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Prostanoid Therapy for Pulmonary Arterial Hypertension

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Prostanoids have played a prominent role in the treatment of pulmonary arterial hypertension (PAH). Several compounds and methods of administration have been studied: chronic intravenously infused epoprostenol, chronic subcutaneously infused treprostinil, inhaled iloprost, and oral beraprost. Chronic intravenous epoprostenol therapy has had a substantial impact on the clinical management of patients with severe PAH. It improves exercise capacity, hemodynamics, and survival in patients with idiopathic pulmonary arterial hypertension (IPAH). It also improves exercise capacity and hemodynamics in patients with PAH occurring in association with scleroderma. The complexity of epoprostenol therapy (chronic indwelling catheters, reconstitution of the drug, operation of the infusion pump, and others) has led to attempts to develop other prostanoids with simpler modes of delivery. Treprostinil, a stable prostacyclin analogue with a half-life of 3 h, has been developed for subcutaneous delivery. It has beneficial effects on exercise and hemodynamics, which depend somewhat on the dose achieved. This, in turn, is determined by the patient's ability to tolerate the drug's side effects, including pain and erythema at the infusion site. Inhaled iloprost therapy may provide selectivity of the hemodynamic effects to the lung vasculature, thus avoiding systemic side effects. In a randomized and controlled trial, iloprost resulted in improvement in a combined end point incorporating the New York Heart Association functional class, 6-min walk test, and deterioration or death. Beraprost is the first orally active prostacyclin analogue. In the first of two randomized controlled trials, beraprost increased exercise capacity in patients with IPAH, with no significant changes in subjects with associated conditions. Hemodynamics did not change significantly, and no difference in survival was detected between the two treatment groups. The second study showed that beraprost-treated patients had less disease progression at six months and confirmed the results of the previous trial. However, this improvement was no longer present at 9 or 12 months. In conclusion, though treatment with prostanoids is complicated by their generally short half-lives and complicated drug delivery systems, they continue to play an important role in the treatment of PAH. (J Am Coll Cardiol 2004;43:56S–61S) © 2004 by the American College of Cardiology Foundation

A metabolite of arachidonic acid, prostacyclin is endogenously produced by vascular endothelium. It is a potent vasodilator in both the pulmonary and systemic circulations, and has antiplatelet aggregatory activity. A relative deficiency of prostacyclin may contribute to the pathogenesis of pulmonary arterial hypertension (PAH). Clinical studies have explored the possibility that chronic therapy with exogenous prostacyclin analogues might be of long-term benefit in patients with moderately severe to severe PAH. To date, the following compounds and methods of administration have been studied: chronic intravenously infused epoprostenol, chronic subcutaneously infused treprostinil, inhaled iloprost, and oral beraprost. This report summarizes the rationale for therapy utilizing each of these prostanoids, and it provides currently available evidence supporting the use of each in the treatment of PAH.

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EPOPROSTENOL

Rationale. Christman et al. (1) reported a deficiency of prostacyclin and an excess of thromboxane in patients with PAH. Tuder et al. (2) showed decreased expression of prostacyclin synthase in lungs from patients with severe PAH. Exogenously administered prostanoid analogues might help to overcome the adverse effects of decreased endogenously produced prostacyclin. Epoprostenol has a very short half-life in the bloodstream, requiring constant intravenous (IV) administration.

Treatment. In a multicenter, randomized, controlled trial in 81 patients with severe idiopathic pulmonary arterial hypertension (IPAH, formerly known as primary pulmonary hypertension or PPH), continuously intravenously infused epoprostenol plus conventional therapy (oral vasodilators, anticoagulation, others) was compared to conventional therapy alone. The epoprostenol-treated group demonstrated improved survival and exercise tolerance, increased cardiac output, and decreased pulmonary vascular resistance (3). The beneficial effects of epoprostenol therapy are often sustained. Barst et al. (4) reported long-term

