Treprostinil for pulmonary hypertension

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Treprostinil (Remodulin®, United Therapeutics) is a stable, long-acting prostacyclin analog, which has been shown to improve clinical state, functional class, exercise capacity and quality of life in patients with pulmonary arterial hypertension, an uncommon disease with poor prognosis. The drug is administered as a continuous subcutaneous infusion using a portable miniature delivery system. Side effects include facial flush, headache, jaw pain, abdominal cramping and diarrhea. These are all typical of prostacyclin impregnation and manageable by symptom-directed dose adjustments. Infusion site pain, a more serious side effect, may limit the treatment in 10% of patients. Otherwise, treprostinil has an excellent safety profile and compares favorably with reference continuous intravenous epoprostenol (Flolan®, GlaxoSmithKline) therapy. Treprostinil has a place in currently proposed treatment algorithms of pulmonary arterial hypertension.

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of congenital left-to-right shunts, especially those with high flows and pressures, such as large ventricular septal defects of persistent ductus arteriosus [2].

Until the early 1990s, PAH was a uniformly fatal disease, with a median life expectancy of approximately 2.5 years. Uncontrolled studies showed that a small proportion of patients responded to high-dose calcium channel blockers, retrospective studies supported the use of anticoagulant therapy and ‘conventional treatment’ was otherwise limited to lifestyle counseling, diuretics, digitals and supplemental oxygen [5]. Chronic continuous intravenous prostacyclin such as epoprostenol (Flolan®, GlaxoSmithKline, Middlesex, UK) was introduced in the 1980s as an effective treatment to bridge PPH patients to transplantation [6] and thereafter shown by two randomized controlled trials to improve functional state, exercise capacity and survival in patients with PPH [7], and to improve functional state and exercise capacity in patients with PAH associated with scleroderma spectrum of disease [8]. The first of these trials led to the US Food and Drug Administration (FDA) approval for epoprostenol for New York Heart Association (NYHA) functional classes III and IV patients with PPH in 1996. This was extended to include scleroderma spectrum of disease in 2000. Extensive experience of long-term treatment with chronic intravenous epoprostenol confirms persistent clinical benefit over time, with an approximate doubling of life expectancy [9,10]. The treatment is also effective in PAH associated with congenital heart disease [11], portal hypertension or liver cirrhosis [12], and HIV infection [13] and may help in bridging CTEPH patients to thromboendarterectomy [14].

However, chronic intravenous epoprostenol is not an ideal treatment. Due to instability and a very short half-life (2–7 min), epoprostenol must be administered as a continuous infusion through a permanently implanted central venous catheter. This exposes the patients to a series of complications, including catheter-related embolism or thrombosis, infections and delivery-system malfunctions, resulting in poorly tolerated rapid overdosing or underdosing. Therefore, more stable prostacyclin derivatives and different routes of administration are being sought. Randomized controlled trials have reported favorable results with oral beraprost (Dorner®, Procyclin®, Kaken Pharmaceutical Co Ltd, Tokyo, Japan) [15], inhaled prostacyclin [16] and subcutaneous treprostinil [17]. In the meantime, randomized controlled trials have also reported favorable results with orally administered bosentan (Tracleer®, Actelion Pharmaceuticals Ltd, Allschwil, Switzerland), a dual endothelin receptor blocker, in patients with PPH and PAH associated with connective tissue diseases [18].

Bosentan, a subcutaneous treprostinil received the FDA approval for the treatment of NYHA class III and IV patients with PAH in 2001 and 2002, respectively. Inhaled prostacyclin received the European Agency for the Evaluation of Medicinal Products (EMEA) approval for the treatment of NYHA class III patients with PAH in 2003. Thus, an increasing number of treatments have become available for the treatment of PAH patients, and it is important to define the indications for each in the light of current experience from reference centers and the literature.

