e. those with PAH—and how prostanoid therapy is used in these individuals.

## Prostacyclins

Eicosanoids are the 20-carbon essential fatty acids derived from arachidonic acid. This family of biologically active mediators includes the prostacyclins (prostaglandin I<sub>2</sub>, PGI<sub>2</sub>), thromboxanes, and leukotrienes. Epoprostenol and the structurally related compounds treprostinil, iloprost, and beraprost are collectively referred to as prostanoids. Prostacyclins are produced in endothelial cells from prostaglandin H<sub>2</sub> (PGH<sub>2</sub>) by the action of the enzyme prostacyclin synthase. These drugs are potent vasodilator agents that inhibit platelet aggregation. Epoprostenol has been studied extensively in the laboratory, and recent observations suggest its role as a mediator of vascular remodeling.<sup>3</sup>

The parenteral prostacyclins include intravenous (IV) iloprost (not available in

the US), IV epoprostenol, and subcutaneous and IV treprostinil. These are generally reserved for patients with more advanced disease. An approach to choosing PH therapy is outlined in *Table 1*, offering a general guide as to when more aggressive (parenteral) prostanoid therapy should be considered.

These drugs cause characteristic adverse effects, particularly when administered parenterally. These include headache, flushing, nausea, diarrhea, jaw pain, and, particularly with more long-term treatment, leg or foot pain. Dose escalation can often be slowed and/or a lower dose can be targeted, which may alleviate or better control these symptoms. Chronic leg and foot pain can often be controlled with gabapentin; narcotics are rarely needed. Parenteral prostacyclins should be administered by physician/nursing teams with expertise in this area. Patients must be closely monitored by outpatient visits and by telephone.

## Epoprostenol

This was the first prostanoid shown to be promising based on laboratory studies. It is unstable at normal body pH and has a very short half-life, requiring continuous IV infusion through a central venous catheter. Side effects can include jaw pain, headache, flushing, nausea, diarrhea, and vomiting. This drug has been used in severe PAH by the continuous IV route since the early to mid-1990s. Patients are generally admitted to the hospital to begin this drug, and a central catheter is placed for delivery. The drug is initiated and intense teaching is undertaken regarding the drug and its side effects, use of the delivery pump, and central-line care. Patients are taught to be vigilant for line infections and remain in contact with their physician/nursing team regarding the above issues. The target dose of IV epoprostenol is in the range of 40ng/kg/min; it generally takes more than six weeks to achieve this.

## Clinical Trials

There have been three randomized, controlled studies comparing prostacyclin with conventional treatment. In 1996, Barst et al. reported a 12-week prospective, randomized, multicenter trial comparing the effects of continuous IV infusion of epoprostenol plus conventional therapy with those of conventional therapy alone in 81 patients with severe IPAH who were functional class III or IV. The conventional therapy included oral calcium channel blockers, anticoagulation, diuretics, digoxin, and oxygen. Exercise capacity improved in the 41 patients treated with epoprostenol—median 6-minute walk test (6MWT) distance 362m at 12 weeks versus 315m at baseline—and decreased in the 40 patients treated with conventional therapy alone—median 6MWT distance 204m at 12 weeks versus 270m at baseline (p=0.002 for comparison of the treatment groups). There were also improvements in quality of life, hemodynamics, and survival.<sup>4</sup> In 2000, Badesch et al.<sup>2</sup> reported a multicenter, randomized, controlled, open-label

**Table 1: Determining Therapy for Pulmonary Arterial Hypertension**

Lower Risk (consider oral therapy)	Determinants of Risk*	Higher Risk† (consider parenteral therapy)
No	Clinical RV failure‡	Yes
Gradual	Progression	Rapid
II, III	WHO class§	III, IV
Longer (>400m)	6MWT distance	Shorter (<300m)
Minimal or none	Oxygen requirement	Moderate or high
Minimally elevated	NT-pro-BNP	Significantly elevated
Minimal RV enlargement and dysfunction	Echocardiographic findings	Severely enlarged, hypofunctional RV Pericardial effusion
Normal/near normal RAP and CI	Hemodynamics¶	High RAP, low CI

