# What's on the Horizon in Therapy, From Current Approaches to Experimental Agents

**Richard N. Channick, MD**
Associate Professor of Medicine
Pulmonary and Critical Care Division
University of California
San Diego Medical Center
San Diego, California.

The past several years have seen dramatic changes in the therapeutic options and outlook for patients with pulmonary arterial hypertension (PAH). Increasing experience with existing therapies, development of new therapies, and expanding knowledge of how to follow patients undergoing therapy have ushered in great excitement for patients and healthcare professionals alike.

This article provides an overview of new therapeutic strategies in PAH, discussing where current treatments fit in and what applications of current therapy or new therapies are on the horizon. A standard approach to following patients during therapy and making decisions regarding changes in management is also proposed

## CURRENT THERAPIES

### Calcium Channel Antagonists

This class of vasodilating drugs has been utilized in the treatment of PAH for many years. Medications such as amlodipine, nifedipine, and diltiazem are readily available and relatively inexpensive. Although there has never been a randomized trial of these agents in PAH, early reports suggested that a subgroup of patients who were acutely vasoreactive benefited from long-term calcium channel antagonist therapy.[1] Recent data, however, suggest that only a very small percentage of patients fall into this group. Sitbon et al., in a recent retrospective analysis of more than 500 patients found that 12% of patients were acutely vasoreactive and thus were given calcium channel blockers.[2] Of this group, only one half were felt to have achieved a long-term benefit from these agents, with improved functional status and no need for additional therapy. Analysis of these data suggested fall in PAP and PVR toward normal (mean PAP <37 mm Hg, PVR <8 Wood units) during the acute vasodilator test predicted who would be in this "favorable" group

Given that only about 5% of all PAH patients appear to benefit from calcium channel blockers and that these agents can have substantial adverse effects, including symptomatic leg edema and hypotension, empiric therapy with calcium channel blockers is strongly discouraged.

### Bosentan

Bosentan, an endothelin receptor antagonist and the only approved oral medication in the United States has quickly arrived as a mainstay of therapy for PAH. The drug is currently approved for patients with WHO functional class 3 or 4 status, a result of two randomized, placebo-controlled trials showing significant efficacy in improving 6-minute walk distance.[3,4] Additionally, improvement in pulmonary hemodynamics and functional status and prevention of clinical worsening were noted. The improvement in hemodynamic and functional status appears to be sustained, as demonstrated in a recent report by Sitbon et al.[5] in which these parameters persisted at 1-year follow-up.

Additional long-term data have clarified and strengthened the role of bosentan as first-line therapy in most patients with PAH. Analysis of 169 patients enrolled in the pivotal bosentan trials who continued bosentan therapy demonstrated a 3-year Kaplan-Meier estimate of survival of 86%, compared with a predicted survival of 48% based on an NIH equation using baseline hemodynamic parameters.[6] In this cohort, at 1 and 2 years, the percentage of patients being maintained on bosentan alone was 85% and 70%, respectively. The remainder of the patients had died, had been switched to another therapy, or had had additional PAH therapy added. It should be noted that 82% of this cohort was in functional class 3 and 9% in class 4 at initiation of bosentan therapy.

These data suggest that beginning oral bosentan as sole first-line therapy is associated with excellent long-term outcome even if additional or alternative therapy is sometimes necessary.

Data are now emerging on bosentan as part of a combination regimen with epoprostenol. One placebo-controlled study, BREATHE-2, demonstrated that in patients beginning epoprostenol therapy, concomitant oral bosentan was well tolerated, and there was a trend toward greater improvement in total pulmonary resistance with the combination compared with epoprostenol alone (-36% vs –22%).[7] Beneficial effects of bosentan added to inhaled iloprost have also been demonstrated. In one study, patients receiving long-term inhaled iloprost demonstrated further improvement in $VO_2$max when bosentan was added.[8] Clearly, further data are needed before firm recommendations can be made regarding combination regimens for treating PAH.

Another new area of study is the potential of transitioning patients from parenteral to oral therapy. In one recently published study, 4 patients who had been receiving long-term epoprostenol maintenance therapy and who had achieved near-normal pulmonary hemodynamics were weaned from

epoprostenol to oral bosentan (as well as calcium channel blockers in 3 and sildenafil in 1).[9] Follow-up of at least a year demonstrated continued excellent functional and hemodynamic status without epoprostenol. A similar study, recently presented at the American Thoracic Society's annual conference, found that 14 of 59 patients were able to be weaned from parenteral prostenoid therapy after the addition of bosentan.[10] Given the potential serious risk of weaning epoprostenol, however, additional follow-up and experience are necessary before routine "transitioning" can be recommended

Finally, data are emerging or being generated regarding other potential indications for bosentan, such as use in functional class 1 or 2 patients and in patients with fibrotic lung disease, HIV, or congenital heart disease.