Overview of the market
It must be emphasized that, although the introduction of prostacyclin and antiendothelin therapies have represented a major step forward, PAH remains incurable, and is still associated with unacceptably high mortality. Only 63% of epoprostenol-treated PPH patients are still alive after 3 years [9,10]. All available effective therapies present with significant side effects or difficulties. These primarily include nonspecific side effects of prostacyclins, such as jaw pain, flushing, headache and abdominal cramping, pain at the subcutaneous infusion site (treprostinil), cumbersome inhalation devices and procedures with need of excessively high frequency of administration (prostacyclin) and liver intolerance in 5 to 10% of patients (bosentan). Transition from one of these therapies to another is not straightforward in fragile PAH patients, who are easily destabilized by changes in drug dosing and associated stress. Multidrug approaches after failure of a single drug are expanding, but at this stage evidence-based recommendations are lacking, and whether a multidrug approach will achieve a higher success rate is not yet known. In addition, all PAH categories do not seem to be equally sensitive to available therapies. Until now, the best results have been obtained in PPH and in connective tissue-associated PAH. However, while efficacy in many patients with congenital heart disease-associated PAH is debatable [15,17], it remains uncertain whether CTEPH is responsive to pharmacotherapies at all [16]. Favorable results of the oral selective endothelin A receptor antagonist, sitaxsentan (Encysive Pharmaceuticals, TX, USA), has been reported in a randomized controlled trial in patients with PAH (mainly PPH and connective tissue disease-associated PAH) [19] and uncontrolled observations are suggesting efficacy of the oral phosphodiesterase-5 inhibitor sildenafil (Viagra®, Pfizer Inc., NY, USA) [20]. While oral therapies obviously have become first line in the management of NYHA class III patients with PAH, parenteral prostacyclin therapy remains the reference treatment for NYHA class IV patients and for NYHA class III patients after other approaches have failed.

Pharmacology
Treprostinil is a tricyclic benzindene analog of prostacyclin and as such has similar antiplatelet and vasodilatory actions, including acute pulmonary vasodilation [21–23]. It has no apparent direct cardiac effects as assessed by indices of contractility and by electrocardiogram, no intrinsic effect on the autonomous nervous system, and no significant effect on respiratory mechanics. Treprostinil tends to inhibit gastrointestinal motility and decrease pentagastrin-stimulated gastric acid secretion, and therefore has gastric antiulcer and mucosal protective actions [23]. These favorable gastrointestinal effects are in contrast to abdominal cramping and diarrhea observed in patients treated with treprostinil (or with any prostacyclin derivative) [17]. The safety profile of treprostinil is favorable, with, in particular, no reproductive toxicity and no mutagenetic effects are observed [23].

Treprostinil is rapidly and completely absorbed after subcutaneous administration and has an absolute bioavailability of 100% [24]. Continuous subcutaneous infusion of treprostinil is
associated with steady-state plasma concentrations after about 10 h, with administration rates from 1.25–22 ng/kg/min associated with 0.83–8 µg/l. Treprostinil is 91% bound to human plasma proteins. The metabolism of treprostinil is hepatic, although the enzymes involved are not entirely known. One of the metabolites is a glucurononoconjugate of treprostinil. The other metabolites are formed by the oxidation of the 3-hydroxy octyl side chain and subsequent oxidation or dehydration. Treprostinil does not inhibit cytochrome P450 isoenzymes. Treprostinil is eliminated in a biphasic distribution and has a terminal half-life of about 2 to 4 h. Approximately 79% of the administered dose is excreted in the urine either as unchanged drug (4%) or an identifiable metabolite (64%) [23].

The clearance of treprostinil is decreased by up to 80% in patients with hepatic insufficiency, therefore cautious dosing is required in patients with PAH associated with liver disease [23]. There are no studies on the pharmacokinetics of treprostinil in patients with renal insufficiency. Although only 4% of treprostinil is excreted unchanged in the urine, five identified metabolites are excreted in the urine and cautious dosing is therefore recommended in patients with PAH and also altered renal function [23]. Treprostinil does not interfere with the metabolism of paracetamol, warfarin, or digoxin (DigiFab™, Protherics PLC, Cheshire, UK) [23,25].

Treprostinil is chemically stable in either sterile water or 0.9% sodium chloride and 5% dextrose solutions at room temperature and has a close to neutral pH [26]. These characteristics and relatively long half-life, in the range of 2 to 4 h make treprostinil suitable for subcutaneous administration [23]. Subcutaneous treprostinil is advantageous compared with intravenous epoprostenol because it has a less cumbersome delivery system and there is no need for a surgically implanted central venous line. Epoprostenol requires sterile daily or twice-daily reconstitution with or without ice packing, and is administered with a variety of more or less bulky portable pump systems, which are on average the size of a portable compact disk player. In contrast, treprostinil is supplied in 20 ml vials containing either 1, 2.5, 5 or 10 mg/ml of the drug, that may be stored at room temperature. In addition, treprostinil is delivered using a mini-infusion pump, which is the size of a small cell phone. During drug administration, aseptic techniques are required at the injection site, which is changed approximately every three days. However, while this is not recommended, many patients find it more convenient to leave the subcutaneous catheter in place for longer periods of time, up to 2 to 3 weeks, and this seems to be generally well-tolerated.