RV = right ventricular; WHO = World Health Organization; 6MWT = 6-minute walking test; NT-pro-BNP = N-terminal pro-brain natriuretic peptide; RAP = right atrial pressure.  
 \* While no one parameter may influence decisions in all cases, hemodynamics often have the most profound influence on the decision to proceed to aggressive, parenteral therapy, or to be more conservative and employ oral therapy. The use of inhaled therapy may be less straightforward, but it is often added when a patient fails to improve on oral therapy yet is not deemed advanced enough for parenteral treatment.  
 † There is no clear algorithm for choice of prostacyclin analog. Some clinicians feel that epoprostenol should be used in patients with the most advanced disease based on available mortality data. Treprostinil does have several advantages over epoprostenol (see text).  
 ‡ Edema, ascites, hepatic congestion, neck vein distension, right-sided S3.  
 § Most patients have class II or III symptoms. A patient may have advanced symptoms and yet not actually be class IV. Advanced class III patients may be appropriate for parenteral therapy. Class III is sometimes divided into class IIIa and class IIIb, but the true implications of such a division have not been prospectively validated.  
 ¶ A cardiac index of <2l/min/m<sup>2</sup> or a right atrial pressure of >20mmHg have been associated with a particularly poor prognosis.  
 Modified from: McLaughlin VV, McGoon MD, *Circulation*, 2006;114:1417–31.

12-week trial of long-term IV epoprostenol treatment in 111 patients with moderate to severe PAH occurring in the setting of the scleroderma spectrum of disease. Exercise capacity improved with epoprostenol—median 6MWT distance 316m at 12 weeks compared with 270m at baseline—but decreased with conventional therapy—median 6MWT 192m at 12 weeks compared with 240m at baseline. The difference between treatment groups in the median distance walked at week 12 was 108m (95% confidence interval (CI) 55.2–180; p=0.001). Hemodynamics also improved; however, a survival advantage was not demonstrated. Trends suggesting greater improvement in severity of Raynaud’s phenomenon and fewer new digital ulcers were seen in the epoprostenol group.<sup>5</sup> Two large, long-term observational series have documented an improvement in survival in patients with IPAH treated with epoprostenol compared with either historical control subjects or predicted survival based on the NIH Registry equation.<sup>6,7</sup>

## Treprostinil

This synthetic prostacyclin analog is approved for the treatment of PAH in patients with New York Heart Association (NYHA) class II, III, or IV symptoms as a continuous subcutaneous or IV infusion, with the IV route utilized when subcutaneous infusions are not tolerated. Intolerance of subcutaneous delivery is common. As with epoprostenol therapy, treprostinil is most commonly used in patients with advanced class III or IV symptoms together with hemodynamics and a 6MWT distance that parallel these symptoms.

Treprostinil has a more favorable administration profile than epoprostenol. The subcutaneous delivery system utilizes a smaller pump and is less cumbersome than a central venous line access; associated complications such as sepsis, thrombosis, and the risk of a major delivery disruption are thus avoided. Unfortunately, local infusion-site pain is quite common and may be

intolerable in a substantial proportion of patients, even with supportive management. IV treprostinil compares favorably with epoprostenol as it is stable at room temperature (alleviating the need for ice-packs) and has a longer half-life, which increases safety in the event of delivery system malfunctions. The 48-hour infusion interval allows for medication preparation and cassette changing every other day. The target dose of IV treprostinil is at least twice that of epoprostenol—i.e. usually at least 80ng/kg/min. Drug initiation and teaching protocols are similar to those for epoprostenol.

