Oral Therapies for PAH: State-of-the-Art and Investigational Approaches


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The development of intravenous epoprostenol was an exciting advance in treating pulmonary arterial hypertension, offering patients improved functional capacity and prolonged survival. However, this form of therapy is complicated, requiring an indwelling central venous catheter, with attendant risks of infection, thrombosis, and dislodgement. The desire to simplify therapy and improve safety has led to a variety of oral agents, generally classified as endothelin receptor antagonists and phosphodiesterase inhibitors. An oral prostanoid is also under development.

Pulmonary arterial hypertension is often difficult to diagnose and challenging to treat. Untreated, it is characterized by a progressive increase in pulmonary vascular resistance leading to right ventricular dysfunction, impairment in activity tolerance, and death. Pulmonary arterial hypertension is defined as a mean pulmonary artery pressure greater than 25 mmHg with a pulmonary capillary wedge pressure under 15 mmHg measured by cardiac catheterization.[1] It may occur in the setting of a variety of underlying medical conditions, such as connective tissue disease or congenital heart disease, or as a vascular disease that primarily affects the pulmonary circulation.

Significant advances in the treatment of pulmonary arterial hypertension have occurred over the past 15 years. The first therapy approved by the Food and Drug Administration (FDA) was chronic intravenous epoprostenol (Flolan). This therapy was shown in randomized and controlled trials to improve exercise capacity in patients with primary or idiopathic disease (IPAH)[2] and of pulmonary arterial hypertension occurring in association with scleroderma.[3] It has since been shown to improve longer-term outcomes[4,5] and remains a very important part of our therapeutic armamentarium.[6] However, because of its complexity and risks associated with the requisite indwelling central venous catheter, clinical investigators have sought simpler methods for the administration of prostanoid therapy. Such options now include chronic subcutaneously administered treprostinil (Remodulin)[7] and inhaled iloprost (Ventavis),[8,9] both of which are approved by the FDA. Prostanoids have also been developed for oral use, but are not yet approved by the FDA. Oral beraprost was studied, but did not appear to demonstrate sustained clinical benefit.[10] Another oral prostanoid is currently in clinical trials. The desire for simpler therapies has led to the development of two FDA-approved oral therapies, an endothelin receptor antagonist and a phosphodiesterase inhibitor, and the study of at least two other oral agents.

This article will address these oral therapies and their place in current treatment. The American College of Chest Physicians (ACCP) convened a multidisciplinary panel of experts in 2003-2004 to develop guidelines for the approach to management of pulmonary arterial hypertension patients. These evidence-based guidelines, including a comprehensive overview of treatment, were published as a supplement to *Chest* in 2004.[11] The guidelines are currently being updated to incorporate advances that have occurred since that publication.

Vasoreactivity and Use of Calcium Channel Antagonists

Although calcium channel blockers were among the earliest forms of therapy utilized in IPAH, it is now recognized that only a small proportion of patients do well with this form of therapy. This subgroup of patients often demonstrates a favorable response to acute vasodilator testing at the time of cardiac catheterization. Although it was initially thought that perhaps 20% to 25% of patients with IPAH demonstrated acute pulmonary vasoreactivity and a subsequent longer-term response to calcium channel blockers, it has more recently been shown by Sitbon and colleagues in a retrospective analysis of 557 IPAH patients tested acutely with intravenous epoprostenol or inhaled nitric oxide[12] that only 12.6% displayed vasoreactivity as defined by a greater than 20% decrease in both mean pulmonary artery pressure (PAPm) and pulmonary vascular resistance. Furthermore, of the 70 patients who displayed acute vasoreactivity, only 38 (6.8% of the overall study group) had a favorable long-term clinical response to chronic calcium channel blocker therapy. These patients reached a PAPm of 33 ± 8 mmHg with acute vasodilator testing.

As a result, the consensus definition of a favorable response has been revised to require a fall in PAPm of 10 mmHg or more, to a PAPm of 40 mmHg or less, with

unchanged or increased cardiac output. True responders to calcium channel blockers are relatively rare among patients with other forms of pulmonary arterial hypertension. In general, long-acting preparations of nifedipine or diltiazem, or amlodipine are suggested, and because of potential negative inotropic effects, verapamil should probably be avoided. Patients should be followed closely for safety and efficacy, and alternative therapy considered if the patient fails to improve.