Basic studies
Prostacyclin therapy in PAH stems from a pathobiological concept relating PAH to an endothelium-derived vasoconstrictor/vasodilator imbalance, with an excess of the vasoconstrictor-mitogenic endothelin and a deficit of the vasodilating antiproliferative nitric oxide and prostacyclin [27]. Essentially all of the anti-inflammatory, antiplatelet, vasorelaxant and antiproliferative effects of proteaclyins are cyclic adenosine monophosphate (cAMP)-mediated. Recent studies have compared the antiproliferative activities of several prostacyclin analogs on isolated pulmonary artery smooth muscle cells [28]. Serum induced proliferation as assessed by [3H] thymidine incorporation or cell number, was significantly inhibited by all of them, including, in order of decreasing potency, treprostinil, inhaled prostacyclin, cicaprost and beraprost. The antiproliferative effects of these prostacyclins were blocked by an adenlylclase inhibitor. Treprostinil also appeared to be the most potent prostacyclin analog to induce a sustained increase in cAMP.

As inflammation appears to play a role in advanced PAH [27], another mode of action of treprostinil possibly accounting for reported beneficial effects may be the blockade ofNFκB nuclear translocation in alveolar macrophages, leading to dose-dependent inhibition of inflammatory cytokine secretion and gene expression [29].

Clinical efficacy
Pilot trials
The effects of treprostinil and epoprostenol in patients with PPH were compared in three pilot trials [3]. In the first trial, both drugs were given intravenously. In the second trial, intravenous treprostinil was compared to subcutaneous treprostinil. Intravenous epoprostenol and treprostinil at comparable doses resulted in similar short-term decrements in PVR, in the range of -22 to -28%. The third trial was a Phase II, 8-week, multicenter, double-blind, randomized, parallel comparison of treprostinil plus conventional therapy versus conventional therapy alone in 26 NYHA class III/IV patients with PPH. The treprostinil dose ranged from 1.25 to 5 ng/kg/min during the first week and was then increased in increments ranging from 2.5 to 5 ng/kg/min per week. Maximum treprostinil doses were achieved during the last two weeks of the study and ranged up to 50 ng/kg/min. Treprostinil improved the 6-minute walk distance by 24 m in 17 patients, with no change in Borg dyspnea score. Dyspnea-fatigue rating improved by 0.57 (0–12 scale), cardiac output (Q) increased by 0.42 l/min/m², Ppa did not change and PVR decreased by 4.8 Wood units/m². In the nine placebo-treated patients, the 6-minute walk distance decreased by 6 m, the Borg dyspnea score increased by 0.97 (0–10 scale), the dyspnea-fatigue rating decreased by 0.25, Q decreased by -0.03 l/min/m², Ppa by 2.4 mmHg and PVR increased by 0.2 Wood units/m². However, none of the differences between treprostinil- and placebo-treated groups reached a p < 0.05 level of significance [30].

Pivotal trial
The pivotal 12-week trial included two parallel North American and European international, multicenter, double-blind, randomized, parallel, placebo-controlled studies in a total of 470 patients with PAH aged 8 to 75 years. To date this is the largest randomized controlled trial ever performed in PAH. All the patients who completed the placebo-controlled studies were allowed to continue therapy in an open-label extension protocol. Entry criteria included stability under optimal
conventional treatment. Randomization was stratified according to associated condition (PPH, PAH associated to connective tissue disease and PAH associated to congenital cardiac shunts), baseline exercise capacity (6-minute walk distance 50–150 vs. 151–450 m) and baseline vasodilator use (yes/no). The primary end point was exercise capacity, as assessed by the 6-minute walk distance, which was determined by a trained, blinded test administrator after a previous practice walk test within the 6 weeks before randomization. A Borg dyspnea score was obtained immediately after each 6-minute walk test (0 = no dyspnea, 10 = maximum dyspnea). Principal reinforcing endpoints were a dyspnea-fatigue rating and a clinical score. The dyspnea-fatigue rating consisted of three components, each of which rated on a scale of 0–4 (worst to best): magnitude of task, magnitude of pace and functional impairment, with an aggregate score of 0–12. The clinical score included a specified list of symptoms (dyspnea, orthopnea, fatigue, chest pain, dizziness, syncope, palpitations and edema) and signs (loud pulmonic sound, right ventricular third sound, right ventricular fourth sound, right ventricular heave, tricuspid insufficiency murmur, pulmonic insufficiency murmur, hepatomegaly and jugular vein distention at 45°). A simplified clinical score of only five of these items, dyspnea, fatigue, chest pain, dizziness, and syncope was also used and proved equally sensitive to therapy. Signs and symptoms of the disease were also evaluated on discontinuation of the study due to patient’s deterioration requiring intravenous epoprostenol, transplantation, or death. The secondary end points were the Borg score and hemodynamics (right atrial pressure, Ppa, pulmonary artery wedge pressure, Q, heart rate and mixed venous oxygenation saturation [SvO₂]). Quality of life (QOL) was assessed using the Minnesota Living with Heart Failure questionnaire. 6-minute walk test, Borg score, dyspnea-fatigue rating, clinical score and QOL were obtained at baseline and 1, 6 and 12 weeks after randomization. The hemodynamic measurements were obtained at baseline and 12 weeks after randomization.