While treprostinil has been used in patients with advanced PAH, many experts feel that the ‘sickest’ PAH patients, i.e. those with unfavorable hemodynamics and a rapidly progressive symptom complex, merit IV epoprostenol based on a proven mortality benefit.<sup>4</sup> In addition, there could be an increased rate of Gram-negative bloodstream infections among patients with PAH treated with IV treprostinil compared with epoprostenol.<sup>8</sup> The latter data, however, were not collected in a controlled manner, so this possibility has not been verified.

## Clinical Trials

Simonneau and colleagues<sup>9</sup> reported a 12-week, double-blind, placebo-controlled multicenter trial comparing subcutaneous treprostinil with conventional therapy in 470 patients with functional class II, III, or IV PAH. These patients had PAH that was idiopathic, associated with connective tissue disease, or with congenital systemic-to-pulmonary shunts. Improved exercise capacity as measured by the 6MWT distance was demonstrated by a median between-treatment-group difference of 16m (p=0.006). Improvement in exercise capacity was greater in the sicker patients and was dose-related, but was independent of disease etiology. Concomitantly, treprostinil significantly improved indices of dyspnea, symptoms and signs of PH, and hemodynamics.<sup>9</sup>

Tapson and associates<sup>10</sup> investigated the safety and efficacy of continuous IV treprostinil in patients with PAH in a 12-week, prospective, open-label, uncontrolled, multicenter trial in 16 functional class III or IV IPAH patients, or those with PAH related to connective tissue disease or congenital heart disease. 6MWT distance (mean ± standard error, SE) increased by 82m from baseline (319±22m) to week 12 (400±26m; n=14; p=0.001). There were also significant improvements in the secondary end-points of Naughton-Balke treadmill time (p=0.007), Borg dyspnea score (p=0.008), and hemodynamics (mPAP: p=0.03; cardiac index: p=0.002; pulmonary vascular resistance (PVR): p=0.001) at week 12 compared with baseline. These results are very optimistic, but it should be emphasized that this was not a randomized study. One death, which was unrelated to the study drug, occurred during the 12-week study in a patient who received three days of IV treprostinil and died two weeks later.<sup>10</sup> In a similar open-label trial, Gomberg-Maitland et al.<sup>11</sup> transitioned 31 functional class II and III PAH patients from IV epoprostenol to IV treprostinil. Twenty-seven patients completed the 12-week study, and four patients were transitioned back to epoprostenol. Exercise endurance as measured by the 6MWT distance was maintained among the patients completing the transition (438±16m at baseline and 439±16m at week 12, ± standard deviation, SD). At week 12, there was a modest increase in mPAP of 4±1mmHg (p<0.01) and a reduction in cardiac index of 0.4±0.1l/min/m<sup>2</sup> (p=0.01). Notably, the dose of IV treprostinil at the end of 12 weeks was more than twice the dose of IV epoprostenol at the start of the study: 83 versus 40ng/kg/min.<sup>11</sup>

In 2004, the FDA approved the use of IV treprostinil in NYHA functional class II, III, and IV PAH patients in whom subcutaneous infusion is not tolerated. Barst and associates<sup>12</sup> reported the effects of subcutaneous treprostinil

followed by the addition of other therapies if needed in 860 PAH patients for up to four years. Of the 860 patients, 199 (23%) discontinued due to adverse events, 136 (16%) died, 117 (14%) discontinued due to deterioration, 29 (3%) withdrew consent, and 11 (1%) underwent transplantation. In total, 97 patients (11%) switched from treprostinil to an alternative prostacyclin analog. Bosentan was added in 105 patients (12%) and sildenafil in 25 (3%). Survival was 87% at one year and 68% at four years for all 860 patients, and nearly identical for patients on subcutaneous treprostinil monotherapy. For the IPAH subset with baseline hemodynamics (n=332), survival was 91% at one year and 72% at four years. In contrast, predicted survival for IPAH using the NIH formula was 69 and 38% for years one and four, respectively. The rate of adverse effects was 23%, with 94% of these being pain at the infusion site.<sup>12</sup>

### **Iloprost**

This is a synthetic stable analog of epoprostenol that can be delivered via IV or inhaled routes. The IV preparation is not approved in the US. The inhaled form was approved by the FDA in 2004. Iloprost has a relatively short half-life (20–30 minutes) and requires six to nine inhalations daily through a hand-held nebulizer device, with each treatment taking at least five to 10 minutes. Typically, patients do not interrupt sleep for their inhaled treatments.