Abbreviations and Acronyms

IPAH = idiopathic pulmonary arterial hypertension
IV = intravenous
NO = nitric oxide
NYHA = New York Heart Association
PAH = pulmonary arterial hypertension
PPH = primary pulmonary hypertension

benefit in a small group of patients from centers involved in the earliest clinical use of epoprostenol. Shapiro et al. (5) and McLaughlin et al. (6) have described sustained benefit in larger numbers of patients. McLaughlin et al. (7) more recently reported experience with long-term epoprostenol therapy in 162 consecutive patients with IPAH followed for a mean of 36.3 months (median, 31 months) (Fig. 1). Data followed included functional class, exercise tolerance, and hemodynamics. Observed survival with epoprostenol therapy at one, two, and three years was 87.8%, 76.3%, and 62.8%, respectively, and was significantly greater than the expected survival of 58.9%, 46.3%, and 35.4%, respectively, based on historical data. Baseline predictors of survival included exercise tolerance, functional class, right atrial pressure, and vasodilator response to adenosine. Predictors of survival after the first year of therapy included functional class and improvement in exercise tolerance, cardiac index, and mean pulmonary artery pressure.

Sitbon et al. (8) evaluated the factors associated with long-term survival in patients with PPH/IPAH treated with continuous epoprostenol infusion. A total of 178 patients in New York Heart Association (NYHA) functional class III or IV were treated with epoprostenol. Survival rates at one, two, three, and five years were 85%, 70%, 63%, and 55%, respectively. Baseline variables associated with a poor outcome were a history of right-sided heart failure, NYHA functional class IV, 6-min walk test ≤250 m (median value), right atrial pressure ≥12 mm Hg, and, paradoxically, mean pulmonary artery pressure ≤65 mm Hg. Multivariate analysis, including both baseline variables and those measured after three months on epoprostenol, demonstrated that a history of right-sided heart failure, persistence of NYHA functional class III or IV at three months, and the absence of a decline in total pulmonary resistance of ≥30%, relative to baseline, were associated with poor survival. The investigators concluded that survival of patients with IPAH treated with epoprostenol depends both on severity of disease at baseline and the response to three months of therapy.

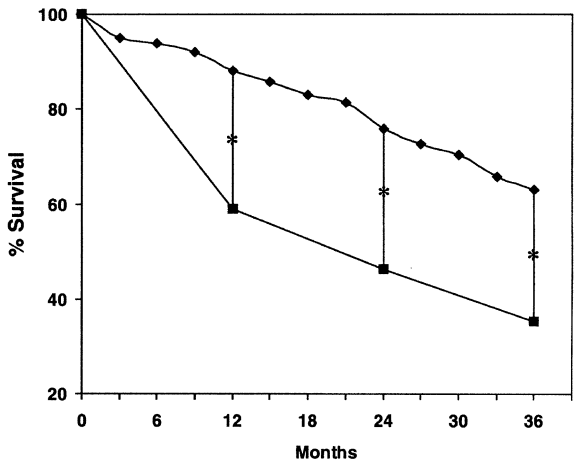

Figure 1. McLaughlin et al. (7) reported 162 consecutive patients diagnosed with primary pulmonary hypertension and treated with epoprostenol who were followed for a mean of 36.3 months (median, 31 months). Observed survival **(diamonds)** with epoprostenol therapy at one, two, and three years was 87.8%, 76.3%, and 62.8%, respectively, and was significantly greater than the expected survival **(squares)** of 58.9%, 46.3%, and 35.4%, respectively, based on historical data. Baseline predictors of survival included exercise tolerance, functional class, right atrial pressure, and vasodilator response to adenosine. Predictors of survival after the first year of therapy included functional class and improvement in exercise tolerance, cardiac index, and mean pulmonary artery pressure. Reprinted with permission from *Circulation* (Lippincott Williams & Wilkins).