## Epoprostenol

Epoprostenol as continuous intravenous therapy has been available in the United States since 1995. The beneficial effects this drug has had on the course of patients with even severe "end-stage" PAH cannot be overstated. Reports over the years have confirmed both the short- and long-term efficacy of epoprostenol.[11-14] Three-year survival with epoprostenol has been reported to be 63% by both Sitbon et al.[13] and McLaughlin et al.[14] Desired benefits from other therapies should use epoprostenol as a benchmark.

As experience has been gained, some new approaches to using epoprostenol have developed. For one, the dosing level of epoprostenol has decreased significantly, partially based on findings that some patients can have worsening symptoms of fatigue due to overdosing of the drug causing a high cardiac output state.[15] Also the myriad side effects related to epoprostenol are gaining greater appreciation. Thrombocytopenia, painful neuropathy of the lower extremities, and significant weight loss with ascites are all now recognized effects of long-term treatment with epoprostenol.

In addition, contrary to what was previously thought, patients often do not develop tolerance to epoprostenol and, in fact, therapy is sometimes maintained with a constant dose for years. Although there is no "standard" dosing of epoprostenol, current experience would suggest that most patients are receiving 30 to 40 ng/kg/min after one year of therapy. The caveat of "give enough but not too much" applies well to epoprostenol therapy.

There are also new data to suggest that the benefit epoprostenol will have is generally clear by the end of one year of therapy. Sitbon et al demonstrated that subsequent survival in patients treated with epoprostenol was correlated with improvement in total pulmonary resistance of >30% and functional status to class 2 after 3 months of epoprostenol therapy.[13] This concept is an important one; the status of a patient prior to initiation of therapy may be less important than the response to that therapy.

Despite the "downside," epoprostenol is felt to be first-line therapy for the most severely ill PAH patients. Although experts differ on who these patients are, it is generally agreed that a patient with late class 4 status who is short of breath at rest, who has syncope, and who has right ventricular failure on catheterization (high right atrial pressure, low cardiac output) should receive epoprostenol therapy as soon as possible.

## Treprostinil

The prostacyclin analogue treprostinil is approved as a continuous subcutaneous infusion for functional class 2, 3, and 4 patients with PAH based on efficacy demonstrated in a randomized controlled trial of 470 patients demonstrating a 16-meter 6-minute walk treatment effect.[16] Further analysis of these data suggested that most of the benefit on 6-minute walk distance occurs at higher doses of the drug (over 12 ng/kg/min). Recently presented data reported a sustained benefit of treprostinil.[17]

The potential advantages of subcutaneous treprostinil over intravenous epoprostenol include avoidance of an indwelling intravenous catheter, a more portable pump, no need for reconstitution of the medication, and stability at room temperature.

The major challenge to treprostinil has been the side effect of infusion site pain. This symptom has led to a high rate of discontinuation of therapy, need for opioid analgesia, and reduced quality of life for some patients. No clearly effective remedy for this problem has emerged. Thus, where treprostinil fits in the treatment scheme is not clear. Given the longer half-life of treprostinil compared with epoprostenol, the possibility of its use as an effective intravenous or inhaled therapy is being examined.

## Iloprost

Inhaled iloprost, delivered via a hand-held nebulizer, has recently been approved in Europe, based on positive results from a large randomized, placebo-controlled trial.[18] In this 12-week study of 203 patients, 17 % of patients receiving inhaled iloprost met the combined clinical end point of improvement by one functional class and increase in post-inhalation 6-minute walk distance of at least 10% compared with only 5% of placebo patients meeting this end point.

The drug, in addition, appears to have fewer systemic effects than intravenous or subcutaneous prostacyclin preparations. One challenge of this therapy is the need for six to nine treatments daily, potentially limiting patient acceptability. Early reports suggest that addition of oral sildenafil may prolong iloprost's hemodynamic benefits,[19] but further study is needed. Nevertheless, inhaled iloprost offers the possibility of an effective inhaled prostacyclin and plans to study the medication in the United States are under way.

On the basis of existing data and level of evidence, a treatment algorithm was recently developed at the Third World Symposium on Pulmonary Hypertension held in Venice, Italy, the results of which were published in the previous edition of *Advances in Pulmonary Hypertension*.

## Lung Transplantation

Lung or heart-lung transplantations for treatment of PAH have been performed since about 1980. The role of transplantation for this disease, however, is changing. With the advent of effective medical therapies, it appears that significantly fewer transplantations are being performed for PAH. Patients doing "well" on medical therapy are often placed on the inactive list (status 7). In addition, recent data confirm that overall 5-year survival after lung transplantation is 50% to 60%, not a clear advantage over medical therapies. Nevertheless, in patients in whom medical therapies fail, lung transplantation may be the only option.

