Combination Therapy for PAH: Current Rationale, Future Concepts

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The prostanoids have revolutionized treatment of pulmonary arterial hypertension. Intravenous, subcutaneous, and inhaled formulations are approved for use in the United States, while oral preparations are being investigated (**Table**). Prostacyclin (PGI2; epoprostenol; Flolan) is an endothelium-derived prostaglandin with potent pulmonary and systemic vasodilatory and antiplatelet aggregation properties.[1-6] Continuous intravenous epoprostenol has been widely used in patients with advanced idiopathic pulmonary arterial hypertension (IPAH), resulting in substantial clinical benefit and improvement in survival.[1-3] Favorable observations have also been made in other forms of pulmonary arterial hypertension,[4-6] although survival benefit in these diseases has not been clearly confirmed.[6] Despite the clear benefits, treatment with continuous intravenous epoprostenol has drawbacks. Because of its very short half-life (1 to 2 minutes), epoprostenol must be administered as a continuous infusion through a dedicated central venous catheter. Although life-threatening adverse effects of this drug and delivery system are rare, complications such as catheter-related thrombosis or infection, sepsis, and pump or intravenous-line malfunctions or mishaps can occur. Sudden discontinuation may cause severe symptoms and even death. In view of these issues, other modes of prostacyclin delivery have now been studied using stable prostacyclin analogues administered orally, by inhalation, or via the subcutaneous route.[7,8] The oral prostacyclin, beraprost, approved in Japan, is covered by Dr Badesch[9] in this issue. We will briefly review the initial clinical trials and then more recent data involving subcutaneous and intravenous treprostinil (Remodulin, previously UT-15), and then focus on newer data involving intravenous treprostinil. Subsequently, we will provide an update on inhaled prostanoids. Although the clinical trials for oral treprostinil are only now getting under way, we will offer the background and rationale for these studies.

Treprostinil: Background

Treprostinil sodium is a stable tricyclic benzidine analog of epoprostenol (prostacyclin) that is currently available in subcutaneous and intravenous formulations for the treatment of pulmonary arterial hypertension (inhaled and oral treprostinil are under investigation). This drug has pharmacologic actions similar to those of epoprostenol and it has been shown to have comparable acute hemodynamic effects.[8] Unlike epoprostenol, however, it is chemically stable at room temperature and neutral pH and has a longer half-life, permitting continuous subcutaneous administration in addition to the more recently studied and approved intravenous route.[10,11] The elimination half-life at steady state has been shown to be 4.4 hours for intravenous and 4.6 hours for subcutaneous treprostinil and the pharmacokinetics of this drug have been reviewed extensively.[10-12] Its major pharmacological actions are direct vasodilation of the pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation.[13,14] Treprostinil is metabolized extensively by the liver, and the majority of the metabolites are excreted in the urine with 4% excreted unchanged. Treprostinil has not been studied in patients with renal insufficiency. Treprostinil is rated category B for pregnancy, with no human data available. It is unknown if the compound is excreted in breast milk. No long-term data are available on the carcinogenic or mutagenic potential of treprostinil. There has been no proven change in the binding, concentration, or pharmacokinetics of digoxin or warfarin.[15] Adverse effects of subcutaneous or intravenous treprostinil are similar to those commonly associated with other prostanoids[1,6,9] and include headache, diarrhea, flushing, and jaw and foot or leg pain, as well as infusion site pain with subcutaneous delivery. As with epoprostenol, rapid up-titration may cause hypotension, flushing, nausea, vomiting, diarrhea, dizziness, and anxiety or restlessness.