A multicenter, randomized, and controlled study of chronic IV epoprostenol in patients with PAH occurring in association with the scleroderma spectrum of disease showed improvement in exercise capacity and hemodynamics at 12 weeks as compared to the control group (9). Trends were seen toward greater improvement in severity of the Raynaud phenomenon and fewer new digital ulcers in the epoprostenol group. A survival difference between groups was not seen in this population over the period of study, but the study was not adequately powered to detect such a difference.

Epoprostenol therapy requires continuous IV infusion. The drug has a very short half-life (<6 min), is unstable at acidic PpH, and cannot be taken orally. It is unstable at room temperature, and is generally kept cold prior to infusion. Patients are usually begun on a low dosage of epoprostenol (1 to 2 ng/kg/min), and gradually titrated upward in increments of 1 to 2 ng/kg/min, based upon side effects and tolerance. Many patients seem to reach a "plateau" dose and may not require continued up-titration from that point. Whereas this dose may be between 20 and 40 ng/kg/min for many patients, the dose range is wide, with considerable interindividual variability.

Common side effects of epoprostenol therapy include flushing, headache, jaw pain with the first bite of food, (which is usually tolerable), diarrhea, nausea, a blotchy erythematous rash, and musculoskeletal aches and pain (predominantly involving the legs and feet). These side effects tend to be dose dependent, and they often respond to a cautious reduction in dose. Abrupt or inadvertent interruption of the epoprostenol infusion should be avoided, as this may lead to a rebound worsening of pulmonary hypertension with symptomatic deterioration and perhaps even death. Complications of chronic IV therapy with epoprostenol include line-related infections (which range from exit site reactions, to tunnel infections and cellulitis, to bacteremia or sepsis), catheter-associated venous thrombosis, thrombocytopenia, and ascites (although this may also be a manifestation of severe disease).

Chronic IV epoprostenol therapy has had a substantial impact on the treatment of patients with moderately severe to severe PAH. It has been best studied in patients with IPAH and PAH occurring in association with the scleroderma spectrum of disease. Because of the complexity of epoprostenol therapy (chronic indwelling catheters, reconstitution of the drug, operation of the infusion pump, and so forth), and the relative rarity of severe PAH, strong consideration should be given to referral to centers of excellence.

TREPROSTINIL

Rationale. Although epoprostenol is effective therapy for PAH, the nature of the delivery system has a number of potential complications, which range in severity from local exit site infections easily treated with oral antibiotics to life-threatening sepsis. Because of the short half-life of epoprostenol, interruptions in therapy related to catheter displacement or pump malfunction may be life-threatening. Rare adverse events associated with the delivery system include pneumothorax, deep venous thrombosis, and paradoxical embolus. The efficacy of epoprostenol, coupled with the limitations of the delivery system, has led to the development of prostacyclin analogues with alternative routes of delivery. Treprostinil, a stable prostacyclin analogue with a half-life of 3 h, has been developed for subcutaneous delivery.

Treatment. In 14 patients with IPAH, treatment acutely with IV epoprostenol and IV treprostinil had similar hemodynamic effects (10). To test the alternative subcutaneous delivery method, the effects of IV treprostinil and subcutaneous treprostinil were compared in 25 patients with IPAH. Acute hemodynamic effects were similar. An eight-week, placebo-controlled, 2:1 randomized trial of subcutaneous treprostinil was subsequently performed in 26 patients with IPAH. An improvement of 37 ± 17 m in the 6-min walk distance occurred in patients receiving the active therapy (from 373 m to 411 m), compared to a 6 ± 28-m reduction in those receiving placebo (379 m vs. 384 m), a nonstatistically significant trend. There was a favorable, but not statistically significant, trend in hemodynamics, with a 20% reduction in pulmonary vascular resistance index over the eight-week period in the group receiving active treprostinil. Adverse events including headache, diarrhea, flushing, jaw pain, and foot pain were common in the treprostinil group, similar to what had been previously reported with epoprostenol. Pain (occasionally severe), erythema, and induration at the site of the subcutaneous infusion occurred frequently.