Most experts take the approach of listing patients when they begin parenteral prostenoid therapy and potentially placing patients on hold if significant improvement occurs with the medication.

More recently, proposals for prioritizing lung transplant recipients have been set forth with the goal of transplanting the "sickest" patients first. As of this writing, no priority protocol is in place for PAH patients.

## NEW APPROACHES TO FOLLOWING PATIENTS DURING THERAPY

Once one of the above medical therapies is initiated, determining if that therapy is benefiting the patient is critical in assessing the need for additional or alternative therapy, the need for lung transplantation, or even the need for referral to a pulmonary hypertension center. What are the important measures of improvement? Data are now available that suggest both invasive and noninvasive markers of prognosis and response to treatment. As mentioned above, for instance, a fall in total pulmonary resistance of >30% after 3 months of epoprostenol therapy has been shown to predict subsequent 5-year survival.[13] It follows then, that lack of significant fall in total pulmonary resistance should trigger additional therapy, such as lung transplantation. Noninvasively, a recent report has shown that beta natriuretic peptide (bNP) levels, which have been shown to be elevated in PAH patients at baseline, also predict survival, with levels greater than or equal to 150 picograms/milliliter being associated with increased mortality.[20] Finally, in a recent study, troponin levels correlated with survival in PAH patients.[21]

Although exactly how to use these various markers in making treatment decisions is still evolving, one reasonable approach would be as follows for a functional class 3 PAH patient:

1. Start bosentan therapy.
2. Check functional class, exercise capaci, and bNP levels after 3 months of therapy. Consider repeat right heart catheterization to confirm at least 30% improvement in total pulmonary resistance. If favorable parameters are not met, consider additional therapy (epoprostenol, treprostinil, iloprost) or referral to a pulmonary hypertension center for additional options, including enrollment in a clinical trial.
3. Repeat right heart catheterization 6 to12 months after therapy to ensure fall in total pulmonary resistance; if not, consider referral as above.
4. In patients given epoprostenol, refer for lung transplantation.
5. After 1 year of epoprostenol therapy, if patient is in functional class 2 and 6-minute walk distance is >370 meters, change to inactive status on transplantation list.

This algorithm is only one potential approach. However, the concept of beginning with approved oral therapy and escalating therapy based on defined outcome measures is an important new advance in treating PAH.

## EXPERIMENTAL APPROACHES

The above-mentioned treatments are available in Europe or the United States and can be characterized as representing standard therapy. What new treatments are on the horizon? The following therapies are currently under investigation.

**Table—Summary of Current and Experimental Therapies.**

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| **Approved** |
| Oral bosentan (Tracleer®) |
| Intravenous epoprostenol (Flolan®) |
| Subcutaneous treprostinil (Remodulin®, approved in United States and Canada) |
| Inhaled iloprost (Ventavis®, approved in Europe only) |
| Lung transplantation |
| **Experimental** |
| Sildenafil |
| Sitaxsentan |
| Ambrisentan |
| Statins |
| l-arginine |
| Vasoactive intestinal peptide |

### Sildenafil

Sildenafil, a PDE5 inhibitor, has been suggested as an effective therapy for PAH. Its mechanism of action is likely enhancement of endogenous nitric oxide effects via inhibition of cGMP breakdown. Uncontrolled reports suggest that oral sildenafil improves functional status, pulmonary hemodynamics, or 6-minute walk distance.[22,23] However, no convincing long-term benefit of sildenafil has yet been demonstrated. A large, multicenter, placebo-controlled trial of sildenafil is nearing completion. Until the results from this trial are available, sildenafil must be considered experimental therapy and not used in place of the above-mentioned approved therapies.

### Selective ET-A Antagonists

Two oral endothelin-A receptor antagonists, sitaxsentan and ambrisentan, are currently under investigation. The rationale behind selective endothelin-A receptor antagonism is that the B receptor may serve beneficial roles in increasing endothelin clearance and possibly pulmonary vasodilation. Whether these benefits are significant in patients with PAH is not known.

Sitaxsentan was shown in a 12-week trial of 178 patients to lead to an improvement in 6-minute walk distance of 34 meters.[24] Although the primary end point, improvement in $VO_2$max, was not met, a second and pivotal trial of this agent is now under way. Investigators studying ambrisentan recently completed a phase 2 trial and will soon begin a phase 3 study.

Other agents for which early reports are emerging and which may represent future therapies include statins, l-arginine, and vasoactive intestinal peptide. The **Table** summarizes current and experimental therapies.

### Conclusions

A wealth of new data and experience have emerged on the treatment of pulmonary arterial hypertension. Randomized placebo-

controlled trials have led to approval of new therapies with significant benefit to patients in terms of symptoms, functional capacity, and survival. Refinement of which therapy should be provided to which patient, when therapy should be changed or supplemented, what the role of combination therapies should be, and which experimental therapies work best, awaits further experience and data.

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