### **Clinical Trials**

IV use of iloprost has been evaluated in only two small studies, suggesting similar acute and intermediate-term (seven weeks) improvement in hemodynamic response and exercise tolerance compared with epoprostenol.<sup>13,14</sup> The first of these was by Olschewski et al.,<sup>15</sup> who compared inhalations of iloprost six to nine times daily with inhalation of placebo in 203 patients with selected forms of severe PAH or chronic thromboembolic PH with functional class III or IV symptoms in spite of conventional therapy. This three-month randomized, double-blind, placebo-controlled, multicenter trial utilized a composite primary end-point of a 10% improvement in 6MWT distance and functional class improvement in the absence of clinical deterioration or death. This composite end-point was achieved in 17% of treated patients compared with 5% of patients receiving placebo (p=0.007). The treatment effect on 6MWT distance was a mean increase of 36m in the overall population in favor of iloprost (p=0.004) and 59m in the subgroup of patients with IPAH. This study also found statistically significant improvement in hemodynamics (p<0.001), NYHA functional class (p=0.03), dyspnea (p=0.015), and quality of life (p=0.026).<sup>15</sup>

In the second, more recent, study, Opitz et al.<sup>16</sup> evaluated the long-term clinical efficacy of inhaled iloprost as first-line monotherapy in patients with IPAH. Clinical, hemodynamic, and exercise parameters were obtained at baseline, after three and 12 months of therapy, and yearly thereafter for five years prospectively in 76 IPAH patients with four end-points: death, transplantation, change to IV therapy, and addition of other active oral therapy. During this follow-up period, 11 patients (14%) died, six patients (9%) underwent transplantation, 25 patients (33%) were switched to IV prostanoids, 16 patients (23%) received additional oral PAH therapies, and 12 patients (17%) discontinued inhaled iloprost for other reasons. Event-free survival rates at one and two years were 53 and 29%, respectively.<sup>16</sup> While these long-term results may not appear optimal, it must be considered that this was a non-randomized study. At present, inhaled iloprost is most commonly utilized when oral therapy provides suboptimal results in a patient not deemed ill enough for IV therapy, or in some patients

who appear well enough to be weaned off IV therapy. However, weaning IV therapy is a scenario in which there is not a clear standard of care.

### **Beraprost**

Beraprost is a prostanoid that is stable at body temperature and gastric pH and was thought to be promising due to oral dosing. Okano et al.<sup>17</sup> reported an improvement in mean PVR from 19.3 to 14.3 Wood units, and an improvement in mPAP from 66 to 58mmHg in 10 of the 12 WHO class III or IV IPAH patients after two months of oral beraprost. A long-term benefit of at least one functional class was observed in eight patients with a mean follow-up of five months. The remaining four patients died of progressive disease.<sup>17</sup> Galie et al.<sup>18</sup> reported the results of a randomized, double-blind, placebo-controlled, multicenter study designed to determine the effects of 12 weeks of oral administration of beraprost sodium on exercise capacity, symptoms, and cardiopulmonary hemodynamics in 130 NYHA class II and III patients with PAH. The mean difference in 6MWT distance between the two groups was 25m (p=0.036) at 12 weeks. There were no statistically significant differences in either cardiopulmonary hemodynamics or functional class.<sup>18</sup> Another double-blind, randomized, placebo-controlled study in 116 PAH patients with oral beraprost failed to show long-term improvement.<sup>19</sup> This medication has not been approved by the FDA.