A large international, placebo-controlled, randomized study was conducted assessing the efficacy of chronic subcutaneously delivered treprostinil in patients with IPAH or PAH occurring in association with collagen vascular disease or congenital systemic-to-pulmonary shunts (11). Four hundred-seventy patients enrolled between November 1998 and October 1999 in 24 centers in North America and 16 centers in Europe, Australia, and Israel were randomly assigned to receive either continuous subcutaneously infused treprostinil plus conventional therapy or continuous infusion of placebo plus conventional therapy. Owing to the infusion-site pain and reaction that occurred in the proof-of-concept trial, the dosing strategy called for lower doses at initiation, with a maximal allowable dose at the end of 12 weeks of 22.5 ng/kg/min. The primary end point was exercise capacity as measured by the 6-min walk distance, which improved in the treprostinil group and was unchanged with placebo. The median difference between treatment groups was 16 m ($p = 0.006$), and the effect on exercise tolerance appeared to be dose related. The patients in the lowest two dosing quartiles experienced little improvement in the 6-min walk distance, whereas patients in the highest quartile in terms of dose (>13.8 ng/kg/min) demonstrated an improvement of 36 m. Treprostinil therapy was also associated with a significant improvement in mean right atrial pressure, mean pulmonary artery pressure, cardiac index, pulmonary vascular resistance, and mixed venous oxygen saturation. Common side effects included headache, diarrhea, nausea, rash, jaw pain, and infusion-site pain. Of the patients, 85% complained of pain at the infusion site, and 83% had erythema or induration at the infusion site. Although statistically significant, improvement in the 6-min walk distance was relatively modest. The reasons for this may be multifactorial. Entry criteria for the treprostinil trial were much more broad than for either of the epoprostenol trials.

INHALED ILOPROST

Rationale. Inhaled therapy for pulmonary hypertension may provide selectivity of the hemodynamic effects to the lung vasculature, thus avoiding systemic side effects. Pulmonary selective vasodilation has been described for inhaled nitric oxide (NO), but this agent has several drawbacks. Most importantly, there are no data demonstrating improved survival during therapy with inhaled NO, and this agent possesses less vasodilative potency than do prostanoids in IPAH patients (12,13). In contrast, prostacyclin (epoprostenol) has been shown to improve survival, exercise capacity, and hemodynamics in patients with severe IPAH (3,4,6), and the continuous IV infusion of this drug has been approved for therapy in certain groups of patients in the U.S. and several European countries.

Treatment. Iloprost is a prostacyclin analogue and has the same biologic profile as the natural substance with respect to prostaglandin receptor binding and cellular effects (14). Its effects and its side effects are similar to those seen during epoprostenol infusion (15). In contrast, the chemical stability of iloprost is considerably better. Where epoprostenol has to be freshly dissolved, continuously cooled, and protected from light to provide full activity, iloprost is stable at room temperature, at pH 7.4, and normal light. Epoprostenol has a half-life of <6 min, whereas iloprost has a

serum half-life of 20 to 25 min (16). Iloprost has been approved for the treatment of PAH in New Zealand, and was recently approved for the treatment of IPAH in Europe. Although epoprostenol is available in the United States and Europe, iloprost is not approved in the U.S.

Owing to the fact that the intra-acinar pulmonary arteries are tightly surrounded by alveolar surfaces, it is possible to vasodilate these vessels by means of alveolar deposition of a prostanoid. For long-term therapy, repetitive inhalations of iloprost are administered six to nine times daily. Each inhalation requires 10 to 15 min. With alternative devices it is possible to reduce the inhalation time to about 4 min (17) and to avoid any noise by use of ultrasound energy for nebulization.

In patients with severe PAH, inhalation of aerosolized iloprost resulted in a substantial decrease in pulmonary artery pressure and resistance, concomitant with an increase in cardiac output, in the absence of significant systemic artery pressure drop and ventilation–perfusion mismatch (18,19). In severe lung fibrosis, an increase of the pulmonary shunt blood flow may limit the use of IV epoprostenol (19), whereas inhaled iloprost can safely be administered. In uncontrolled studies, inhaled iloprost was effective in decompensated right heart failure (20) and showed favorable long-term hemodynamic improvement (21).