Analysis was performed on an intention to treat basis. The patients who failed to complete the study were given the worst rank. Those who failed to complete the study due to an adverse effect or for administrative reasons, had their last double-blind rank carried forward. The two studies were analysed individually and together. Changes in the 6-minute walk distance from baseline to week 12 were compared between treatment groups using an intention-to-treat, nonparametric analysis of covariance, prespecified as the primary analysis. Changes from baseline to week 12 in signs and symptoms score, dyspnea-fatigue rating, Borg dyspnea score and QOL were compared between treatment groups, using the Wilcoxon Rank Sum test without imputation. Between treatment group changes in hemodynamic variables were compared using a parametric analysis of covariance adjusting for baseline value without imputation.

Trentoprinil was initiated at a fixed dose of 1.25 ng/kg/min (or half of this dose if not tolerated) and then progressively increased if tolerated by 1.25 ng/kg/min during the first 4 weeks, then by 2.5 ng/kg/min per week until a maximum of 22.5 ng/kg/min was reached at week 12. In fact, the final doses achieved remained below these target doses, at 9.3 ± 0.4 ng/kg/min in the treprostinil group and 19.1 ± 0.3 ng/kg/min in the placebo group. This was explained by slowing of dose escalation because of infusion site pain.

The two study groups were comparable in age, gender distribution and severity of pulmonary hypertension, with 82% of the patients in NYHA functional class III, 11% in NYHA class II and 7% in NYHA class IV, and an average baseline 6-minute walk distance of 326 m. PAH was primary in 58% of the patients, connective tissue disease-associated in 19% and congenital cardiac shunt-associated in 23%.

In analyzing both studies together, the overall median 6-minute walk increased by 10 m in the treprostinil group and did not change in the placebo group, with a between group effect of 16 m (Hodges–Lehman estimate, p = 0.0064) (FIGURE 1). Results of the two different studies were consistent with each other and the pooled analysis (p = 0.0607 and 0.055, respectively). Although the individual trials did not reach the prespecified criteria (i.e., pooled p < 0.01 with one of the two trials, p < 0.05), it was reasonably concluded that the results showed a treatment effect of treprostinil in PAH. This conclusion was supported by significant improvements in dyspnea-fatigue ratings, clinical score, Borg dyspnea score, pulmonary hemodynamics and physical dimension of QOL. Like in other prostacyclin trials in PPH or PAH, hemodynamic changes after 12 weeks of treatment, though
significant, were relatively minor, within the treprostinil and placebo groups respectively, showing Ppa + 2.3 versus -0.7 mmHg, Q + 0.12 versus -0.06 l/min/m², PVR - 3.5 vs. + 1.2 Wood units/m² and SvO₂ + 2 vs. -1.4%. On the other hand, the clinical score was already significantly improved by treprostinil after 6 weeks of treatment, illustrating the sensitivity of the 6-minute walk distance to clinical state in PAH patients. Both the 6-minute walk distance and the Borg score were already significantly improved at 6 weeks of treatment, in spite of a relatively low dose of treprostinil (FIGURE 1).

A covariate analysis showed no interactions between treprostinil treatment effect and age, gender, race or diagnostic category. However, a posteriori subgroup analysis showed similar responses to treprostinil in PPH and connective tissue disease-associated PAH but no significant change in 6-minute walk distance in congenital shunt-associated PAH. This difference was explained by the inhomogeneous character of that subgroup and also by the fact that congenital cardiac shunt-associated PAH tends to be stable for much longer periods of time than other PAH categories. On the other hand, there were significant interactions between treprostinil treatment effect and NYHA functional class, baseline 6-minute walk distance and SvO₂. Thus, the 6-minute walk distance was improved by 54 m in the 34 patients in NYHA class IV, 17 m in the 382 patients in NYHA class III and only 2 m in the 53 patients who were in NYHA class II.

In fact, patients with PPH or connective tissue disease-associated PAH who started in NYHA functional class III/IV showed a treatment effect that was comparable to other randomized controlled trials in PAH patients [31]. Furthermore, there was a dose relationship such that the higher the treprostinil dose achieved, the greater the increase in 6-minute walk distance (FIGURE 2). Based on this observation, it is to be regretted that the average dose achieved in the treprostinil group was only 9.3 ng/kg/min, far below the target 22.5 ng/kg/min dosing, thereby preventing full disclosure of treprostinil efficacy. It was only found later, from the experience of many centers, that infusion site pain is not directly dependent on rate of treprostinil dose increase.

