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Therapeutic Options for the Treatment of Pulmonary Hypertension

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Treatment Options for Pulmonary Hypertension

Pulmonary hypertension refers to an abnormal elevation of pulmonary artery (PA) pressure (mean PA pressure > 25 mm Hg at rest and 30 mm Hg with exercise) and can be caused by or associated with a wide variety of conditions. According to the most recent classification of pulmonary hypertension developed in Venice in 2003,[1] pulmonary hypertension can be attributed to:

The therapy of pulmonary hypertension depends on the identification of underlying contributing factors. PAH, which can be idiopathic (formerly referred to as primary pulmonary hypertension) or related to connective tissue disease (usually scleroderma), portal hypertension, HIV disease, ingestion of certain drugs or toxins, or congenital heart disease, had no specific therapy until recently. However, the past decade has seen remarkable progress, and these heretofore devastating and usually lethal forms of pulmonary hypertension now often respond to one form of therapy or another, leading to improved functional capacity and even survival. The following will consider the major pharmacotherapies now available for PAH and suggest a framework for therapeutic decision-making.

General Approach

Some therapies have long been available to treat pulmonary hypertension and are still of value. Fluid retention is common, and adequate diuresis frequently brings about substantial symptomatic improvement. Oxygen supplementation should be provided to hypoxemic patients, either at rest or with exertion or during sleep. Digoxin is often administered for supraventricular arrhythmias or right ventricular dilatation. Based on uncontrolled trials, warfarin anticoagulation is routinely administered to patients with moderate to severe PAH, usually aiming for an INR between 1.5 and 2.5. Phlebotomy has been recommended when the hematocrit exceeds 56, particularly in patients with congenital heart disease. Calcium channel blockers, sometimes in high doses, were considered the most effective pharmacotherapies for pulmonary hypertension prior to the advent of newer specific therapies.[2] Responders to calcium channel blockers, who usually manifest substantial acute vasoreactivity, have an excellent prognosis. Unfortunately, they constitute only 5% to 10% of PAH patients. With the exception of anticoagulation and calcium channel blocker therapy in responders, these therapies should be considered mainly palliative, and although they can be quite useful for ameliorating symptoms, they do not significantly affect the natural history of the disease.

Newer and more effective pharmacotherapies for PAH are now available, starting with prostacyclins in 1996 and, more recently, endothelin receptor antagonists and phosphodiesterase 5 inhibitors. Randomized controlled trials have demonstrated significant benefits for these therapies, but they all have limitations and must be used judiciously. Relative merits of the different therapies, suggested applications, possible combinations, and newer therapies are discussed below.

Prostacyclins

Epoprostenol. Discovered in 1976 by the Nobel Prize-winning team led by John Vane, prostacyclin is a potent vasodilator prostaglandin that is synthesized and released by vascular endothelium and participates in the maintenance of low vascular tone.[3] Possessing antiproliferative and platelet antiaggregatory effects as well, the enzyme that synthesizes it, prostacyclin synthase, has been reported to be reduced in patients with idiopathic PAH.[4] The therapeutic administration of prostacyclin (epoprostenol) as a continuous intravenous infusion to patients with idiopathic PAH was first reported during the 1980s,[5] and a

pivotal randomized, controlled trial on patients with idiopathic PAH was reported in 1996.[6] Enrolling 81 patients, this trial demonstrated a significant improvement in 6-minute walk distance, the major outcome variable, as well as in pulmonary hemodynamics, oxygenation, and survival. Based on these findings, the US Food and Drug Administration (FDA) approved epoprostenol as a continuous intravenous therapy for patients with class III or IV idiopathic PAH. Subsequent studies have demonstrated a substantially improved survival of idiopathic PAH patients treated with intravenous epoprostenol compared with historical controls.[7] In addition, a subsequent randomized controlled trial showed efficacy in improving exercise capacity and hemodynamics in patients with PAH related to scleroderma,[8] although survival was not significantly improved. Other smaller uncontrolled studies suggest that epoprostenol is effective in the treatment of PAH related to congenital heart disease, HIV, and portopulmonary hypertension. These favorable effects of epoprostenol in patients with various forms of PAH are better substantiated than with any other pulmonary hypertension therapy, and it is still considered the therapy of first choice for patients in the New York Heart Association class IV and the last resort when other therapies have failed.

Despite its demonstrated efficacy, intravenous epoprostenol is far from an ideal therapy. It requires daily mixing and must be kept in a cold pack to avoid degradation at room temperature. The infusion pump and cold pack can be carried in a fanny pack, but are cumbersome for many patients. In addition, the need for a permanent transcutaneous intravenous catheter poses risks for line infection and sepsis (estimated to occur in 0.14 patients/year), and sudden occlusion of the catheter can precipitate hemodynamic collapse because of the several minute half-life of the drug. The cost of the drug and administration system are also substantial, amounting to $100,000 to $250,000 annually.