### **Combination Therapy With Prostacyclins**

Combination therapy is an appealing and promising concept that is being studied in randomized clinical trials.<sup>20</sup> It has a sound scientific basis, with multiple available agents working through different mechanisms. Nonetheless, properly designed studies are required to prove the benefit of this approach.

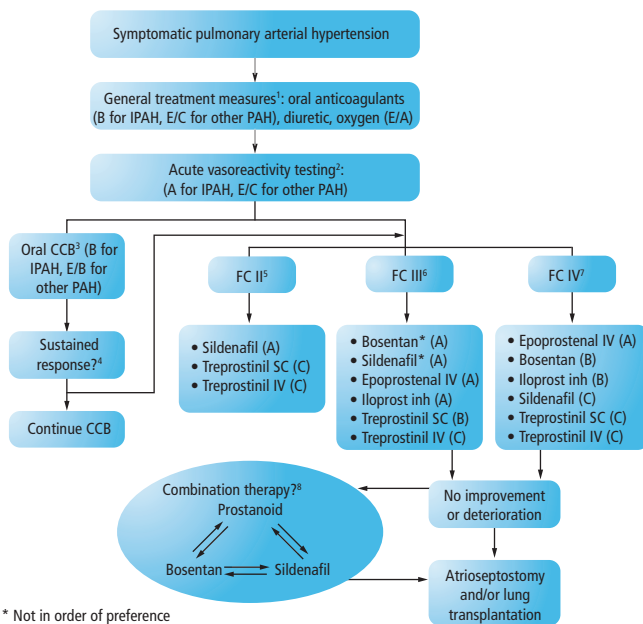
### **Intravenous Epoprostenol and Oral Bosentan Combination Therapy (The BREATHE-2 Trial)**

In a double-blind, placebo-controlled prospective study, 33 patients with PAH on epoprostenol therapy were randomized for 16 weeks in a 2:1 ratio to bosentan 62.5mg twice daily for four weeks then 125mg twice daily, or placebo.<sup>21</sup> At the end of 16 weeks, there was a trend suggesting greater improvement (although statistically non-significant) with the combination treatment in all measured hemodynamic parameters. Total pulmonary resistance declined by 41% from baseline to week 16 of treatment (from 1,697±142 to 1,016±78dyn/s/cm<sup>2</sup>) in the bosentan–epoprostenol group compared with 23% in the placebo–epoprostenol group (p=0.08). Cardiac index rose by 49% in the bosentan–epoprostenol group compared with 38% in the placebo–epoprostenol group. mPAP fell by 9% (versus 2%) and PVR declined by 35% (versus 26%) in the bosentan–epoprostenol group. Functional class improved in 59% of patients receiving combination therapy compared with 45% of patients receiving epoprostenol monotherapy.<sup>21</sup> In the combination group there were two deaths during the study and one death shortly after study drug withdrawal due to clinical worsening. There were no deaths in the placebo group.

### **Inhaled Iloprost and Oral Bosentan Combination Therapy (The STEP Trial)**

McLaughlin et al.<sup>22</sup> studied inhaled iloprost in patients who remained symptomatic (functional class III or IV) after receiving a stable dose of bosentan for at least three months. In this multicenter, placebo-controlled, randomized safety trial, 67 patients with PAH (94% NYHA functional class III, mean baseline 6MWT 355m) were randomized to receive inhaled iloprost six to nine times per day or placebo. After 12 weeks, the primary efficacy

**Figure 1: Treatment Algorithm for Pulmonary Arterial Hypertension (American College of Chest Physicians)**



measure—post-inhalation 6MWT distance—improved by 30m in the iloprost group and by 4m in the placebo group, for a placebo-adjusted difference of 26m ( $p=0.051$ ). There were also improvements in NYHA functional class ( $p=0.002$ ), time to clinical worsening ( $p=0.02$ ), post-inhalation mPAP ( $p=0.001$ ), and PVR  $p=0.001$ ). Although limited by a small sample size, this combination therapy appeared to be safe and well tolerated.<sup>22</sup>