Endothelin Receptor Antagonists

Endothelin receptor antagonism is a promising therapeutic approach supported by evidence of the pathogenic role of endothelin-1 in pulmonary arterial hypertension.[11,13] Endothelin-1 is a vasoconstrictor and a smooth muscle mitogen that might contribute to the development of pulmonary arterial hypertension.[14] In addition, endothelin-1 expression, production, and concentration in plasma[15,16] and lung tissue[17] are elevated in pulmonary arterial hypertension, and these levels are correlated with disease severity.[17] Two distinct endothelin receptor isoforms, ET_A and ET_B, have been identified.[18] There is controversy as to whether it is preferable to block both the ET_A and ET_B receptors or to target the ET_A receptor.

Bosentan

Bosentan (Tracleer) is a relatively nonselective antagonist of both the ET_A and ET_B receptors that is currently approved by the FDA for patients with WHO functional class III-IVdisease. The first small, randomized, double-blind, placebo-controlled, multicenter study of bosentan demonstrated improvement in the distance walked in 6 minutes of 70 m (from 360 ± 19 m at baseline to 430 ± 14 m at week 12; $P < .05$), whereas none was seen with placebo (355 ± 25 m at baseline and 349 ± 44 m at week 12).[19] Bosentan also improved cardiopulmonary hemodynamics and functional class. It was associated with asymptomatic increases in hepatic aminotransferases in two patients. In a second larger, double-blind, placebo-controlled study (the BREATHE-1 study), bosentan (125 or 250 mg bid) was evaluated in 213 patients with either IPAH or pulmonary arterial hypertension associated with connective tissue disease for a minimum of 16 weeks (62.5 mg bid for 4 weeks followed by uptitration to the target dose).[20] The distance walked in 6 minutes improved by 36 m whereas deterioration (–8 m) was seen with placebo. The difference between groups in the mean change in the 6-minute walking distance was 44 m in favor of bosentan (95% CI: 21 to 67 m, $P = .0002$). The risk of clinical worsening was reduced by bosentan compared with placebo ($P = .0015$, with the log-rank test). Abnormal hepatic function tests, syncope, and flushing occurred more often in the bosentan group. Longer-term outcomes with bosentan therapy have been more recently published. McLaughlin et al[21] reported that first-line therapy with bosentan, with the subsequent addition or transition to other therapy as needed, resulted in Kaplan-Meier survival estimates of 96% at 12 months and 89% at 24 months. At the end of 12 and 24 months, 85% and 70% of patients, respectively, remained alive and receiving bosentan monotherapy. Sitbon et al[22] compared survival in functional class III IPAH treated with bosentan with historical data from similar patients treated with epoprostenol. Baseline characteristics for the 139 patients treated with bosentan and the 346 treated with epoprostenol suggested that the epoprostenol cohort had more severe disease. Kaplan-Meier survival estimates after 1 and 2 years were 97% and 91%, respectively, in the bosentan-treated cohort and 91% and 84% in the epoprostenol cohort.

Bosentan has more recently been studied in other patient populations or subgroups. In a retrospective study of 86 children with IPAH and pulmonary arterial hypertension associated with congenital heart disease or connective tissue disease,[23], bosentan was used with or without concomitant intravenous epoprostenol or subcutaneous treprostinil therapy. At the time of cutoff, 68 patients (79%) were still treated with bosentan, 13 (15%) were discontinued, and 5 (6%) had died. Median bosentan exposure was 14 months. In 90% of the patients (n = 78), functional class improved (46%) or was unchanged (44%) with bosentan treatment. PAPm and pulmonary vascular resistance decreased, and Kaplan-Meier survival estimates at one and two years were 98% and 91%, respectively. Galie et al reported the results of a multicenter, double-blind, randomized, and placebo-controlled study of bosentan therapy in patients with functional class III Eisenmenger syndrome (the BREATHE-5 study).[24] Fifty-four patients were randomized 2:1 to receive bosentan or placebo for 16 weeks. Bosentan did not worsen oxygen saturation. Compared with placebo, bosentan reduced pulmonary vascular resistance index, decreased PAPm, and increased exercise capacity. Four patients discontinued because of adverse events, 2 (5%) in the bosentan group and 2 (12%) in the placebo group.

