Oral and Subcutaneous Prostacyclin Analogs: Analyzing the Latest Evidence on Efficacy and Safety

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Epoprostenol therapy has revolutionized the treatment of pulmonary arterial hypertension (PAH).[1-3] Patients realized an improvement in quality of life, hemodynamics, and survival and this therapy has offered hope to patients with advanced disease.[1,4] However, these attributes must be balanced against the complicated nature of the intravenous delivery system. Infections may 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. Additionally, the patient's life is radically changed by the need to mix the medication on a daily basis, store the medication under refrigerated conditions, and carry a mechanical pump. The success of epoprostenol coupled with the limitations of the delivery system has provided the impetus to develop prostacyclin analogs with alternative routes of delivery. This article will focus on the analogs beraprost and treprostinil (the analog iloprost is discussed in another article in this issue).

Beraprost

Beraprost sodium is an orally administered prostacyclin analog. When taken with food the half-life is approximately 3 to 3½ hours, requiring dosing four times daily. Enthusiasm for the treatment of PAH with beraprost arose from the initial experience in Japan and subsequent experience in Europe.

In 1999 Nagaya and colleagues reported the benefit of beraprost on survival in patients with primary pulmonary hypertension (PPH).[5] They followed 58 consecutive patients with PPH between 1981 and 1997. The 34 patients diagnosed before December 1992 were treated with conventional therapy alone, and the 24 patients diagnosed after January 1993 were treated with beraprost in addition to conventional therapy. Oral beraprost was initiated at a rate of 60 mcg per day and increased by increments of 60 mcg per day over 1 to 2 weeks to the highest tolerated dosage. Survival was estimated from the date of initial diagnosis until the conclusion of the study in November 1998. Of the 34 patients in the conventional therapy group, 27 patients died of cardiopulmonary causes after a mean follow-up of 44 ± 45 months. In contrast, only 4 of the patients in the beraprost group died of cardiopulmonary causes during a mean follow-up of 30 ± 20 months. Kaplan-Meier survival curves demonstrated the 1-, 2-, and 3-year survival rates in the beraprost group to be 96%, 86%, and 76%, respectively, compared with 77%, 47%, and 44%, respectively, in the conventional therapy group, differences that were statistically significant.

A subgroup of 15 patients treated with beraprost underwent repeat cardiac catheterization after receiving therapy for a mean of 53 days. There was a reduction in mean pulmonary artery pressure of 13% and in total pulmonary resistance of 25% as well as an increase of 17% in cardiac output. Sixty-seven percent of the patients treated with beraprost demonstrated an improvement in New York Heart Association (NYHA) Functional Class. Although these results suggested an improvement in survival with beraprost therapy, several limitations of the study bear mention. These include the small size of the cohort and retrospective analysis. Other medical therapies were not controlled and there was a significant difference in the use of calcium channel blockers and digitalis between the conventional therapy group and the beraprost group. The mean follow-up was substantially longer in the conventional therapy group than in the beraprost group. Additionally, a larger proportion of the patients in the beraprost group went on to treatment with intravenous epoprostenol.

More recently Vissa and colleagues reported their results of long-term treatment of PAH with beraprost.[6] They studied 13 patients, 9 with PPH, 3 with thromboembolic pulmonary hypertension, and 1 with PAH related to congenital heart disease. The mean daily dose of beraprost was 116 ± 24 mcg after the first month of treatment and 193 ± 74 mcg at the end of 12 months. One patient died at 40 days of treatment and 1 patient was lost to follow-up. Twelve-month follow-up data were achieved in 11 patients. Patients demonstrated an improvement in NYHA Functional Class from 3.4 ± 0.7 at baseline to 2.9 ± 0.7 at the end of 1 month ($P < .016$). No further improvement was noted after a full year of therapy. The 6-minute walk distance increased by 63 ± 47 meters from a baseline distance of 213 ± 64 meters. This improvement was noted at 1 month and was maintained over the

12-month period. This prospective uncontrolled trial suggested that beraprost improved symptoms and exercise capacity in patients with PAH.