Infusion site pain occurred in 85% of the treprostinil-treated patients and in 27% of the placebo-treated patients. The study was discontinued in 18 patients (8%) in the treprostinil group due to intolerable abdominal infusion site pain versus one in the placebo group. Other adverse events were those classically related to the use of prostacyclin, such as diarrhea, jaw pain, flushing and lower limb edema, which occurred more often in the treprostinil group. There were no other significant side effects.

Long-term observations
By the end of 2002, 843 patients with PAH had been treated with open label treprostinil [32]. The average dose was approximately 25 ng/kg/min at 1 year, 37 ng/kg/min at 2 years and 44 ng/kg/min at 3 years, ranging from 0.3 to 137 ng/kg/min. Along with this progressive increase in dose, there was a continued increase in exercise capacity in those patients who remained on treprostinil therapy. The mortality at 3 years was similar to that observed with epoprostenol (survival rates of 70% and 63% respectively), compared with 46% in historical controls from before the prostacyclin era [9,10,32]. More prolonged experience, stretching up until the end of 2003 in some centers, with patients having been treated for up to 5 years, confirm trends of persistent improvement and decreased mortality (FIGURE 3) [33]. Overall, the tolerance and safety profile of long-term treprostinil appear to be excellent, with local infusion site pain that is manageable in the majority of patients, prostacyclin-related side effects most often controlled by dose adjustments and no significant changes in clinical chemistry, hematology, anticoagulation (question of mild increase, INR 0.2 to 0.3) and urine analysis [32,33].
Transitioning

Transition from intravenous epoprostenol to subcutaneous treprostinil has been achieved in a number of patients. Initially undertaken because of life-threatening complications of chronic intravenous epoprostenol therapy, such as embolic stroke and repeated sepsis [34], the procedure is now also performed in several centers on the request of patients for the purpose of increased autonomy and comfort. Transitioning is to be performed in a hospital environment under the supervision of a medical team experienced in the treatment of PAH. Under non-invasive hemodynamic monitoring including heart rate and blood pressure measurements and echocardiography as needed, epoprostenol is progressively decreased and treprostinil increased, with overdosing and underdosing symptoms-directed adjustments, in no more than 1 to 4 days [34]. Usually the same clinical state and exercise capacity is obtained with a treprostinil dose that is about 80% of the previous epoprostenol dose [34]. Most transitioned patients express satisfaction and relief, in spite of local infusion site pain in most of them and present with continued improvement in exercise capacity over time [33,34].

There is no reported experience of transitioning treprostinil to epoprostenol or other prostacyclin or endothelin receptor blocker therapies.

Indications & usage

Chronic subcutaneous treprostinil should be considered in the treatment algorithm of patients with PAH in functional classes II, III and IV.

Although the treatment has been used in patients of all ages, clinical studies did not include a sufficient number of patients aged under 16 or over 65 years to allow for specific recommendations for pediatric or geriatric use.

As stated above, dosage should be decreased and adapted more slowly and cautiously in patients with liver or renal diseases. No clinically significant interferences with other therapies, including paracetamol, warfarin or digoxin, have been reported.

The official recommendation is to start treprostinil at a dose of 1.25 ng/kg/min, which is increased by 1.25 ng/kg/min per week during the first 4 weeks, then by 2.5 ng/kg/min per week until the maximum clinical improvement is achieved with no excessive prostacyclin-type side effects. However, most centers now start at 1 ng/kg/min and increase at the same rate as with intravenous epoprostenol, allowing for an optimal dose around 10 to 12 ng/kg/min or more to be reached during the first week, with weekly adaptations thereafter aiming at optimal clinical efficacy with minimal side effects. This strategy appears to be safe, allows for more rapid and effective relief in severely ill patients and out-runs the local infusion site pain, which is of course better tolerated in the context of decreased dyspnea and fatigue.

Local infusion site pain will occur in around 80% of patients and may be intolerable in 10 to 15% of them. It varies markedly from one patient to another, from one infusion site to another, is primarily related to initiation of infusion and often not always, improves after several months. This side effect is generally manageable by relocation of infusion site, cold or hot compresses, a variety of local ointments and paracetamol. Sometimes, a short course of high-dose corticosteroids, such as prednisolone 2 mg/kg/day during several days may help the patient through, and narcotic drugs have been used in some centers. These more aggressive interventions may appear necessary when patients present with severe pain altering QOL. In these cases, especially if on high dose treprostinil, transitioning to intravenous epoprostenol may fail because of major prostacyclin-type side effects of equivalent dose intravenous epoprostenol and carries the risk of clinical destabilization.