Subcutaneous Treprostinil

The drug was first studied in large clinical trials via the subcutaneous route. It is initiated at approximately 1 to 2 ng/kg/min. The infusion rate should be increased in increments of no more than 1.25 ng/kg/min per week for the first 4 weeks and then no more than 2.5 ng/kg/min per week for the remaining duration of the infusion, depending on clinical response as tolerated.[16-17] While early studies[18] have suggested that low doses of subcutaneous treprostinil are effective, longer-term subcutaneous studies have utilized higher dosages (approximately 40 ng/kg/min)[19] and intravenous studies suggest that much higher dosages (80 to

120 ng/kg/min) may be required.[20,21] An international 12-week double-blind placebo-controlled multicenter trial of 470 patients with pulmonary arterial hypertension was completed in 1999, clearly proving the efficacy of the drug and leading to FDA approval in May 2002 for patients with New York Heart Association (NYHA) functional class II-IV pulmonary arterial hypertension.[18] Importantly, infusion-site pain occurred in 85% of patients, was deemed severe in 38%, and led to discontinuation in about 8%. Subsequently, the subset of 90 patients with connective tissue disease from the above randomized multicenter trial was examined and, on the basis of hemodynamic and symptomatic improvement, continuous subcutaneous treprostinil appeared beneficial in this specific population of patients with pulmonary arterial hypertension.[22]

The modest improvement (16 meters on 6-minute walk testing) noted in the pivotal subcutaneous treprostinil trial[18] as opposed to improvement (47 and 99 meters in IPAH and scleroderma patients, respectively) noted in epoprostenol trials may be related to functional class since those patients with more severe disease tend to achieve the greatest benefit.[16,18] Underdosing may be a critical factor in the modest clinical response that was obtained. Additional studies have suggested that stable patients receiving continuous intravenous epoprostenol could be effectively transitioned to subcutaneous treprostinil,[23] potentially solving recurrent difficulties with intravenous line infections or other access-related problems, and facilitating delivery in view of the smaller pump and simpler delivery system. Current clinical use of subcutaneous treprostinil includes de novo initiation (initial therapy), addition to an existing nonprostanoid regimen, and conversion from intravenous epoprostenol.

The primary problem in clinical practice has been pain at the subcutaneous site of delivery, sometimes requiring analgesia or discontinuation of the drug. Less frequent needle site changes may help. However, a recent retrospective multicenter European trial with long-term follow-up has suggested both efficacy and excellent tolerance with sustained use of subcutaneous treprostinil.[19] Ninety-nine patients with pulmonary arterial hypertension and 23 patients with inoperable chronic thromboembolic pulmonary hypertension in NYHA functional class II-IV were followed for a mean of 26.2 ± 17.2 months (range, 3 to 57 months). At 3 years significant improvements from baseline were observed in mean 6-minute walk distance (305 ± 11 to 445 ± 12 meters; $P = .0001$), Borg dyspnea score, and NYHA functional class; the mean dosage was 40 ± 2.6 ng/kg/min (range, 16 to 84 ng/kg/min). The drug was well tolerated, and local pain at the subcutaneous site accounted for treatment interruption in only 5% of the cases. Survival was 88.6% and 70.6% at 1 year and 3 years, respectively. While the study reinforces the earlier pivotal trial data,[18] it is limited by its retrospective, open-label design.

Intravenous Treprostinil

In view of difficulty with site pain with subcutaneous treprostinil in some patients, the use of continuously infused intravenous treprostinil has been prospectively evaluated. The pharmacokinetics for the intravenous route have been discussed above. Intravenous treprostinil must be diluted in sterile water or normal saline prior to infusion and is stable for 48 hours at room temperature; ice packs are not required as with epoprostenol. Gomberg-Maitland and colleagues[20] evaluated the safety and efficacy of transitioning pulmonary arterial hypertension patients from intravenous epoprostenol to intravenous treprostinil over a 24-to-48-hour period. The intravenous treprostinil dose was adjusted to minimize pulmonary hypertension symptoms as well as side effects. Of the 31 patients, 27 completed the protocol, with 4 requiring transitioning back to epoprostenol. The 6-minute walk distance, Naughton-Balke treadmill test time, functional class, and Borg score were all maintained with intravenous treprostinil at week 12 compared with intravenous epoprostenol prior to transition. At week 12, mean pulmonary artery pressure increased by 4 ± 1 mmHg (n = 27; $P < .01$), cardiac index decreased by 0.4 ± 0.1 L/m/m^2 (n = 27; $P = .01$), and pulmonary vascular resistance increased by 3 ± 1 Wood units/m^2 (n = 26; $P < .01$). Whether the latter hemodynamic changes are clinically meaningful or not remains unclear. The dosage of treprostinil at hospital discharge was 47 ± 24 ng/kg/min (range, 15 to 115 ng/kg/min) and at 12 weeks was 83 ± 38 ng/kg/min (range, 24 to 180 ng/kg/min). It is feasible that some patients were underdosed as the appropriate dose of treprostinil may be two to three times that of epoprostenol.[20,21] No serious adverse events were attributed to treprostinil. These data suggest that transition from intravenous epoprostenol to intravenous treprostinil is safe and effective; preliminary long-term follow-up data are submitted for publication.[24]