The only prospective, double blind, placebo-controlled, randomized study of beraprost in the study of PAH has recently been completed in Europe.[7] Galie and colleagues studied 130 patients with PAH, including PPH and PAH associated with collagen vascular disease, congenital heart disease, portal hypertension, and human immunodeficiency virus infection. Patients were randomized to receive the maximal tolerated dose of beraprost or placebo for 12 weeks. The primary end point of distance walked in 6 minutes improved by 25.1 meters ($P = .036$) in the active treatment group. They also noted an improvement in symptoms as measured by the Borg dyspnea index, which decreased by 0.94 in the beraprost group ($P = .009$). Subgroup analysis demonstrated that patients with PPH realized the greatest improvement, with a mean change in 6-minute walk distance of 46.1 meters. They noted no statistically significant differences in cardiopulmonary hemodynamics or NYHA Functional Class. The median dosage of beraprost in the study was 80 mcg four times per day.

The most common side effects of beraprost reported in these studies were headache, flushing, jaw pain, diarrhea, leg pain, and nausea. Side effects can be minimized when the drug is taken with a meal. Beraprost is currently available in Japan and may become available in Europe. A placebo-controlled trial with beraprost in the United States was terminated prematurely and this drug will not likely become commercially available in the United States. Presumably the early termination was because of a lack of efficacy estimation by the Data and Safety Monitoring Board.

Treprostinil

Treprostinil is a prostacyclin analog with a half-life of 3 hours when administered subcutaneously. The drug is stable at room temperature. Animal studies suggest that the hemodynamic effects of treprostinil are similar to those of epoprostenol.[8,9] To test this hypothesis in humans, we studied 14 patients with PPH acutely with intravenous epoprostenol and then intravenous treprostinil.[10] Both drugs had similar effects on hemodynamics. There was no difference in reduction in pulmonary vascular resistance (22% with epoprostenol versus 20% with treprostinil).

To then test the alternative subcutaneous delivery method, we compared the effects of intravenous and subcutaneous treprostinil in 25 patients with PPH. In the intravenous treprostinil and subcutaneous treprostinil groups there was a 6% and 13% decline in mean pulmonary artery pressure and a 23% and 28% decline in pulmonary vascular resistance respectively.

Having demonstrated that the drug favorably affects cardiopulmonary hemodynamics when given subcutaneously acutely, we embarked on an 8-week, placebo controlled, 2:1, randomized trial of subcutaneous treprostinil. Twenty-six patients with PPH were enrolled. Two patients in the treprostinil group did not complete the study because of intolerable side effects. The remaining 15 patients randomized to active drug were receiving a mean dosage of 13.0 ± 3.1 ng/kg/min

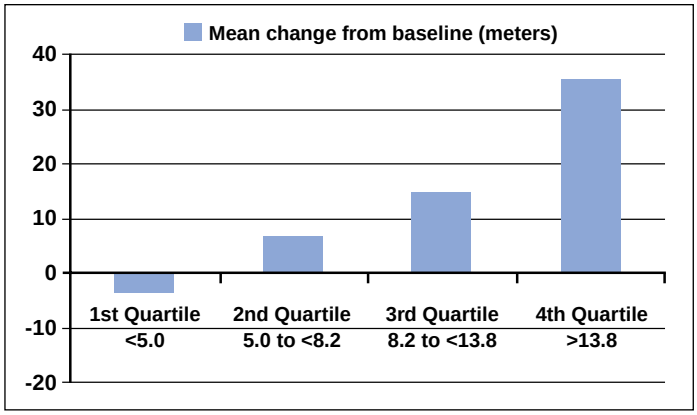

Fig. 1—Change in exercise as function of dose.[11]

of treprostinil, and the 9 patients randomized to placebo were receiving 38.9 ± 6.7 ng/kg/min at the end of the 8-week period. There was an improvement of 37 ± 17 meters in the 6-minute walk distance in patients receiving the active therapy (from 373 meters to 411 meters) compared with a 6 ± 28 meter reduction in those receiving placebo (from 384 meters to 379 meters), which was not statistically significant. There was a favorable, but again not statistically significant trend in hemodynamics, with a 20% reduction in pulmonary vascular resistance index over the 8-week period in the group receiving active treprostinil. Adverse events, including headache, diarrhea, flushing, jaw pain, and foot pain, were as common in the treprostinil-treated as in the epoprostenol-treated group. An unexpected adverse effect was pain at the site of the subcutaneous infusion. This pain was occasionally severe, was often associated with erythema, and occurred in nearly all the patients undergoing active therapy. This proof-of-concept trial demonstrated that this novel subcutaneous agent could be given safely and effectively on an outpatient basis and paved the way for a larger pivotal trial.

