PAH Treatment Options: A Concise Summary

Current Treatment Options

Several therapies that delay disease progression and reduce the risk of hospitalization for individuals with pulmonary arterial hypertension (PAH) have been developed in recent years. These treatment options target the endothelin-1, prostacyclin, and nitric oxide pathways.[1,2] Therapies approved by the Food and Drug Administration (FDA) for the treatment of PAH include:[3]

- Prostacyclin analogs and receptor agonists (epoprostenol, iloprost, treprostinil, selexipag)
- Endothelin receptor antagonists (ERA; ambrisentan, bosentan, macitentan)
- Phosphodiesterase-5 inhibitors (PDE-5; sildenafil, tadalafil)
- Soluble guanylate cyclase stimulator (riociguat)

Each of these medications has its own side effect profile and method of dosing and administration. Familiarity of the adverse events associated with each medication is necessary for timely recognition and optimal treatment of the patient with PAH.

Prostacyclin Analogs and Receptor Agonists

Prostacyclin analogs and receptor agonists work by increasing cyclic adenosine monophosphate and cause nonselective pulmonary vasodilation, and they have antiplatelet, antithrombotic, anti-inflammatory, and antiproliferative effects on pulmonary endothelial tissue.[2]

Epoprostenol is one of the most successful therapies used to treat PAH.[4] It is a synthetic analogue of prostacyclin that dilates blood vessels and was approved for PAH by the FDA in 1995.[4] Epoprostenol requires a continuous intravenous infusion through central access and is recommended in patients with rapidly progressing disease.[1,2] American College of Chest Physicians (CHEST) guidelines recommend epoprostenol to improve functional class (FC), six-minute walk distance (6MWD), and cardiopulmonary hemodynamics.[5] It has demonstrated a direct survival benefit in a 3-month controlled study of idiopathic PAH patients. Adverse events may include headache, nausea, vomiting, diarrhea, flushing, hypotension, and jaw pain.[2]

Treprostinil is often used interchangeably with epoprostenol and can also be delivered intravenously or through a disposable dry powder inhaler.[2] It has been shown to stall disease progression when administered early, possibly by delaying pulmonary vascular remodeling if initiated in the early disease course.[1] CHEST guidelines recommend continuous IV Treprostinil to improve both 6MWD.[5] Moreover, for patients with PAH who remain symptomatic on stable and appropriate doses of an endothelin receptor antagonist (ETRA) or a PDE-5 inhibitor, the addition of inhaled treprostinil to improve 6MWD is recommended.[3] Common adverse effects include flushing, headache, diarrhea, jab pain, and limb pain.[6]

Iloprost is an inhaled formulation of prostacyclin that has been shown to improve exercise capacity and FC.[2] Clinical trial data found a significant improvement in 6MWD among patients receiving iloprost compared to those on placebo.[7] Guidelines recommend the addition of iloprost to improve FC in patients with PAH who remain symptomatic on stable and appropriate doses of an ERA.[5] Common adverse effects include flushing, headache, jaw pain, and cough.[6]

Selexipag is an oral selective prostacyclin receptor agonist that increases time to clinical worsening.[6] Clinical trial data found a significant decrease in death and disease progression for patients receiving selexipag compared to those receiving placebo.[7] Adverse events include headache, diarrhea, nausea, flushing, and jaw pain.[6,7] Given methodological issues in clinical trials, the CHEST expert panel report concluded that there is insufficient evidence to make a recommendation for or against the use of selexipag.[5]

Endothelin Receptor Antagonists (ERA)

Ambrisentan is an orally administered FDA-approved ERA for the treatment of PAH that functions by 1) binding to the endothelin receptor type A and some type B, and 2) blocking endothelin-mediated vasoconstriction.[2,3,6] In clinical trials, ambrisentan was shown to improve time to clinical worsening and 6MWD.[6] Patients treated with ambrisentan tended to develop peripheral edema, headache, and nasal congestion more frequently than in patients receiving placebo.[3] Occasional liver function test monitoring for hepatotoxicity is recommended.[2] As monotherapy, CHEST guidelines recommend ambrisentan to improve 6MWD.[5] It is also recommended as initial combination therapy with tadalafil to improve 6MWD in treatment-naïve PAH patients.[5] Ambrisentan in combination with tadalafil is currently the only FDA-approved combination endorsed by CHEST guidelines.[2] This combination is recommended to improve 6MWD.[5]

Bosentan, like ambrisentan, is an oral ERA that binds to endothelin receptors types A and B and blocks endothelin-mediated vasoconstriction.[6] In clinical trials it was shown to increase time to clinical worsening and significantly improve 6MWD compared to placebo.[7] Bosentan is recommended to improve 6MWD, decrease hospitalizations related to PAH, and delay time to clinical worsening.[5] Of the FDA-approved ERAs, bosentan is the most toxic and requires regular liver function tests.[2] Common side effects include increased hepatic transaminases, peripheral edema, respiratory tract infections, and fluid retention.[2,6]