It has been the experience in expert centers in general that prostacyclin-type side effects tend to be less severe with treprostinil than with epoprostenol, allowing for more rapid increase in dosing and symptomatic relief. The reasons for this better tolerance of treprostinil are unclear, but may be related to smoother, more progressive increases in plasma levels.

Expert opinion & recommendations

Treprostinil has a place in current therapy of PAH

Patients with PAH have to undergo an acute reversibility testing with short acting pulmonary vasodilator interventions, inhaled NO, intravenous epoprostenol, intravenous adenosine or even inhaled iloprost, which is now used for this purpose in many centers, for initial diagnostic right heart catheterization. This is a complex and potentially risky procedure, therefore preferably

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**Figure 3.** Progressive increase over time in mean ± SE 6-minute walk distance in patients on long-term treprostinil therapy. Patients who can be maintained on chronic subcutaneous treprostinil experience a continuing improvement in exercise capacity.
done in the intensive care environment of a specialized center. A positive acute response, defined as a decrease in both Ppa and PVR of at least 25%, ideally with near normalization of pulmonary hemodynamics [34], which is observed in around 5% of the patients [35], is an indication for a trial of calcium channel blocker therapy. Calcium channel blocker therapy has to be evaluated after a few weeks and continued only in case of persistent clinical improvement, with patients in NYHA class I or II, which is to be expected in only half of the acute responders [35]. Conventional therapy, which includes lifestyle counseling, anticoagulants, diuretics and sometimes digitals and supplemental oxygen, has to be optimized in all the patients [34]. Patients with PAH and no positive response to acute vasodilator testing, or no sustained response to calcium channel blocker therapy, may be treated either with endothelin receptor blockers (oral bosentan) or with a prostacyclin analogs (inhaled prostacyclin, subcutaneous treprostinil or intravenous epoprostenol).

The therapeutic strategy now used in most centers is to start NYHA class III patients on an oral drug. For this purpose, only bosentan is currently registered. Beraprost has not been approved. There is no validated strategy for NYHA class II patients. In practice, many of them are already being started on bosentan in many centers. Patients in NYHA class IV may be started on either intravenous epoprostenol, subcutaneous treprostinil, or inhaled prostacyclin. Intravenous epoprostenol and inhaled prostacyclin are indicated in unstable patients, in whom a rapid prostacyclin impregnation is desirable. Patients on bosentan therapy who present with hepatic intolerance (estimated around 5 to 10%) or with a clinical deterioration can be transitioned or supplemented with inhaled prostacyclin, intravenous epoprostenol, or subcutaneous treprostinil. Probably most patients under intravenous epoprostenol can be transitioned to treprostinil. Choices between prostacyclin derivatives will be influenced by local experience, drug availability and patients’ choices. It must be emphasized that the safety of combined therapies has not yet been sufficiently documented to allow evidence-based recommendations to be made.

A specific concern has been raised with respect to intravenous epoprostenol for patients with PAH associated with connective tissue disease, portal hypertension, or HIV infection, in whom the responses to this therapy may be less favorable because of delivery system problems, mainly sepsis, and also the risk of thrombocytopenia and ascites in hypersplenic patients. Better results may be expected with subcutaneous treprostinil in these patients. In addition, due to a concern about the liver toxicity of endothelin receptor blockers, there may be a preference to start patients with portopulmonary hypertension on prostacyclin therapy, which will then be preferably treprostinil or iloprost.

Hope has been recently raised about phosphodiesterase-5 inhibitors, in particular sildenafil but these agents have not yet been evaluated by a randomized-controlled study, so no recommendation about their use can be made.

In conclusion, the availability of continuous subcutaneous treprostinil therapy has provided an important additional therapeutic agent in PAH. Apart from NYHA class IV patients, the first line of therapy in PAH has to be an oral drug and for this purpose the only registered one until now is bosentan. However, as not all patients respond to a single drug, responses may not be sustained and any treatment may have to be interrupted because side effects, it is important that prostacyclin analogs remain available with a choice of different routes of administration, allowing for replacements and/or combination therapy.

**Five-year view**

The management of PAH will continue to improve with earlier diagnosis, and better drugs and modes of administration. Longer acting prostacyclin analogs will be proposed, administered by inhaled, oral, subcutaneous and intravenous routes. Selective endothelin receptor blockers are currently being evaluated in randomized controlled trials. Phosphodiesterase-5 inhibitors show promise, with results of a first randomized controlled trial expected in 2004. The challenge will be to design face-to-face comparison and combination trials as soon as possible. As it currently stands, none of the newly proposed drugs have been shown to be superior to prostacyclins and it remains uncertain whether multi-drug approaches improve clinical state and survival. As the 3 year mortality of patients with PAH remains distressingly high and none of the currently evaluated drugs offers a cure, more innovative fundamental research will be needed to identify new therapeutic approaches.