Subsequently, the largest placebo-controlled randomized study involving PAH patients was an international trial assessing the efficacy of subcutaneously delivered treprostinil in patients with PAH, either primary or associated with collagen vascular disease or congenital systemic-to-pulmonary shunts.[11] Patients were enrolled between November 1998 and October 1999 in 24 centers in North America and 16 centers in Europe, Australia, and Israel. Four hundred-seventy patients were randomly assigned to receive either continuous subcutaneous infusion of treprostinil plus conventional therapy or continuous infusion of placebo (vehicle solution without treprostinil) plus conventional therapy. Because of the infusion-site pain and reaction noted in the proof-of-concept trial, the dosing strategy called for lower doses at initiation and a maximal allowable dose at the end of 12 weeks of 22.5 ng/kg/min. The primary end point of this trial was exercise capacity as measured by the 6-minute walk distance, which improved in the treprostinil group and was unchanged with placebo. The median between treatment group difference was 16 meters ($P = .006$). This effect on exercise tolerance appeared to be dose-related. The patients in the lowest two quartiles of dosing experienced little improvement in 6-minute

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Pull-Out Algorithm

Table 1—Hemodynamic Response to Subcutaneous Treprostinil

	Treprostinil	Placebo	*P* Value
Mean right atrial pressure, mmHg	-0.5 ± 0.4	+1.4 ± 0.3	.0002
Mean pulmonary artery pressure, mmHg	-2.3 ± 0.5	+0.7 ± 0.6	.0003
Cardiac index, L/min/m^2	+0.12 ± 0.04	-0.06 ± 0.04	.0001
Pulmonary vascular resistance index, units/m^2	-3.5 ± 0.6	+1.2 ± 0.6	.0001
Mixed venous oxygen saturation, %	+2.0 ± 0.8	-1.4 ± 0.7	.0001

Adapted from Simonneau et al.[11]

Table 2—Subgroup Analysis of Treprostinil Trial

NYHA Class	Treatment Effect*
II	+2 m
III	+17 m
IV	+54 m
Baseline Walk	**Treatment Effect**
50 – 150 m	+51 m
151 – 250 m	+33 m
251 – 350 m	+16 m
351 – 450 m	-2 m
Disease	**Treatment Effect**
Primary pulmonary hypertension	+13.0 m
Collagen vascular disease	+10.4 m
Congenital heart disease	-1.0 m

*Refers to primary end point of 6-minute walk distance.

walk distance, and patients in the highest quartile of dosing (greater than 13.8 ng/kg/min) demonstrated a mean improvement of 36 meters (**Figure 1**). Secondary end points, including the dyspnea fatigue rating and the Borg dyspnea scale, confirmed an improvement with treprostinil therapy. Treprostinil also demonstrated a significant improvement in the hemodynamic parameters of mean right atrial pressure, mean pulmonary artery pressure, cardiac index, pulmonary vascular resistance, and mixed venous oxygen saturation (**Table 1**). Common side effects included headache, diarrhea, nausea, rash, and jaw pain. Side effects related to the infusion site were common. Eighty-five percent of patients experienced infusion site pain and 83% had erythema or induration at the infusion site. Eight percent of the patients in the active treatment group were withdrawn from the study because of site pain.

Although statistically significant, the 16-meter improvement in 6-minute walk distance was relatively modest and less than the improvements demonstrated in the trials with intravenous epoprostenol for both PPH and PAH related to the scleroderma spectrum of diseases, which demonstrated treatment effects of 47 meters and 99 meters, respectively.[1,3] The reasons for the less impressive effects are multifactorial. The entry criteria for the treprostinil trial were broader than those for either of the epoprostenol trials. Key subgroup analyses are listed in **Table 2**. The epoprostenol trials included only patients who were in NYHA Func-tional Class III or IV. Fifty-three patients who were in NYHA Functional Class II were enrolled in the treprostinil trial. Their treatment effect in the 6-minute walk distance was only two meters in the Functional Class II patients compared with 17 meters for the 382 patients who were in Functional Class III and 54 meters for the 34 patients who were in Functional Class IV. The baseline 6-minute walk distance in the treprostinil study was 326 ± 5 meters in the active treprostinil group and 327 ± 6 meters in the placebo group.

In comparison the baseline 6-minute walk distance in the PPH epoprostenol trial was 315 meters in the epoprostenol plus conventional therapy group versus 270 meters in the conventional therapy group alone.[1] In the scleroderma epoprostenol trial the baseline 6-minute walk distance was 272 meters in the epoprostenol plus conventional therapy group and 240 meters in the group receiving conventional therapy alone.[3] This demonstrates that the patient population was less ill in the treprostinil trial, which may have contributed to the less impressive treatment effect.