### Intravenous Treprostinil and Oral Sildenafil Combination Therapy

Gomberg-Maitland and colleagues<sup>23</sup> reported an open-label pilot study assessing the impact of adding oral sildenafil to subcutaneous treprostinil among a cohort of nine stable PAH patients in modified WHO functional class II–IV. Change in exercise tolerance was the primary end-point. Treprostinil doses ranged from 35 to 90ng/kg/min. At the end of the study period patients demonstrated a statistically significant increase in mean treadmill times (using the Naughton-Balke protocol) from 465±167 seconds at baseline to 656±205 seconds after 12 weeks (42% increase;  $p=0.049$ ). Predictable prostanoid-type effects, including headache, flushing, and jaw discomfort, were reported. One patient withdrew because of onset of dyspnea and chest pain.<sup>23</sup> Such studies are too small for firm conclusions, but are promising.

### Inhaled Iloprost and Oral Sildenafil Combination Therapy

Ghofrani et al.<sup>24</sup> reported a very short-term randomized, controlled, open-label trial in 16 patients with NYHA stage III or stage IV PAH ( $n=16$ ), chronic thromboembolic PH ( $n=13$ ), or PH due to aplasia of the left pulmonary

artery ( $n=1$ ). All patients received inhaled nitric oxide and aerosolized iloprost (inhaled dose 2.8ug). They were then randomly assigned to receive 12.5mg of oral sildenafil, 50mg of sildenafil, 12.5mg of sildenafil plus inhaled iloprost, or 50mg of sildenafil plus inhaled iloprost. Hemodynamic measurements were monitored up to two hours after the doses. The 50mg dose of sildenafil plus iloprost, followed by 12.5mg of sildenafil plus iloprost, showed maximum reduction of PVR and maximum increase in cardiac index.<sup>24</sup> Improvements in symptoms and hemodynamics have also been suggested in small investigational studies with sildenafil in combination with subcutaneous treprostinil<sup>23</sup> and oral beraprost.<sup>25</sup>

Based on the available evidence, the American College of Chest Physicians (ACCP) recently published an algorithm for various treatment options (see Figure 1).<sup>2</sup> This algorithm indicates the particular functional class for which these therapies are approved; however, certain regimens—such as bosentan as initial therapy for class IV patients or treprostinil as initial treatment for class II patients—would not be typical approaches; class II patients are nearly always handled with oral regimens and class IV patients with parenteral therapy.

### Other Ongoing Trials

Several trials are ongoing that clearly the role of inhaled and oral prostanoids. The TRIUMPH study is a large, phase III, multinational, randomized, placebo-controlled trial examining the efficacy and safety of inhaled treprostinil as add-on therapy to bosentan or sildenafil. The FREEDOM-C study is a major trial using oral treprostinil in combination with an endothelin receptor antagonist and/or phosphodiesterase-5 inhibitor, while the FREEDOM-M study will compare oral treprostinil with placebo. Since parenteral prostacyclins have proved to be effective modes of therapy in very ill patients with PAH, gaining additional insight to the inhaled and oral routes will hopefully prove fruitful. The PACES study, in which patients on IV epoprostenol are randomized to sildenafil or placebo, is ongoing.

### Summary

The introduction of prostacyclins has significantly improved therapeutic options and survival in patients with PAH, irrespective of the etiology. These drugs have dramatically changed the face of PAH therapy. Based on quality of evidence, therapeutic benefit, and safety, IV prostanoids remain the medication of choice for PAH patients with advanced disease. In less severely ill functional class II and III patients, the choice should be based on clinical judgment, medication safety profiles, and, if possible, convenience. However, the reluctance of a patient with very advanced PAH to agree to parenteral therapy should be strongly countered. The parenteral and inhaled routes are cumbersome, but proven efficacy outweighs the inconvenience, particularly for parenteral therapy. Combination therapy appears to be the way of the future, and a number of trials are under way. Hopefully, future regimens will become increasingly effective, safe, and convenient. ■

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