Macitentan is an oral ERA developed by modifying the structure of bosentan to improve efficacy and safety.[7] It works by binding to endothelin receptor type A and some type B, and by blocking endothelin-mediated vasoconstriction.[6] Clinical trials found that macitentan increased time from initiation of treatment to first event-related to PAH.[7] It is taken orally and recommended for delaying the time to clinical worsening, improving FC, and improving 6MWD.[3,5] Occasional liver function test monitoring for hepatotoxicity is recommended.[2] Common adverse effects include anemia, headache, nasopharyngitis, and increased liver enzymes.[6]

Phosphodiesterase-5 (PDE-5) Inhibitors

Sildenafil was the first PDE-5 inhibitor approved for the treatment of PAH, based in part on clinical trial evidence showing significant improvement in exercise capacity compared to placebo.[7] It is taken orally and enhances the nitric oxide-cGMP pathway and slows cGMP gradation in addition to acting as a pulmonary vasodilator.[6] Sildenafil is recommended to improve 6MWD and FC.[5] Reported side effects include headache, flushing, epistaxis, hypotension, and diarrhea.[6,7]

Tadalafil, like sildenafil, is taken orally and acts by enhancing the nitric oxide-cGMP pathway, slowing cGMP degradation, and acting as a pulmonary vasodilator.[6] In combination with ambrisentan it is currently the only FDA-approved combination endorsed by CHEST guidelines.[2] CHEST guidelines recommend its use as monotherapy for improving 6MWD, improving FC, and delaying time to clinical

worsening.[5] In combination with ambrisentan, it is recommended to improve 6MWD.[5] Common side effects include headache, flushing, nausea, myalgia, and hypotension.[6]

Soluble Guanylate Cyclase Stimulator

Riociguat is a soluble guanylate cyclase (sGC) stimulator taken orally that enhances the production of NO through a direct stimulation of sGC and increase in intracellular cGMP.[2] In clinical trials it was shown to improve exercise capacity, pulmonary vascular resistance, NT-proBNP, time to clinical worsening, and FC.[2] Moreover, clinical trial data also showed that in patients who did not respond to PDE-5 inhibitors, riociguat improved both exercise capacity and hemodynamics.[2] It is recommended as additional therapy in patients who remain symptomatic on stable doses of bosentan, ambrisentan, or an inhaled prostanoid to improve 6MWD.[5] Common adverse events include headache, dizziness, dyspepsia, peripheral edema, hypotension, respiratory hemoptysis, and epistaxis.[2,6] It is recommended to improve 6MWD, to improve FC, and to delay time to clinical worsening.[5]

Drugs in Late-Stage Development

Emerging Therapies and Treatment Pathways. The growing understanding of the physiology of PAH is identifying new treatment pathways that target the underlying mechanisms of the disease. Studies over the past 20 years have revealed a role for circulating and resident vascular cells in pulmonary vascular remodeling, unveiling therapeutic potential for circulating endothelial progenitor cells and mesenchymal stem cells.[8]

eNOS. The endothelial nitrous oxide level in the pulmonary vasculature was shown to be reduced in PAH patients. Studies have found that eNOS-transfected early outgrowth endothelial progenitor cells (EPCs) delivered into the right atrium of seven patients with idiopathic PAH showed no evidence of short-term hemodynamic deterioration, a trend toward short-term hemodynamic improvements, and sustained increases in exercise capacity at 3 and 6 months.[9] The phase II SAPPHIRE trial is evaluating the efficacy and safety of angiogenic therapy to restore the microvasculature with repeat dosing of autologous EPCs transfected with human eNOS in patients with refractory PAH, and results are anticipated in 2025.[10]

Ralinepag is an emerging non-prostanoid prostacyclin receptor agonist that has been studied in PAH patients receiving either mono or dual PAH-targeted background therapy. The data showed that ralinepag reduced PVR in patients on monotherapy by 41% and in patients on dual combination therapy by 59% compared to placebo.[11]

Other therapies. Other new therapies for PAH are in clinical trials or are otherwise emerging. These include sotatercept, a novel fusion protein; targeted therapies for chronic thromboembolic pulmonary hypertension (CTEPH); and targeted therapies for right ventricular (RV) failure.[12-14] Additionally, recent research in combination therapies has created a paradigm shift in the treatment of PAH.[2] However, ambrisentan and tadalafil is currently the only FDA-approved combination endorsed by CHEST guidelines.[2]

Autoimmunity and inflammation is another pathway that has recently received attention as a potential therapeutic target in PAH. It has been widely recognized that patients with connective tissue diseases or viral infections—including COVID-19—are more susceptible to PAH.[15,16] However, recent evidence now supports that patients with idiopathic PAH with no known autoimmune diseases also have auto-antibodies. Local immunoglobulin production may play a role in association with maladaptive immune

responses in pulmonary tissue, and this provides a theoretical basis for future drug development and precision therapies in patients with PAH.[16]

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