**Key issues**

- Treprostinil is for the treatment of pulmonary arterial hypertension, an uncommon disease defined by an increase in pulmonary vascular resistance without identifiable causal cardiac or pulmonary disease.
- Treprostinil is a prostacyclin analog, administered as a chronic subcutaneous infusion.
- Subcutaneous treprostinil is generally a safe and efficacious alternative to reference intravenous epoprostenol therapy in patients with pulmonary arterial hypertension.
- Treprostinil is currently prescribed for NYHA class III patients who have shown an unsatisfactory response to the oral endothelin receptor blocker, bosentan, and for NYHA class IV patients as first line therapy or transition from intravenous epoprostenol.
- The success of subcutaneous treprostinil therapy relies on rapid increase in dosing, aiming at a target dose of maximum clinical response for minimal side effects after one week of treatment.
- Treprostinil has a place in multi-drug approaches currently being developed in the treatment of pulmonary arterial hypertension.
References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest
1 Rubin LJ. Primary pulmonary hypertension. N. Engl. J. Med. 336, 111–117 (1997).
•• Reference review on primary pulmonary hypertension.
2 Humbert M, Nunes H, Sitbon O et al. Risk factors for pulmonary arterial hypertension. Clin. Chest Med. 22, 459–475 (2001).
3 Humbert M, Trembath RC. Genetics of pulmonary hypertension: from bench to bedside. Eur. Respir. J. 20, 741–749 (2003).
•• Reference updated classification of pulmonary hypertension.
4 Fishman AP. Clinical classification of pulmonary hypertension. Clin. Chest Med. 22, 385–391 (2001).
5 Naeije R, Vachiéry JL. Medical treatment of pulmonary hypertension. N. Engl. J. Med. 347, 322–329 (2002).
•• The first randomized controlled trial in primary pulmonary hypertension, which led to FDA approval of prostacyclin therapy.
6 Higenbottam TW, Spiegelhalter D, Scott JP et al. Prostacyclin (epoprostenol) and heart-lung transplantation as treatments for severe pulmonary hypertension. Br. Heart J. 70, 366–370 (1993).
7 Barst RJ, Rubin LJ, Long WA et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N. Engl J. Med. 334, 296–301 (1996).
•• Parallel randomized controlled trial of epoprostenol in pulmonary arterial hypertension associated to scleroderma spectrum of disease.
8 Badesch DB, Tapson VF, McGoon MD et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. Ann. Intern. Med. 132, 425–434 (2000).
•• Parallel randomized controlled trial of epoprostenol in pulmonary arterial hypertension associated to scleroderma spectrum of disease.
9 Sitbon O, Humbert M, Nunes H et al. Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: prognostic factors and survival. J. Am. Coll. Cardiol. 40, 780–788 (2002).
•• Survival data for patients on chronic intravenous epoprostenol.
10 McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. Circulation 106, 1477–1482 (2002).
•• Survival data for patients on chronic intravenous epoprostenol.
11 Rosenzweig EB, Kerstein D, Barst RJ. Long-term prostacyclin for pulmonary hypertension with associated congenital heart defects. Circulation 99, 1858–1865 (1999).
12 Herve P, Lebrec D, Brenot F et al. Pulmonary vascular disorders in portal hypertension. Rev. Respir. J. 11, 1153–1166 (1998).
13 Nunes H, Humbert M, Sitbon O et al. Prognostic factors for survival in human immunodeficiency virus-associated pulmonary arterial hypertension. Am. J. Resp. Crit. Care Med. 167, 1433–1439 (2003).
14 Nagaya N, Sasaki N, Ando M et al. Prostacyclin therapy before pulmonary thromboendarterectomy in patients with chronic thromboembolic pulmonary hypertension. Chest 123, 338–343 (2003).
15 Galí N, Humbert M, Vachiéry JL et al. Effects of beraprost sodium, an oral prostacyclin analog, in patients with pulmonary arterial hypertension. J. Am. Coll. Cardiol. 39, 1496–1502 (2002).
•• Randomized controlled trial showing efficacy of oral beraprost.
16 Olszewsky H, Simonneau G, Galí N et al. Inhaled iloprost is an effective treatment for severe pulmonary hypertension. A double-blind, placebo-controlled, multicenter study. N. Engl J. Med. 347, 322–329 (2002).
•• Randomized controlled trial showing efficacy of inhaled iloprost.
17 Simonneau G, Barst RJ, Galí N et al. Continuous subcutaneous infusion of treprostinil, a prostacyclin analog, in patients with pulmonary arterial hypertension. Am. J. Respir. Crit. Care Med. 162, 800–804 (2002).
•• Randomized controlled trial showing efficacy of subcutaneous treprostinil.
18 Rubin LJ, Badesch RM, Barst R et al. Bosentan therapy for pulmonary arterial hypertension. N. Engl J. Med. 346, 896–903 (2002).
•• Randomized controlled trial showing efficacy of oral bosentan.
19 Barst RJ, Langleben D, Frost A et al. Sitaxsentan therapy for pulmonary arterial hypertension. Am. J. Resp. Crit. Care Med. 169(4), 441–447 (2004).
•• Randomized controlled trial showing efficacy of oral sitaxsentan.
20 Michelakis ED, Tymchak W, Noga M et al. Long-term treatment with oral sildenafil is safe and improves functional capacity and hemodynamics in patients with pulmonary arterial hypertension. Circulation 108, 2066–2069 (2003).
21 Steffen RP, de la Meta M. The effects of 15AU81, a chemically stable prostacyclin analog, on the cardiovascular and renin–angiotensin systems of anesthetized dogs. Prostaglandins Leukot. Essent. Fatty Acids 43, 277–286 (1991).
22 McNulty MJ, Saitild JM, Steffen RP. The pharmacokinetics and pharmacodynamics of prostacyclin analog 15AU81 in anesthetized beagle dog. Prostaglandins Leukot. Essent. Fatty Acids 48, 159–166 (1993).
23 Remodulin™, Treprostinil sodium. Investigators Brochure. United Therapeutics Corporation, MD, USA (2002).
24 Wade M, Baker FJ, Roscigno R et al. Absolute bioavailability and pharmacokinetics of treprostinil sodium administered by acute subcutaneous infusion. J. Clin. Pharmacol. 44, 83–88 (2004).
25 Wade M, Hunt TL, Lai AA. Effect of continuous subcutaneous treprostinil therapy on the pharmacodynamics and pharmacokinetics of warfarin. J. Cardiovasc. Pharmacol. 41, 908–9015 (2003).
26 Phares KR, Weiser WE, Miller SP, Myers MA, Wade M. Stability and preservative effectiveness of treprostinil sodium after dilution in common intravenous diluents. Am. J. Health Syst. Pharm. 60, 916–922 (2003).
27 Eddahibi S, Morrell N, d’Ortho MP, Naeije R, Adnot S. Pathobiology of pulmonary arterial hypertension. Eur. Respir. J. 20, 1559–1572 (2002).
28 Clapp LH, Finney P, Turcato S, Tran S, Rubin LJ. Tinker Differential effects of stable prostacyclin analogs on smooth muscle proliferation and cyclic AMP generation in human pulmonary artery. Am. J. Respir. Cell Mol. Biol. 26, 194–201 (2002).
29 Raychaudhuri B, Malur A, Bonfield TL et al. The prostacyclin analog treprostinil blocks NFκB nuclear translocation in human alveolar macrophages. J. Biol. Chem. 277, 33344–33348 (2002).
30 McLaughlin VV, Gaïne SP, Barst RJ et al. Efficacy and safety of treprostinil: an epoprostenol analog for primary pulmonary hypertension. J. Cardiovasc. Pharmacol. 41, 293–299 (2003).
• Pilot study on treprostinil in pulmonary arterial hypertension.