Intravenous treprostinil has proved effective in an open-label study in which patients not previously treated with a prostacyclin (de novo patients) were treated with intravenous treprostinil.[21] The 6-minute walk distance increased by 82 meters from baseline to week 12 (319 ± 22 to 400 ± 26 meters; n = 14; $P = .001$). There were also significant improvements in the secondary end points of Naughton-Balke treadmill time, Borg dyspnea score, and hemodynamics at week 12 compared with baseline. Side effects were mild and consistent with those reported with epoprostenol

Table. Prostanoid Regimens for Pulmonary Arterial Hypertension*

Drug		
Generic name	**Brand name**	**Route**
Epoprostenol	Flolan	Intravenous
Treprostinil†	Remodulin	Intravenous Subcutaneous
Iloprost	Ventavis	Inhaled Intravenous
Beraprost		Oral

*All regimens are Food and Drug Administration-approved in the United States except for intravenous iloprost and oral beraprost.
†Treprostinil is currently under investigation in international trials via the inhaled and oral routes.

treatment. While there were no specific guidelines on how quickly to titrate up, the dose was increased approximately three times per week in 1 to 2 ng/kg/min increments (approximately 3 to 6 ng/kg/min per week). At week 12 the mean dosage was 41 ± 4 ng/kg/min (range, 20 to 62 ng/kg/min) in the 14 patients completing the 12-week study. As in the transition study,[20] it appeared that higher doses of treprostinil were necessary compared with those achieved in the pivotal subcutaneous treprostinil trial.[18] Current use of intravenous treprostinil suggests the need for dosing at approximately 80 to 120 ng/kg/min to optimize symptoms. Further studies and clinical experience will clarify dosing. A preliminary study of treprostinil delivered via a miniaturized infusion (407C) pump indicates that this delivery modality is promising and might make intravenous therapy less cumbersome.[25] Treprostinil for intravenous administration was FDA approved in November 2004. While it is approved for functional class II-IV patients, class II patients are generally treated with oral and/or inhaled therapy.

Intravenous Iloprost

Although intravenous iloprost is not approved in the United States for use in pulmonary arterial hypertension, it has been studied[26-28] and is available in some countries. No data are available comparing intravenous iloprost to intravenous epoprostenol; far more data are available with the latter drug. Data from Germany suggest potential efficacy as salvage therapy in patients in whom inhaled iloprost therapy has failed.[28] Iloprost has the advantage of being much more stable than epoprostenol[29] and the longer half-life could help prevent the potential consequences of interruption of drug supply.

Who Should Receive Parenteral Prostanoid Therapy, and Which Route?

The sickest pulmonary arterial hypertension patients, ie, those with poor hemodynamics and rapid progression of symptoms, merit intravenous epoprostenol on the basis of proven mortality benefit.[1] However, intravenous or subcutaneous treprostinil may, in fact, be suitable for certain selected late class III and class IV patients; such patients should be observed carefully and changed to intravenous epoprostenol if there is any concern. Patients with advanced disease were included in the de novo intravenous treprostinil study[21] although it was a small, uncontrolled study. Subcutaneous or intravenous treprostinil is appropriate in less severely ill individuals, particularly those who are not responding to oral and/or inhaled therapy.[16,30] It is possible that non-IPAH patients with pulmonary arterial hypertension may respond differently to different prostanoids, but this has not been proved.[4] If site pain from subcutaneous treprostinil can be tolerated, it is easier for the patient than the intravenous route. If it cannot be tolerated and advanced disease precludes oral and/or inhaled therapy, intravenous treprostinil or epoprostenol should be considered. Although no single infusion site pain remedy is effective in all patients, topical hot or cold packs, lidocaine patches, oral analgesics, anti-inflammatory creams, and pluronic lecithin organogel have met with some success.[31] Another potential adverse effect is the possible increased incidence of gram-negative bacteremia in patients receiving intravenous treprostinil. This is currently being investigated.