Bosentan is currently used relatively widely in the treatment of patients with pulmonary arterial hypertension. Close follow-up over time of both efficacy and safety are encouraged. The FDA mandates that liver function tests be checked monthly, and that the hematocrit should be checked every 3 months. In addition to potential hepatotoxicity, other side effects may include anemia and the development of fluid retention/edema. Hormonal methods of birth control may be less effective with concurrent administration of bosentan, and barrier techniques should be considered.

Sitaxsentan

Sitaxsentan is a more selective antagonist of the ET_A receptor, and is currently an investigational agent. In a randomized, double-blind, placebo-controlled trial (the STRIDE-1 study), 178 NYHA functional class II, III, and IV patients with IPAH, pulmonary arterial hypertension related to connective tissue disease, or pulmonary arterial hypertension related to congenital systemic to pulmonary shunts, sitaxsentan improved exercise capacity and functional class after 12 weeks of treatment.[25] The treatment effects in the sitaxsentan groups were 35 meters ($P < .01$) for the 100 mg dose and 33 meters ($P < .01$) for the 300 mg dose. Functional class and hemodynamics also improved. The incidence of liver function abnormalities was more favorable for the 100 mg dose. The most frequently reported adverse

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events with sitaxsentan treatment were headache, peripheral edema, nausea, nasal congestion, and dizziness, and the most frequent laboratory adverse event was increased international normalized ratio or prothrombin time related to the effect of sitaxsentan on inhibition of CYP2C9 P450 enzyme, the principal hepatic enzyme involved in the metabolism of warfarin. A second double-blind, placebo-controlled trial with sitaxsentan (the STRIDE-2 study)[26] randomized 247 patients (245 were treated) with IPAH, or pulmonary arterial hypertension associated with connective tissue disease or congenital heart disease: placebo (n = 62), sitaxsentan 50 mg (n = 62) or 100 mg (n = 61), or open-label (6-minute walk tests, Borg dyspnea scores, and WHO functional class assessments were third-party blind) bosentan (n = 60). At week 18, patients treated with sitaxsentan 100 mg had an increased 6-minute walk distance compared with the placebo group (31.4 m, $P = .03$), and improved functional class ($P = .04$). The placebo-subtracted treatment effect for sitaxsentan 50 mg was 24.2 m ($P = .07$) and for open-label bosentan, 29.5 m ($P = .05$). The incidence of elevated hepatic transaminases (more than three times the upper limit of normal) was 6% for placebo, 5% for sitaxsentan 50 mg, 3% for sitaxsentan 100 mg, and 11% for bosentan.

Ambrisentan

Ambrisentan, also currently an investigational agent, is a relatively selective antagonist of the ET_A receptor. A phase-2 dose-ranging study examined the efficacy and safety of four doses of ambrisentan in patients with pulmonary arterial hypertension.[27] In this double-blind study, 64 patients with IPAH or pulmonary arterial hypertension associated with connective tissue disease, anorexigen use, or human immunodeficiency virus infection were randomized to receive 1, 2.5, 5, or 10 mg of ambrisentan once daily for 12 weeks. Ambrisentan increased 6-minute walk distance (+36.1 m, $P < .0001$) with similar increases for each dose group (range, +33.9 to +38.1 m). Improvements were also seen in Borg dyspnea index, WHO functional class, subject

global assessment, PAPm, and cardiac index. Adverse events were generally mild and unrelated to dose, including the incidence of elevated serum aminotransferase concentrations greater than three times the upper limit of normal (3.1%). Two phase-3 clinical trials of ambrisentan in patients with pulmonary arterial hypertension have been completed, and publication of the results is pending.