The treatment effect was also related to the baseline walk distance in the treprostinil trial (**Table 2**). Patients who were able to walk between 351 and 450 meters did not demonstrate a treatment effect at all, whereas those patients who were able to walk in the lowest category of 50 to 150 meters demonstrated a treatment effect of 51 meters. The etiology of PAH was also more broad in the treprostinil trial. In addition to the inclusion of PPH patients and PAH associated with collagen vascular disease, PAH associated with congenital heart disease was included. This group had been untested in the past and in the treprostinil study did not demonstrate any treatment effect at all. This may in part be related to the patients' long-standing disease and the difficulty of making an impact on such a process over a short 12-week period.

The nemesis of subcutaneous treprostinil has been pain and erythema at the infusion site (**Figure 2**). A variety of therapies have been used to control this adverse effect, although none has emerged as uniformly successful. Local remedies such as topical hot and cold packs, topical analgesics and anti-inflammatory agents have been variably effective. Some patients also responded to oral analgesics, such as nonsteroidal anti-inflammatory drugs. More recently, a pharmaceutical transdermal delivery vehicle, pluronic lecithin organogel, has been compounded with a variety of analgesic and anes-

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Clinical Algorithm

Elective Initiation of Epoprostenol

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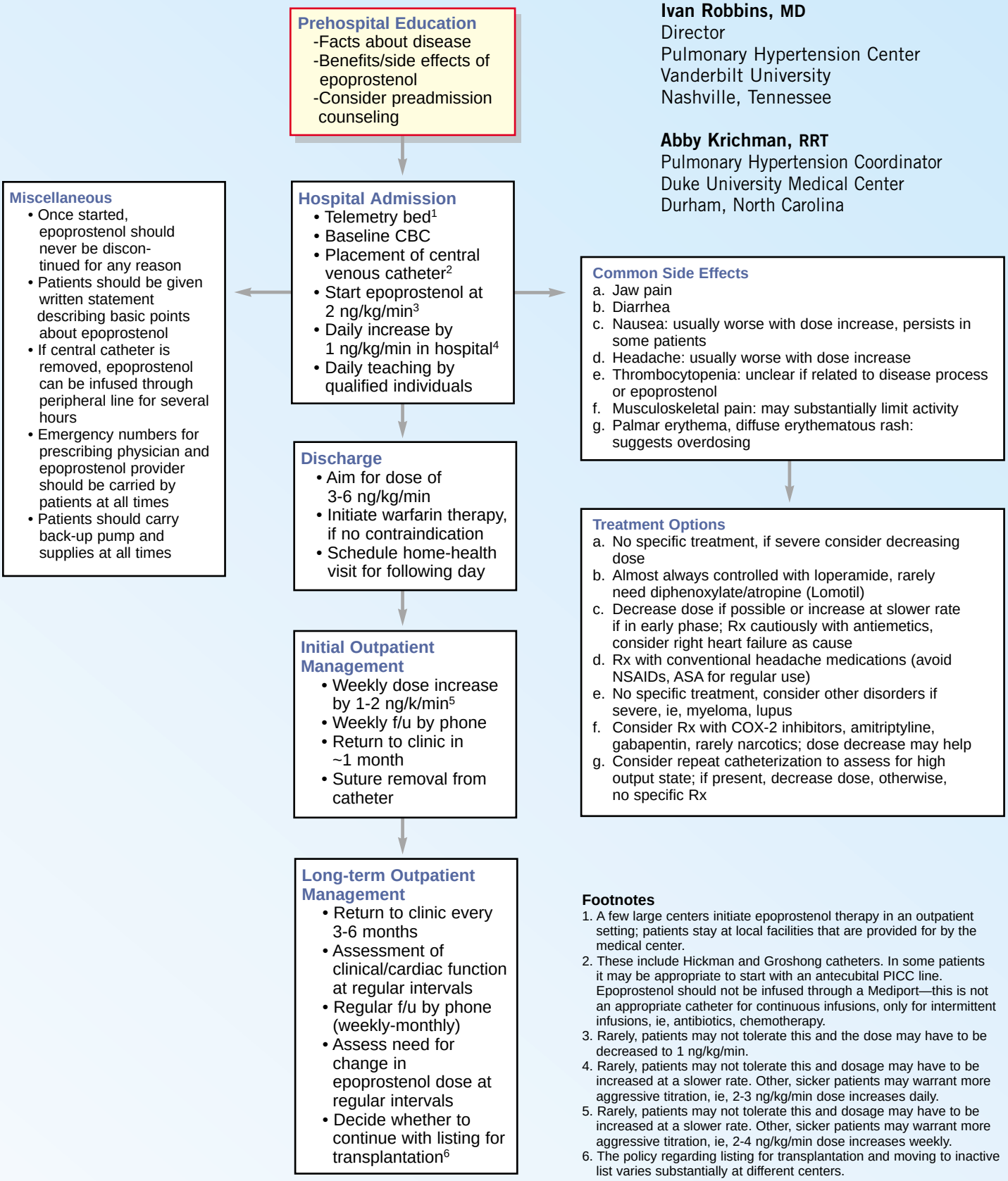