Inhaled Prostanoid Therapy

Inhaled iloprost

Inhaled therapy for pulmonary arterial hypertension offers the potential for selectivity of the hemodynamic effects to the pulmonary vasculature, avoiding the difficulties and potential systemic adverse effects associated with parenteral therapy. Iloprost is a prostacyclin analogue and has the same biologic profile as the natural substance with respect to prostaglandin receptor binding and cellular effects.[29] For long-term therapy, repetitive inhalations of iloprost are administered at least six times daily. Each treatment may take up to 10 and occasionally 15 minutes.

In patients with severe pulmonary arterial hypertension, inhalation of aerosolized iloprost has been shown to result in a substantial decrease in mean pulmonary arterial pressure and pulmonary vascular resistance, concomitant with an increase in cardiac output, in the absence of significant systemic arterial pressure drop and ventilation-perfusion mismatch.[32,33] In uncontrolled studies, inhaled iloprost was effective in decompensated right ventricular failure,[34] and showed favorable long-term hemodynamic improvement.[35]

While the large randomized double-blind placebo-controlled European multicenter (Aerosolized Iloprost Randomized; AIR) study[36] was published more than 5 years ago, it was a pivotal trial, leading to FDA approval of inhaled iloprost in the United States in December 2004. This trial included 203 patients with IPAH or pulmonary arterial hypertension occurring in association with appetite-suppressant use, connective tissue disease, or nonoperable chronic thromboembolic pulmonary hypertension. Approximately 50% of patients had IPAH; 60% were in functional class III and 40% were in functional class IV. The primary end point of the study was a composite of improvement in NYHA functional class; at least 10% improvement in the 6-minute walk test; and no deterioration or death. This end point was reached by more than three times as many patients in the iloprost group than in the placebo group (16.8% vs 4.9%; $P = .007$). The 6-minute walk test results favored the iloprost group, with an improvement of 36.4 meters compared with placebo ($P < .01$) and hemodynamics significantly deteriorated in the placebo group. In general, the drug was well tolerated.

A more recently published open-label uncontrolled German study assessed the long-term clinical efficacy of inhaled iloprost as first-line vasodilator monotherapy in 76 patients with symptomatic IPAH.[37] Clinical, hemodynamic, and exercise parameters were obtained at baseline, after 3 and 12 months of therapy, and yearly thereafter. Event-free survival at 3, 12, 24, 36, 48, and 60 months was 81%, 53%, 29%, 20%, 17%, and 13%, respectively. More recent investigations with combinations of inhaled iloprost and oral therapy make firm extrapolation of this monotherapeutic approach to current clinical practice unclear.[38-41] Clinical trials of combination therapy are clearly on the rise. The STEP trial is a randomized double-blind placebo-controlled safety trial that also studied the effects of 12 weeks of treatment with inhaled iloprost in 65 patients with pulmonary arterial hypertension already being treated with bosentan.[18] In this trial the change in 6-minute walk distance

from baseline was +4 meters in the control group and +30 meters in the iloprost group, resulting in a placebo-adjusted difference of +26 meters in favor of the iloprost group (P = .051). This study, as well as other combination trials of bosentan or sildenafil with inhaled iloprost, is covered by Dr. Hoeper elsewhere in this issue.[38]

The VISION study (sildenafil plus inhaled iloprost) is a multicenter international trial evaluating the safety and effectiveness of adding iloprost or placebo to sildenafil therapy in pulmonary arterial hypertension.[42] The study will also examine whether patients taking sildenafil can reduce the number of iloprost inhalations from the approved six doses per day to four doses per day. The primary end point will be change in 6-minute walk distance from baseline following 16 weeks of combination therapy. This study has important implications in potentially facilitating the use of inhaled iloprost.