Treprostinil. The shortcomings of intravenous epoprostenol have stimulated the search for alternative therapies. Treprostinil, a prostacyclin analog with a half-life of several hours, was approved by the FDA for subcutaneous administration in 2002. Stable at room temperature, it requires no cold packs and can be administered using a continuous infusion pump that approximates the size of a pager. The drug was shown to be safe and effective in a pivotal trial that demonstrated an average improvement in 6-minute walk distance of 16 meters, approximately a third that reported for epoprostenol.[9] However, an analysis of the dose response to the drug indicated that many patients in the pivotal trial were underdosed because of reluctance to increase the infusion rate in the face of infusion site pain. Patients treated with 14 or more ng/kg/minute had improvements in 6-minute walk distance averaging 36 meters, whereas patients treated with less than 10 ng/kg/minute had virtually no improvement. Follow-up studies demonstrate improvements in 6-minute walk distance that are comparable to those achieved by epoprostenol as higher doses are reached. Because of its subcutaneous route of administration, no need for mixing, and the highly portable pump system, subcutaneous treprostinil has substantial safety and convenience advantages over intravenous epoprostenol. Unfortunately, many patients encounter pain at the infusion site, and a significant minority of patients finds the drug intolerable. Various topical formulations and narcotics bring some alleviation, but this pain has limited the appeal of this form of therapy.

In late 2004, the FDA approved intravenous treprostinil to treat class II to IV PAH. Although this therapy shares with epoprostenol the risks of continuous intravenous administration, it is more convenient because it requires no daily mixing and safer because sudden interruption of the infusion is less threatening with the drug's longer half-life. Dosing of intravenous treprostinil has not been definitively established, but most investigators recommend doubling the doses ordinarily used during epoprostenol infusions.[10] An inhaled form of treprostinil is currently under investigation, and preliminary reports suggest that the hemodynamic effect is sustained for more than 2 hours after only a few inhalations.[11]

Iloprost. Iloprost, another prostacyclin analog with a half-life between those of epoprostenol and treprostinil, has been available in Germany for several years, but received FDA approval only during 2004. A randomized controlled trial in patients with PAH or chronic thromboembolic pulmonary hypertension showed a significant improvement in the 6-minute walk distance,[12] but 5% of patients experienced syncope, presumably because they exerted excessively after the drug effect had waned. The duration of hemodynamic effect averages approximately 90 minutes after inhalation, and the drug requires 6 to 9 nebulizer treatments per 24 hours, each treatment requiring up to 10 to 20 minutes. Although the inhaled route has obvious safety advantages over the intravenous route and avoids the pain of subcutaneous administration, many patients find the frequency of treatments cumbersome.

Oral Beraprost. Beraprost, another prostacyclin analog with a longer half-life than epoprostenol, is suitable for oral administration. Uncontrolled trials in Japan, where the drug is currently available, have suggested beneficial actions in patients with pulmonary hypertension related to congenital heart disease as well as in chronic thromboembolic pulmonary hypertension.[13] Although a 3-month randomized controlled trial in Europe showed a significant improvement in 6-minute walk distance, a subsequent 12-month randomized controlled trial in the United States failed to show sustained benefit, even though there was significant improvement in the 6-minute walk distance at the 3- and 6-month time points.[14] For this reason, the FDA will not

approve oral prostacyclin therapy in the United States at the present time. However, other oral therapies (treprostinil) are under investigation, and further work will be needed to determine whether the lack of the sustained effect for beraprost might be related to insufficient dose escalation or another remediable problem.

Endothelin Receptor Antagonists

The endothelins are a family of vasoactive peptides synthesized and released by endothelial cells. The main vasoactive endothelin, endothelin 1 (ET-1), a 22 amino acid peptide, has higher plasma levels in patients with idiopathic PAH and PAH related to connective tissue disease than in normal controls.[15] Two endothelin receptors have been identified; the A-receptor that is found mainly on the surface of smooth muscle cells and participates in the mediation of vasoconstriction, and the B-receptor, found mainly on the surface of endothelial cells. The B-receptor mediates not only vasoconstriction, but also vasodilation via release of prostacyclin and nitric oxide, and it serves as a clearance receptor for endothelin as well.[16] A number of endothelin receptor blockers have been developed to treat PAH that vary in their specificity for receptor blockade. Although theoretical arguments based on experimental animal evidence can be mounted to support either nonspecific or specific A-receptor blockade as the preferred mode of therapy, there is no convincing evidence from clinical trials to support any one approach.