A large randomized, double-blind, placebo-controlled European multicenter study with inhaled iloprost (Aerosolized Iloprost Randomized, AIR [22]) involved a total of 203 patients in NYHA functional class III or class IV with IPAH or PAH occurring in association with appetite-suppressant use, collagen vascular disease, or nonoperable thromboembolic disease. In both the iloprost and placebo groups, approximately 50% suffered from IPAH, and about 60% were in NYHA functional class III and 40% in NYHA functional class IV. The primary end point of the study, defined as an improvement in NYHA functional class combined with at least 10% improvement in the 6-min walking test, and no deterioration or death (combined clinical end point), was reached by 3.4 × more patients in the iloprost versus the placebo group (16.8% vs. 4.9%; $p = 0.007$). This effect was achieved with a mean inhaled dose of 0.37 ng/kg/min. In the 6-min walk test, the treatment effect was 36.4 m in favor of iloprost ($p < 0.01$). Hemodynamics significantly deteriorated in the placebo group, whereas in the iloprost group preinhalation values were unchanged compared to baseline, and postinhalation values were significantly improved. Importantly, the number of patients remaining on study medication, a measure corresponding to event-free survival, was significantly higher in the iloprost than in the placebo group. Over three months of therapy, there was no indication of tachyphylaxis. In the iloprost group, one patient (1.0%) died during the double-blind study period versus four patients (4.0%) in the placebo group. Overall, the therapy was well tolerated. Cough occurred more frequently in the iloprost compared to the placebo group (38.6% vs. 25.5%) as well as headache (29.7% vs. 19.6%) and flushing (26.7% vs. 8.8%). These adverse events were mild and mostly transient. Syncope occurring in the iloprost group was more often rated as serious than in the placebo group, but was not commonly associated with clinical deterioration.

An open-label multicenter study of the two-year effects of inhaled iloprost in pulmonary hypertension with an initial three-month controlled randomized phase was performed in Germany. Inhaled iloprost treatment was administered for up to two years to 63 patients (40 with IPAH and 23 with PAH occurring in association with underlying disorders). The median daily aerosolized dose was 100 μg (total inhaled dose ≈24 μg) divided into six inhalations. At study entry, 66.6% of patients were in NYHA functional class III or class IV, and 33.4% in functional class II. During the two-year study period, five IPAH patients were switched to alternative therapy (mostly IV iloprost) but remained in the study, and 13 patients discontinued the study prematurely (7 with IPAH; 6 with other forms of PAH). After two years, 37 patients received inhaled iloprost treatment (25 with IPAH; 12 with other forms of PAH). During the course of the study, eight patients died: three IPAH and five with other forms of PAH. Two of these patients died before receiving inhaled iloprost treatment. The survival rate according to Kaplan-Meier analysis was 0.850 for all patients and 0.914 (95% confidence interval: 0.81; ≈1) for IPAH patients for the two-year study period, including the randomized phase. For IPAH patients, the predicted survival rate according to D'Alonzo et al. (23) was 0.631, which corresponds to ≈14.8 deaths. In contrast, only three IPAH patients died. This suggests that survival on inhaled iloprost treatment is substantially higher than expected.

In addition to treatment of IPAH, the pulmonary selectivity of inhaled iloprost provides the opportunity to apply prostanoids to patients who are prone to decrease in systemic arterial pressure, as in portopulmonary hypertension, and in emergency situations. The intrapulmonary selectivity also allows prostanoid application to patients who are prone to intrapulmonary right to left shunt, like hepatopulmonary syndrome and lung fibrosis (19).