31 Galie N, Manes A, Branzi A. The new clinical trials on pharmacological treatment in pulmonary arterial hypertension. *Eur. Respir. J.* 20, 1037–1049 (2002).

• Update on treatment of pulmonary arterial hypertension.

32 Gibbs JSR, Arneson CP. Chronic infusion of treprostinil is safe and appears to prolong survival over a three-year period in patients with pulmonary arterial hypertension. *Circulation* 106 (Suppl. II), 575 (2002).

33 Vachiery JL, Gautier MT, Huez S, Retailleau K, Naeije R. Long-term subcutaneous treprostinil therapy evokes both survival benefits and continuous dose-dependent efficacy improvements in patients with pulmonary arterial hypertension. *Circulation* 108 (Suppl. IV) 400, (2003).

34 Vachiery JL, Hill N, Zwieck D et al. Transitioning from iv. epoprostenol to subcutaneous treprostinil in pulmonary arterial hypertension. *Chest* 121 1561–1565 (2003).

• Study showing that transition from epoprostenol to treprostinil is feasible.

35 Sitbon O, Humbert M, Loos V et al. Who benefits from long-term calcium-channel blocker therapy in primary pulmonary hypertension? *Am. J. Resp. Crit. Care Med.* 167, A440 (2003).

• Study showing low incidence of benefit of long-term calcium channel blocker therapy in primary pulmonary hypertension.

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