Nonselective Endothelin Receptor Blockade. Presently, only one endothelin receptor antagonist has received FDA approval for clinical use in the United States -- the oral nonselective blocker, bosentan. This drug was studied in an earlier randomized controlled trial that demonstrated not only a significant improvement in 6-minute walk distance, but also improvements in pulmonary hemodynamics.[17] A subsequent 16-week pivotal randomized controlled trial (BREATHE-1) confirmed the improvement in 6-minute walk distance (44 meters greater compared with placebo) and also showed significant improvements in New York Heart Association functional class and quality-of-life scores, as well as a significant decrease in the rate of clinical worsening.[18] Since its FDA approval in 2001, bosentan has been the most widely prescribed specific pulmonary hypertension therapy. Subsequent long-term follow-up studies demonstrate a 2-year survival of 89% in patients begun on bosentan, with 70% remaining on monotherapy.[19]

The drug is usually well tolerated, but can exacerbate fluid retention and may not bring about clinical improvements for as long as 2 to 3 months after initiation. For this reason, even though the drug was approved for therapy of both class III and class IV patients with idiopathic PAH or PAH related to connective tissue disease, routine monotherapy for class IV patients is inadvisable. Also, the drug causes greater than a 3-fold elevation in liver transaminases in approximately 10% of patients, and liver function tests must be monitored monthly for the duration of therapy. The recommendation is to start at 62.5 mg twice daily for a month and then advance to 125 mg twice daily if liver function tests are acceptable.

Specific A-receptor Blockers. Two specific A-receptor blockers are currently under investigation for the therapy of PAH. The first, sitaxsentan, is approximately 6000-fold more specific for the A than B receptor and has a longer half-life that permits once-daily oral administration. Tested in a 12-week randomized controlled trial (STRIDE-1),[20] it failed to show a statistically significant benefit in the major outcome variable, maximal oxygen uptake at the 100 mg per day dose, but it did show significant improvements in the 6-minute walk distance, pulmonary hemodynamics, and New York Heart Association classification. Because of the failure to show significant benefit in the major end point, further trials have been performed including STRIDE-2, in which daily doses of 50 mg and 100 mg were compared with placebo and open-label bosentan at 125 mg twice daily. A preliminary report[21] shows that 100-mg daily dose of sitaxsentan improves 6-minute walk distance and New York Heart Association class compared with placebo and comparably to bosentan, but the 50-mg daily dose failed to show significant benefit. Liver toxicity tended to be less at the 100-mg dose of sitaxsentan compared with bosentan 125 mg twice daily (3% vs 11%), but the difference was not statistically significant. Sitaxsentan offers the advantages of once daily administration and possibly less liver toxicity than bosentan, but efficacy appears to be comparable. It is currently under consideration for approval by the FDA.

Ambrisentan, another endothelin receptor antagonist that is 18 times more specific for the A than B receptor, is currently undergoing investigation. Like sitaxsentan, it is a once-a-day oral therapy, and preliminary findings suggest that it poses a low risk of liver toxicity.

Phosphodiesterase 5 Inhibitors

Cyclic guanosine monophosphate (GMP) is an intracellular second messenger that has vasodilator and antiproliferative actions. Phosphodiesterase-5 metabolizes cyclic GMP, decreasing intracellular levels, and limiting vasodilator effects. Phosphodiesterase-5 inhibitors slow the metabolism of cyclic GMP, intensifying the vasodilator actions, and several have been approved for the treatment of erectile dysfunction. Presently, only one phosphodiesterase inhibitor, sildenafil, has been tested in PAH and was recently approved by the FDA for the therapy of PAH patients at a dose of 20 mg 3 times daily. A pivotal randomized controlled trial of sildenafil (SUPER-1) (thus far only presented in oral abstract form) showed statistically significant improvements in 6-minute walk distance (45-50 meters), pulmonary hemodynamics, and New York Heart Association class over 12 weeks. There was no significant delay in the time to clinical worsening, unlike bosentan, but the drug was well tolerated. Headache and epistaxis were the only side effects encountered more often than with placebo. Favorable effects are often seen within days of drug initiation. A trial to test the efficacy of a longer-acting phosphodiesterase-5 inhibitor, tadalafil, is just being started. This would presumably allow once-daily or even less frequent administration.