Phosphodiesterase Inhibitors

Sildenafil

The vasodilatory effects of nitric oxide are dependent on its ability to augment and sustain cGMP content in vascular smooth muscle. Nitric oxide activates soluble guanylate cyclase, which increases cGMP production. Cyclic GMP then causes vasorelaxation, but its effects are short-lived because of the rapid degradation of cGMP by phosphodiesterases.[28,29] Phosphodieseterases (PDE) are enzymes that hydrolyze cAMP and cGMP, limiting their intracellular signaling properties. Sildenafil is a specific PDE5 inhibitor, previously approved for the treatment of erectile dysfunction, and now approved for the treatment of pulmonary arterial hypertension. Several reports of pulmonary arterial hypertension patients treated with long-term sildenafil suggested therapeutic promise for the drug.[30-32] The SUPER-1 study was a randomized, double-blind, placebo-controlled clinical trial that assigned 278 patients with symptomatic disease (IPAH or pulmonary arterial hypertension associated with connective-tissue disease or with repaired congenital systemic-to-pulmonary shunts) to placebo or sildenafil (20, 40, or 80 mg) orally three times daily for 12 weeks.[33] The 6-minute walk distance increased from baseline in all sildenafil groups; the mean placebo-corrected treatment effects were 45 m (+13.0%), 46 m (+13.3%), and 50 m (+14.7%) for 20, 40, and 80 mg doses of sildenafil, respectively ($P <$ .001 for all comparisons). All sildenafil doses reduced the PAPm, improved functional class, and were associated with side effects such as flushing, dyspepsia, and diarrhea. The incidence of clinical worsening did not differ significantly between the patients treated with sildenafil and those treated with placebo. Long-term data (available only at a dose of 80 mg three times daily) in 222 patients completing one year of treatment with sildenafil monotherapy showed improvement from baseline at one year in the 6-minute walk distance (51 m). The FDA-approved dose of sildenafil in patients with pulmonary arterial hypertension is 20 mg administered orally three times daily.

Tadalafil

Another, longer-acting, phosphodiesterase inhibitor is currently undergoing clinical study. It is approved by the FDA for use in patients with erectile dysfunction, but remains investigational in patients with pulmonary arterial hypertension.

Oral Prostanoids

Beraprost

Beraprost is orally active prostacyclin analogue[34] that has undergone two randomized, double-blind, placebo-controlled trials in pulmonary arterial hypertension. The first study was a 12-week double blind, randomized, placebo-controlled trial performed in 130 functional class II and III patients with disease of various etiologies (IPAH, pulmonary arterial hypertension associated with connective tissue diseases, congenital systemic-to-pulmonary shunts, portal hypertension, or HIV infection).[35] At a median dose of 80 µg administered orally four times a day, beraprost increased exercise capacity as assessed by the 6-minute walk test. There were no significant changes in hemodynamics or survival. Side effects were frequent, mainly in the initial titration period, suggesting that tolerance may affect the long-term results with beraprost. A second trial evaluated the effects of beraprost in 116 NYHA functional class II and III patients. It was a 12-month double-blind, randomized, placebo-controlled study.[36] Beraprost-treated patients had less disease progression at 6 months, and improved 6-minute walk distance at 3 months (+22 m from baseline) and 6 months (+31 m), as compared with placebo. However, this improvement was no longer present at 9 or 12 months. There were no significant changes in hemodynamics at month 12 as compared to baseline. Survival was similar for the treatment groups. Beraprost has previously been approved for pulmonary arterial hypertension in Japan, but is not approved by the FDA.

Another oral prostanoid is currently under study in pulmonary arterial hypertension.

Conclusion

Therapy for pulmonary arterial hypertension has advanced considerably over the last 10 to 15 years, and oral therapies are now available. While it is relatively straightforward to describe the various agents available, as well as the evidence supporting their safety and efficacy, it is far more difficult to create a therapeutic algorithm that guides the provider in choosing the most appropriate therapy for an individual patient. The task of developing such an algorithm generally falls to guidelines or consensus panels of experts in the field, and their challenge is enhanced by the paucity of truly comparative data. Furthermore, the data currently available pertaining to add-on or combination therapy is limited. An update to the previously published ACCP guidelines[11] is anticipated in the near future, as is a consensus statement from another professional society. Therapy should obviously be individualized, taking into account the patient's specific clinical situation. It continues to be strongly recommended that patients be referred to centers of excellence, and that long-term care be shared with the referring physician. Close follow-up, with frequent objective assessment of clinical status and therapeutic response, are essential to optimal long-term outcomes. ■

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