Footnotes

1. A few large centers initiate epoprostenol therapy in an outpatient setting; patients stay at local facilities that are provided for by the medical center.
2. These include Hickman and Groshong catheters. In some patients it may be appropriate to start with an antecubital PICC line. Epoprostenol should not be infused through a Mediport—this is not an appropriate catheter for continuous infusions, only for intermittent infusions, ie, antibiotics, chemotherapy.
3. Rarely, patients may not tolerate this and the dose may have to be decreased to 1 ng/kg/min.
4. Rarely, patients may not tolerate this and dosage may have to be increased at a slower rate. Other, sicker patients may warrant more aggressive titration, ie, 2-3 ng/kg/min dose increases daily.
5. Rarely, patients may not tolerate this and dosage may have to be increased at a slower rate. Other, sicker patients may warrant more aggressive titration, ie, 2-4 ng/kg/min dose increases weekly.
6. The policy regarding listing for transplantation and moving to inactive list varies substantially at different centers.

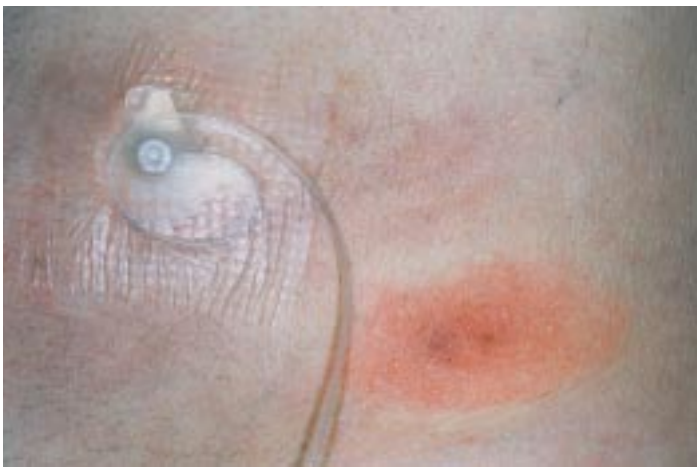

Fig. 2—Subcutaneous treprostinil has been associated with pain and erythema at the infusion site.

thetic therapies for local application in patients treated with treprostinil. Initial observations appear promising, although the therapy has yet to be studied in a controlled fashion.

A common observation has been that site pain and erythema improve after several months of therapy. Additionally, the pain is not related to the dose of treprostinil. Given the dose-response relationship, it is important to increase the dose regularly, so that patients realize an improvement in dyspnea. Under such circumstances, patients are more likely to tolerate site discomfort. Some patients have found that moving the infusion site every 3 days as opposed to every day is useful. The infusion site most commonly used was subcutaneous abdominal fat, although some patients were able to use the outer hips and thighs and underside of the upper arm with some success.

Because of the longer half-life of treprostinil, interruptions of drug due to dislodgment of the catheter or pump malfunction are less serious than with epoprostenol. In such instances, either the catheter could be replaced or a backup pump, which all patients had, could be exchanged without any serious consequences. The Mini-Med pump, used to administer treprostinil, is smaller than the CADD pump used to administer epoprostenol and is about the size of a pager. The drug comes in a premixed-prefilled syringe and therefore patients need only to place the syringe in the pump and do not have to mix the medication in a sterile fashion on a daily basis.

The Food and Drug Administration has approved subcutaneous treprostinil for patients with Functional Class II, III, and IV PAH. One should consider the use of subcutaneous treprostinil in patients who are not candidates for or decline therapy with intravenous epoprostenol, for example someone with poor venous access or recurrent catheter infections. In addition, patients who have contraindications to or transaminase elevations with the oral endothelin-receptor antagonist bosentan might be candidates for subcutaneous treprostinil. Treprostinil has not been studied in combination with bosentan; however, there may be a theoretical benefit to such a combination.

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