New Potential Therapies

A number of other therapeutic approaches to PAH are being tested or contemplated ( ). Most block mediators or signaling pathways known to be involved in PAH pathogenesis. The thromboxane A-2 antagonist, terbogrel, was studied in a randomized controlled trial that was stopped prematurely when many patients in the treatment arm experienced leg pain.[22] Statins are under consideration as a pulmonary hypertension therapy because they possess anti-inflammatory and antiproliferative actions and have been effective in rodent models of PAH.[23] A small clinical trial is currently under way, but preliminary findings are not yet available. Estrogens have been shown to blunt pulmonary hypertension in some animal models,[24] and a phase 1 clinical investigation is currently underway. Serotonin potentiates smooth muscle cell proliferation in some animal models, and gene mutations of the serotonin transporter have been associated with pulmonary hypertension in chronic obstructive pulmonary disease patients. Accordingly, serotonin receptor inhibitors are being considered as pulmonary hypertension therapies. Gene therapy approaches are also under consideration, such as transfection with the nitric oxide or prostacyclin synthase genes, but suitable long-acting vectors have not yet been developed.

Table. Investigational Agents Under Consideration as PAH Therapies

Thromboxane receptor antagonists
Statins (HMG coreductase inhibitors)
K+ channel openers
NO donors
Estrogens
Rho kinase inhibitors
Angiogenesis factors
Gene therapy NOS, K+ channel openers

Combination Therapy

The success of treating malignancies and congestive heart failure with combination therapies has generated enthusiasm and optimism for combination therapy in PAH. The concept of combining agents with fundamentally different mechanisms of action is attractive; however, few clinical data are available to substantiate the theoretical benefits of combination therapy in PAH. In an uncontrolled study, Ghofrani and colleagues[25] demonstrated that the addition of sildenafil in patients who deteriorated while on iloprost therapy alone restored clinical stability, associated with improvements in 6-minute walk distance.

The combination of prostanoids and endothelin receptor antagonists also appears promising. In the randomized controlled BREATHE-2 trial, bosentan combined with intravenous epoprostenol showed trends toward improved pulmonary hemodynamics compared with epoprostenol with placebo, but the study was underpowered to achieve statistical significance. A series of 16 patients with PAH on prostanoid therapy showed improvement in 6-minute walk distance and functional class after bosentan was added,[26] but results from randomized trials are needed. Preliminary results were recently released on the STEP-2 trial that

randomly added inhaled iloprost vs placebo in patients already receiving bosentan therapy. A significant improvement in 6-minute walk distance was attributable to the addition of iloprost when administered an average of 6 times daily.[27] Few data are available on the combination of endothelin receptor antagonists and sildenafil, but a recent case series described improvement in functional status (> 100-m improvement in 6-minute walk distance) after sildenafil was added in 9 patients deteriorating after a year on bosentan monotherapy.[28]

Even in the absence of supportive data, however, many patients in clinical practice have been empirically placed on combination therapy when the initial agent either fails to bring about the desired improvement, or deterioration occurs after an initial favorable response. Some patients, anecdotally, are being treated with all 3 FDA approved PAH therapies, along with statins and traditional therapies. However, this is very expensive, and we cannot be certain, in the absence of data, that these combinations are beneficial. A number of randomized controlled trials are being initiated that should provide answers to many of the questions surrounding combination therapy over the next several years.

Surgical Therapeutic Options

Lung and heart/lung transplantation as well as atrial septostomy have been available for years to treat severe PAH. With the advent of effective pharmacotherapy, however, the need for these interventions has diminished, but they are still considerations for patients who fail to respond favorably and remain in class III or IV after at least several months of optimal pharmacotherapy. When contemplating lung transplantation, it should be considered that different transplant centers have great variability in waiting times, ranging from several weeks to several years.

Summary and Conclusions

Although we have long had a variety of palliative treatments for pulmonary hypertension that should not be forgotten, in recent years, 3 new pharmacotherapeutic categories have been added to our therapeutic regimen for PAH: the prostacyclins, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors. Each year, new agents are being added to each of these new categories, and newer therapeutic avenues are being investigated or contemplated. This burgeoning of therapies has added to the complexity of therapeutic decision-making. Recent guidelines[29] may help, but provide no recommendations on recently approved agents such as inhaled iloprost and sildenafil. Currently, there is no convincing evidence to support treating NYHA class I patients. Most clinicians use an oral therapy to initiate therapy for class II or III patients, but whether to begin with sildenafil or bosentan is currently a matter of debate. A prostacyclin infusion, either intravenous epoprostenol or intravenous or subcutaneous treprostinil, is usually initiated for class IV patients. However, many questions remain unanswered, such as whether some patients should be initiated on combination therapy, what to do when patients fail to respond adequately to initial therapy, and when to use inhaled therapies. Because of the complexity of managing PAH patients, referral to centers specializing in pulmonary hypertension is recommended, partly to give them the opportunity to participate in clinical trials.

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