Inhaled iloprost may provide an alternative to the use of IV epoprostenol. When the clinical effects of inhaled iloprost and IV epoprostenol are compared, inhaled iloprost has some advantages but also certain drawbacks. Most importantly, the inhalation provides potent pulmonary vasodilation with little systemic side effects and no risk of catheter complications. Additionally, it allows therapy in patients with pre-existent ventilation-perfusion mismatch and in those who are prone to develop such a mismatch during systemic prostanoid application. The most important drawback is the fact that the hemodynamic effect of inhaled iloprost plateaus within 30 to 90 min, and that six to nine inhalations per day are needed to achieve satisfactory clinical results. Inhaled iloprost is currently approved in Europe for functional class III IPAH. Long-term survival data are needed.

BERAPROST

Rationale. Beraprost is the first orally active prostacyclin analogue (24). It is rapidly absorbed during fasting, peak concentration is reached after 30 min, and the elimination half-life is 35 to 40 min after oral administration (25). In the monocrotaline-induced pulmonary hypertension model, beraprost has been shown to have a protective effect on the development of pulmonary hypertension lesions (26). High doses of beraprost appear to have inotropic and chronotropic effects in the isolated guinea pig myocardium (27). Beraprost has also been studied in peripheral vascular diseases such as intermittent claudication (28), Raynaud phenomenon, and digital necrosis in systemic sclerosis (29), with variable results.

Treatment. Beraprost has been used to treat PAH since 1995 in Japan; several small open uncontrolled studies have reported beneficial hemodynamic effects with beraprost in patients with IPAH (24,30). Functional class also improved in the majority of the patients after a mean of two months, and pulmonary vascular resistance was reduced by 26% (24, 30). Nagaya et al. (31), in a retrospective open uncontrolled study, reported improved survival in 24 IPAH patients treated with beraprost compared to a similar group of 34 patients on conventional therapy. The three-year survival rate was 76% in the beraprost group and 44% in the conventional-therapy group.

Two randomized, double-blind, placebo-controlled trials of beraprost in PAH have been performed. The first was a 12-week double-blind, randomized, placebo-controlled trial performed in 130 NYHA functional class II and class III patients with PAH of various etiologies (IPAH, and PAH associated with collagen vascular diseases, congenital systemic-to-pulmonary shunts, portal hypertension, or human immunodeficiency virus infection) (32). At a median dose of 80 μg administered orally four times daily, beraprost increased exercise capacity assessed by the 6-min walk test: treatment effect was 25 m in the overall population, and 45 m in the IPAH patients, with no significant changes in the exercise capacity of subjects with the associated conditions. Hemodynamics had no statistically significant changes, and no difference in survival was detected between the two treatment groups. Side effects related to systemic vasodilation were frequent, mainly in the initial titration period.

A second trial evaluated the effects of beraprost therapy for PAH in 116 NYHA functional class II and class III patients. This study was 12 months in duration, double-blind, randomized, and placebo-controlled (33). It showed that the beraprost-treated patients had less disease progression at six months and confirmed the results of the previous trial (32): improved 6-min walk distance at three months (+22 m from baseline) and six months (+31 m), as compared to placebo. However, this improvement was no longer present at 9 or 12 months (33). No significant changes occurred in hemodynamics or survival at month 12 versus baseline. It is possible that the beneficial effects of beraprost may attenuate with time. Beraprost is approved for treatment of PAH in Japan, and is currently under evaluation by the European Agency for the Evaluation of Medicinal Products (EMEA).

SUMMARY

Chronic IV epoprostenol therapy has had a substantial impact on the clinical management of patients with severe PAH. The complexity of epoprostenol therapy has led to attempts to develop other prostanoids with simpler modes of delivery. Subcutaneous treprostinil, inhaled iloprost, and oral beraprost have all been studied, and they have various relative advantages and disadvantages. In conclusion, although treatment with prostanoids is complicated by their generally short half-lives and complicated drug-delivery systems, they continue to play an important role in the treatment of PAH. Together with the other major classes of therapeutic agents currently utilized or under investigation for the treatment of PAH (including anticoagulants, supplemental oxygen, calcium channel antagonists, endothelin receptor antagonists, phosphodiesterase inhibitors, and NO or NO donors), prostanoids remain an important therapeutic option.

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