In summary, inhaled iloprost offers potential efficacy while minimizing the systemic effects of prostanoids as well as the problems with intravenous access. This is particularly attractive in settings in which systemic hypotension is of particular concern. In severely ill patients with very poor right ventricular function and low cardiac output, however, intravenous prostanoid therapy remains the treatment of choice. Medical therapy should probably not be considered as having failed unless intravenous epoprostenol has failed. Patients whose condition deteriorates despite a combination of inhaled iloprost and endothelin antagonists or phosphodiesterase-5 inhibitors should be transitioned to continuous prostanoid therapy.

Inhaled treprostinil

Increasing data are available with inhaled treprostinil.[43,44] Potential advantages of this drug include less frequent and more rapid administration than for inhaled iloprost. Data from Germany on three clinical studies of 123 patients examining the effects of inhaled treprostinil have been published together, utilizing right heart catheterization.[43] These included a randomized crossover-design study of 44 patients, a dose-escalation study of 31 patients, and a study of reduction of inhalation time with a fixed dose of treprostinil in 48 patients. The primary end point was change in pulmonary vascular resistance, and the mean pulmonary arterial pressure of the enrolled population was approximately 50 mmHg in these studies. In the randomized study, both treprostinil and iloprost at an inhaled dose of 7.5 μg displayed a comparable pulmonary vascular resistance decrease, with treprostinil showing a more sustained effect on pulmonary vascular resistance (P < .0001) and fewer systemic side effects. In the dose-escalation study, effects of inhalation were observed for 3 hours and a near-maximal acute pulmonary vascular resistance decrease was observed at 30 μg of treprostinil. In the third study treprostinil was inhaled at increasing concentrations with a pulsed ultrasonic nebulizer, mimicking a metered dose inhaler. A dose of 15 μg treprostinil was inhaled with 18, 9, 3, 2 pulses, or 1 pulse, and each mode achieved comparable, sustained pulmonary vasodilation without significant side effects. Thus, the inhalation time could be reduced to one single breath of treprostinil solution. The results of these studies to date suggest favorable benefit with use of inhaled treprostinil.

The combination of oral therapy and inhaled treprostinil appears promising. Twelve patients remaining symptomatic at NYHA functional class III or IV despite being treated with oral bosentan for at least 12 weeks were treated with treprostinil via a hand-held ultrasonic single-breath inhalation device.[44] Two dosing regimens were evaluated: six inhalations four times daily, and nine inhalations four times daily. Each treatment was completed in approximately 1 minute. Inhaled treprostinil was associated with a peak (post-inhalation) 67 meter improvement in 6-minute walk distance at 12 weeks, based on results in 11 evaluable patients (P = .01). An improvement of 49 meters was observed at the trough period just before inhalation (P < .01). Significant improvement was also noted in hemodynamics and functional class. The results of this open-label study paved the way for the ongoing TRIUMPH trial, an international double-blind placebo-controlled clinical investigation exploring the efficacy and tolerability of inhaled treprostinil added to oral bosentan or sildenafil in patients with severe pulmonary arterial hypertension.[45] The primary outcome is change in 6-minute walk distance from baseline to week 12. Secondary outcomes include NYHA functional class, Borg dyspnea score, signs and symptoms of pulmonary arterial hypertension, and quality of life, as well as time to clinical worsening. This study is currently enrolling patients.[45]

When to Use an Inhaled Prostanoid

At present, FDA approval is only for iloprost. As with parenteral prostanoids, this modality appears to be appropriate for patients with an unsatisfactory response to oral therapy, although also potentially for transitioning (weaning) from parenteral therapy. No large studies yet support the latter indication. It is generally used in combination with oral therapy. Inhaled iloprost should not be considered to be equivalent to utilization of a continuous prostanoid.

Oral Treprostinil

Although oral beraprost is approved for pulmonary arterial hypertension in Japan, no oral prostanoid is currently FDA approved.[9] Clinical trials of oral sustained-release treprostinil are currently under way evaluating both monotherapy and combination therapy with phosphodiesterase-5 inhibitors and/or endothelin antagonists.[46,47] ■

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